Evaluability Status

A total of 50 patients were considered not infected at Baseline (25 patients in the HAC group and 25 patients in the HC group), and 15 patients were considered to be non-evaluable for *H. pylori* status at Baseline (5 patients in the HAC group and 10 patients in the HC group). The Day 38 visit results show that 45 of the 515 patients (9%) 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 6 and 7 in Appendix 1 for the baseline visit and 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 12 for each of the two treatment groups. For the PP analysis, there was no significant difference between the treatment groups in the proportion of patients with a healed DU by the Day 38 visit (75% in the HAC group, 66% in the HC group). Results were similar for the ITT analysis. The proportion of patients with a healed DU by the Day 38 visit in the HAC group (69%) was not significantly different from the proportion of patients in the HC group (62%).

TABLE 12
DU Healed Status by Day 38 Visit
For Patients with an Active DU at Baseline
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[a]
Duodenal Ulcer Healed by Day 38 visit	n/N (%)	n/N (%)	
Per-Protocol	117/156 (75%)	95/144 (66%)	p = 0.087
Intention-to-Treat	127/185 (69%)	104/168 (62%)	p = 0.184

[a] Comparisons between the treatment groups based on logistic regression models with treatment group as the only factor. Comparisons were not significant, (p > 0.050).

Clinical Reviewer's Comment: There were 205 patients randomized to the HAC group and 192 patients randomized to the HC group with an active DU at baseline . In the HAC group, 20 were excluded from the ITT analysis (see Table 3 in Appendix 1) and 37 were excluded from the PP analysis (see Table 4 in Appendix 1). In the HC group, 24 were excluded from

the ITT analysis (see Table 3 in Appendix 1) and 40 were excluded from the PP analysis (see Table 4 in Appendix 1).

For the PP DU Healing Analysis, in addition to Criteria A-H, patients were considered non-evaluable if they did not return for the follow-up endoscopy or if they returned before Day 29 and had an unhealed ulcer. In the HAC group an additional 12 patients were excluded and an additional 8 patients were excluded from the HC group. See table below for final numbers of patients included in each analysis. The denominators used in Table 12 are correct for the ITT and PP Analyses.

Intent-to-Treat (ITT)

	HAC	HC
All Randomized Patients with an Active DU at Baseline	*205*	*192*
Patients Excluded from DU Healing ITT Analysis (Table 3 in Appendix 1)	*20*	*24*
Patients Included in DU Healing ITT Analysis	*185*	*168*

Per-Protocol (PP)

	HAC	HC
All Randomized Patients with an Active DU at Baseline	*205*	*192*
Patients Excluded from DU Healing PP Analysis (Table 4 in Appendix 1)	*37*	*40*
*Additional Patients Excluded from DU Healing PP Analysis**		
No follow-up data or unhealed ulcer before Day 29	*12*	*8*
Patients Included in DU Healing PP Analysis	*156*	*144*

**not listed in Table 4 in Appendix 1*

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 13 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.

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TABLE 13
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 #191

	H 40 qd + A 1000 bid + C 500 bid			H 40 qd + C 500 bid			Both Treatment Groups Combined		
	DU Healed by Day 38								
H. pylori Eradicated at Day 38 Visit	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	104	28	132	59	23	82	163	51	214
No	11	11	22	36	25	61	47	36	83
Total	115	39	154	95	48	143	210	87	297

Clinical and Statistical Reviewers' Comment: The incidence of ulcers (unhealed/recurrent/new) at 4-6 weeks post-treatment in relation to H. pylori eradication was determined. The incidence of ulcers was significantly lower in patients eradicated versus those not eradicated for the HAC treatment group only. Addition of amoxicillin to the HC regimen appeared to slightly decrease prevalence in the eradicated group, but not in the group with persistent infection.

Incidence of Ulcers in Relation to H. pylori Status

Treatment Group	*H. Pylori Eradicated*	*H. Pylori Not Eradicated*	*Difference in Rates (95% CI)*	*Odds Ratio (95% CI)*	*Pearson's χ^2 p-value*
HC	*23/82 (28.0%)*	*25/61 (41.0%)*	*-13% (30.1%, 4.2%)*	*0.561 (0.278, 1.132)*	*0.105*
HAC	*28/132 (21.2%)*	*11/22 (50.0%)*	*-29% (-53.5%, -4.1%)*	*0.269 (0.106, 0.685)*	*0.004*
Combined	*51/214 (23.8%)*	*36.83 (43.4%)*	*-20% (-32.5%, -6.6%)*	*0.408 (0.239, 0.698)*	*0.001*

There were 3 of the 59 patients enrolled in the HAC group and 1 of the 59 patients enrolled in the HC group who did not have an active DU at the baseline endoscopy, but who developed an ulcer at some time during the study period. Three of these patients developed a DU while 1 patient developed a gastric ulcer.

Clinical Reviewer's Comment: These four patients who developed an ulcer during the study period were small in number and the results are not unexpected.

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 are presented 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 77% 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 there were no significant differences between the treatment groups in the proportion of patients with improvement in upper GI symptoms from baseline at either the Day 11 Visit or the Day 38 Visit for any of the symptoms assessed. In addition, there were no significant differences between the treatment groups in the proportion of patients with none or mild symptoms at the Day 11 Visit or the Day 38 Visit for any of the symptoms assessed.

9. Susceptibility

The susceptibility of all available *H. pylori* isolates to amoxicillin and 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.

H. pylori susceptibility results are presented for both amoxicillin and clarithromycin. Only data from patients considered *H. pylori* infected at Baseline are included in the following tables.

Clarithromycin

For both treatment groups combined, a total of 13% of the patients (42 of 313 patients with known susceptibility results) had *H. pylori* isolates which were considered to be resistant to clarithromycin at Baseline, < 1% of the patients (2 of 313 patients with known susceptibility results) had isolates considered to be intermediate, and 86% of the patients (269 of 313 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 alone.

Table 14 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 42 patients with *H. pylori* isolates resistant to clarithromycin at the baseline visit, 21% of the patients (9 of 42 patients) had previously taken *H. pylori* eradication regimens containing clarithromycin while 79% of the patients (33 of 42 patients) had not taken such previous regimens.

TABLE 14
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 #191

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	9	(21%)	33	(79%)	42
Intermediate	1	(50%)	1	(50%)	2
Susceptible	8	(3%)	261	(97%)	269
No Result [a]	7	(5%)	130	(95%)	137
TOTAL	25	(6%)	425	(94%)	450

[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 the patients with baseline resistance to clarithromycin mostly came from patients who had not taken previous H. pylori eradication regimens containing clarithromycin. The explanation for this finding is unknown, but may have to do with other undetermined patient 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 15. Results are presented for each treatment group, as well as for both treatment groups combined.

In this study, of the 269 *H. pylori* isolates susceptible to clarithromycin at Baseline, 20 isolates were known to develop resistance to clarithromycin by the end of the study (1 of the isolates was from a patient who took HAC, and 19 of the isolates were in patients who took HC).

TABLE 15
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 # 191

	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 + A 1000 bid + C 500 bid								
Resistant	7	10	0	0	2	12	2	21
Intermediate	1	0	0	0	0	0	0	1
Susceptible	118	1	0	2	11	14	11	143
No Result [a]	50	1	0	0	9	10	9	69
Total	176	12	0	2	22	36	22	234
H 40 qd + C 500 bid								
Resistant	4	13	0	0	4	17	0	21
Intermediate	0	0	1	0	0	1	0	1
Susceptible	72	19	1	3	25	48	6	126
No Result [a]	36	6	0	0	21	27	5	68
Total	112	38	2	3	50	93	11	216
Both Treatment Groups Combined								
Resistant	11	23	0	0	6	29	2	42
Intermediate	1	0	1	0	0	1	0	2
Susceptible	190	20	1	5	36	62	17	269
No Result [a]	86	7	0	0	30	37	14	137
Total	288	50	2	5	72	129	33	450

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

Amoxicillin

For both treatment groups combined, a total of > 99% of the patients (312 of 313 patients) had *H. pylori* isolates that were considered to be susceptible to amoxicillin at Baseline. Only 1 patient (1459) had a baseline *H. pylori* isolate which was classified as not defined. For this patient, the baseline MIC value from the antral biopsy was 0.5 µg/mL, but the baseline MIC value from the corporeal biopsy was ≤ 0.015 µg/mL. There were no MIC value results for this patient at the Day 38 Visit, but the patient was classified as still infected with *H. pylori* at the Day 38 Visit based on a positive CLOtest® result.

A comparison of the baseline *H. pylori* amoxicillin susceptibility status results and the *H. pylori* eradication status at the Day 38 Visit is presented in Table 16. Results are presented for each treatment group, as well as for both treatment groups combined.

TABLE 16
Baseline *H. pylori* Susceptibility Results vs. *H. pylori* Eradication Status at Day 38
Susceptibility to Amoxicillin Based on Agar Dilution
Number of Patients
All Available Data
Study #191

	Day 38 Visit *H. pylori* Eradication Status						
Baseline *H. pylori* Susceptibility to Amoxicillin	*H. pylori* Eradicated	*H. pylori* Not Eradicated				No *H. pylori* Eradication Result	Total
		Day 38 Visit Susceptibility to Amoxicillin					
		Not Def.	*Susc.*	*No Result*	*Total*		
H 40 qd + A 1000 bid + C 500 bid							
Not defined	0	0	0	0	0	0	0
Susceptible	126	0	13	13	26	13	165
No Result [a]	50	0	1	9	10	9	69
Total	176	0	14	22	36	22	234
H 40 qd + C 500 bid							
Not defined	0	0	0	1	1	0	1
Susceptible	76	0	37	28	65	6	147
No Result [a]	36	0	6	21	27	5	68
Total	112	0	43	50	93	11	216
Both Treatment Groups Combined							
Not defined	0	0	0	1	1	0	1
Susceptible	202	0	50	41	91	19	312
No Result [a]	86	0	7	30	37	14	137
Total	288	0	57	72	129	33	450

[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 515 patients were randomized to one of the two treatment groups in this study. Of these 515 patients, 513 patients were included in the analysis of AEs; 2 patients were not included because they did not take any study medication (AN 1566 in HAC group, and AN 1642 in the HC treatment group). 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.

TABLE 2
Number of Patients Included and Excluded in the Statistical Analyses (Study #193)

	H 40 qd + A 1000 bid + C 500 bid		H 40 qd	
	n	(%)	n	(%)
Total enrolled	85		28	
Included in Efficacy Analysis				
Intention-To-Treat	74	(87%)	24	(86%)
Per-Protocol	71	(84%)	23	(82%)
Excluded from Efficacy Analysis				
Intention-To-Treat	11	(13%)	4	(14%)
A. *H. pylori* not positive at Baseline	11		4	
B. No baseline DU and no history of DU	2		0	
C. No study medication taken	0		0	
Per-Protocol	14	(16%)	5	(18%)
A. *H. pylori* not positive at Baseline	11		4	
B. Baseline DU not at least 0.5 cm and no history of DU within last 5 years	2		0	
C. Took antimicrobials, bismuth, or PPI prior to enrollment	3		1	
D. Noncompliance of study medication	3		0	
E. Concomitant antimicrobials or bismuth compounds	0		0	
F. Concomitant H2-RA, PPI or sucralfate	0		0	
G. Other conditions/diseases	0		0	
H. Enrolled in previous H 199/18 *H. pylori* study (Studies 191 or 192)	0		0	
Included in Safety Analysis	85	(100%)	28	(100%)

Table 2 in Appendix 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 for that analysis.

Patients may have been excluded from either patient population for more than one reason. Two of the 15 patients (13%) who were excluded from the ITT analysis were considered non-evaluable for more than one reason, and 5 of the 19 patients (26%) 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 3 has been modified from the applicant's original tables 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 3 for those patients considered non-evaluable for the ITT analysis. Table 4 in Appendix 3 presents the same results for those patients considered non-evaluable for the PP analysis.

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

3. Demographic Characteristics

A total of 113 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 3 for all 113 randomized patients. There were no significant differences observed between the two treatment groups, HAC and H, for any baseline demographic characteristic for the all randomized patients, ITT, or PP patient populations.

The applicant indicated there were 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 3
Baseline Patient Demographics and Characteristics
All Randomized Patients
Study #193

Baseline Patient Demographic/Characteristic	H 40 qd + A 1000 bid + C 500 bid (N=85)		H 40 qd (N=28)	
	n	(%)	n	(%)
Gender				
Male	51	(60%)	16	(57%)
Female	34	(40%)	12	(43%)
Age (years)				
Mean (SD)	43.6 (13.4)		40.4 (11.1)	
Median	41		39.5	
Range	21 to 79		22 to 62	
≤ 65 years	80	(94%)	28	(100)
> 65 years	5	(6%)	0	(0%)
Race				
Caucasian	61	(72%)	17	(61%)
Black	23	(27%)	8	(29%)
Other	1	(1%)	3	(11%)
Smoking Status				
Smoker	40	(47%)	15	(54%)
Nonsmoker	45	(53%)	13	(46%)
Baseline DU Status				
Active DU	73	(86%)	27	(96%)
No active DU	12	(14%)	1	(4%)
Any Upper GI Symptoms				
Yes	83	(98%)	27	(96%)
No	2	(2%)	1	(4%)
Duration of DU Disease				
< 1 year	61	(72%)	19	(68%)
1 to 5 years	15	(18%)	3	(11%)
> 5 years	9	(11%)	6	(21%)
Number of previous episodes of documented active DU [a]				
0	57	(67%)	19	(70%)
1	24	(28%)	8	(30%)
2	3	(4%)	0	(0%)
≥ 3	1	(1%)	0	(0%)
Number of previous attempts to eradicate *H. pylori*				
0	76	(89%)	26	(93%)
1	8	(9%)	2	(7%)
≥ 2	1	(1%)	0	(0%)

[a] One patient in the H 40 qd 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/clarithromycin placebo, or amoxicillin/amoxicillin placebo).

Table 5 in Appendix 3 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 the patient took at least 75% of the prescribed doses of study medication (for each of the three study drugs). As shown in Table 4, compliance in this study was very high: 96% of the patients (82 of 85 patients) in the HAC group and 100% of the patients (28 of 28 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 4
Patient Compliance with Study Medication
Number (%) of Patients
All Randomized Patients
Study #193

	H 40 qd +A 1000 bid + C 500 bid (N=85)		H 40 qd (N=28)	
Patient Compliance Status	n	(%)	n	(%)
Compliant [a]	82	(96%)	28	(100%)
Noncompliant	3	(4%)	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: Of the three noncompliant patients in the HAC group, two were not infected at baseline and excluded from both analyses (310/001 AN 3048 and 321/002 AN 3018). The third patient (334/007 AN 3231) was withdrawn by the investigator due to persistently elevated liver function tests (SGPT, SGOT, and Alk Phos) on Day 9 and was excluded from the PP analysis only.

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 5, 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 (85%) than the H group (5%). 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 (78%) than the H group (4%).

TABLE 5
***H. pylori* Eradication at Day 38 Visit**
Per-Protocol and Intention-to-Treat Analyses
Study #193

	H 40 qd + A 1000 bid + C 500 bid	H 40 qd	p-value
H. pylori Eradicated Day 38 Visit	n/N (%) [95% CI]	n/N (%) [95% CI]	
Per-Protocol	57/67 (85%) [74%, 93%]	1/22 (5%) [0%, 23%]	$p < 0.0001$*
Intention-to-Treat	58/74 (78%) [67%, 87%]	1/24 (4%) [0%, 21%]	$p < 0.0001$*

* 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 2, as well as Table 4, in Appendix 3 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 5 are correct for the PP Analysis.

	HAC	***H***
Included in PP Eradication Analyses (from Table 2)	*71*	*23*
*Additional Patients Excluded from PP Eradication Analysis**		
No follow-up data or negative for Hp before Day 35	*4*	*1*
Total Included in PP Eradication Analysis	*67*	*22*

**not listed in Table 5, or Table 4 in Appendix 3*

Subgroup Analysis

Table 6 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. Age, baseline smoking status, and baseline clarithromycin susceptibility 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 patients in the PP analysis were compliant in taking their study medication. Both gender and race had a significant effect on *H. pylori* eradication rates at the Day 38 visit; however, with small sample sizes in each subgroup, especially in the H group, clinical interpretation about the effect of these covariates on the *H. pylori* eradication rates at the Day 38 visit is difficult to make. The treatment group effect remained significant when each of the tested covariates was added to the logistic regression model.

TABLE 6
***H. pylori* Eradication at Day 38 Visit - Subgroup Analysis**
Number (%) of Patients
Per-Protocol Analysis
Study #193

	H 40 qd A 1000 bid + C 500 bid		H 40 qd	
	n/N	(%)	n/N	(%)
Overall Eradication Rates	57/67	(85%)	1/22	(5%)
Gender				
Males	38/41	(93%)	1/11	(9%)
Females	19/26	(73%)	0/11	(0%)
Race				
Caucasian	46/49	(94%)	1/13	(8%)
Black	10/17	(59%)	0/7	(0%)
Other	1/1	(100%)	0/2	(0%)
Age				
≤ 65 years	54/64	(84%)	1/22	(5%)
> 65 years	3/3	(100%)	0/0	----
Baseline Smoking Status				
Smokers	29/34	(85%)	1/12	(8%)
Non-Smokers	28/33	(85%)	0/10	(0%)
Baseline Duodenal Ulcer Status				
Active duodenal ulcer	52/59	(88%)	1/22	(5%)
No active duodenal ulcer	5/8	(63%)	0/0	----
Baseline Clarithromycin Susceptibility Status				
Resistant/Intermediate	6/9	(67%)	0/2	(0%)
Susceptible	43/49	(88%)	0/15	(0%)
No Result	8/9	(89%)	1/5	(20%)
Compliance to Study Medication				
Patient compliant	57/67	(85%)	1/22	(5%)
Patient not compliant	0/0	----	0/0	----

Sensitivity Analysis

In the PP population, 5 patients were missing *H. pylori* status at Day 38 (4 patients in the HAC group and 1 patient in the H 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, a sensitivity analysis was conducted by the applicant (see Table 7). 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 7
Per-Protocol Sensitivity Analysis for Missing Data
***H. pylori* Eradication at Day 38 Visit**
[95% Confidence Intervals]
Study #193

	H 40 qd + A 1000 bid + C 500 bid	H 40 qd
H. pylori Eradication at Day 38	n/N (%) [95% CI]	n/N (%) [95% CI]
Worst-case estimation	57/71 (80%) [69%, 89%]	1/23 (4%) [0%, 22%]
Best-case estimation	61/71 (86%) [76%, 93%]	2/23 (9%) [1%, 28%]

Evaluability Status

A total of 14 patients were considered not infected at Baseline (11 patients in the HAC group and 3 patients in the H group), and 1 patient was considered to be non-evaluable for *H. pylori* status at Baseline (H group). At the Day 38 visit, eight of the 113 patients (7%) 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 6 and 7 in Appendix 3 for the baseline visit and 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 8 for each of the two treatment groups.

For the PP analysis, there was no significant difference between the treatment groups in the proportion of patients with a healed DU by the Day 38 visit (57% in the HAC group, 55% in the H group). Results were similar for the ITT analysis. The proportion of patients with a

healed DU by the Day 38 visit in the HAC group (53%) was not significantly different from the proportion of patients in the H group (54%).

TABLE 8
DU Healed Status by Day 38 Visit
For Patients with an Active DU at Baseline
Per-Protocol and Intention-to-Treat Analyses
Study #193

	H 40 qd + A 1000 bid + C 500 bid	H 40 qd	p-value[a]
Duodenal Ulcer Healed by Day 38 visit	n/N (%)	n/N (%)	
Per-Protocol	34/60 (57%)	12/22 (55%)	p = 0.864
Intention-to-Treat	35/66 (53%)	13/24 (54%)	p = 0.924

[a] Comparisons between the treatment groups based on logistic regression models with treatment group as the only factor. Comparisons were not significant, (p > 0.050).

Clinical Reviewer's Comment: There were 73 patients randomized to the HAC group and 27 patients randomized to the H group with an active DU at baseline. In the HAC group, 7 were excluded from the ITT analysis (see Table 3 in Appendix 3) and 10 were excluded from the PP analysis (see Table 4 in Appendix 3). In the H group, 3 were excluded from the ITT analysis (see Table 3 in Appendix 3) and 4 were excluded from the PP analysis (see Table 4 in Appendix 3).

For the PP DU Healing Analysis, in addition to Criteria A-H, patients were considered non-evaluable if they did not return for the follow-up endoscopy or if they returned before Day 29 and had an unhealed ulcer. In the HAC group an additional 3 patients were excluded and one additional was excluded from the H group. See table below for final numbers of patients included in each analysis. The denominators used in Table8 are correct for the ITT and PP analyses.

Intent-to-Treat (ITT)

	HAC	***H***
All Randomized Patients with an Active DU at Baseline	*73*	*27*
Patients Excluded from DU Healing ITT Analysis (Table 3 in Appendix 3)	*7*	*3*
Patients Included in DU Healing ITT Analysis	*66*	*24*

Per-Protocol (PP)

	HAC	***H***
All Randomized Patients with an Active DU at Baseline	*73*	*27*
Patients Excluded from DU Healing PP Analysis (Table 4 in Appendix 3)	*10*	*4*
*Additional Patients Excluded from DU Healing PP Analysis**		
No follow-up data or unhealed ulcer before Day 29	*3*	*1*

Patients Included in DU Healing PP Analysis	*60*	*22*

**not listed in Table 4 in Appendix 3*

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 9 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 9
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 #193

	H 40 qd + A 1000 bid + C 500 bid			H 40 qd			Both Treatment Groups Combined		
	DU Healed by Day 38								
H. pylori Eradicated at Day 38 Visit	Yes	No	Total	Yes	No	Total	Yes	No	Total
Yes	30	22	52	1	0	1	31	22	53
No	3	3	6	11	10	21	14	13	27
Total	33	25	58	12	10	22	45	35	80

Clinical Reviewer's Comment: H. pylori eradication was associated with an ulcer incidence rate (unhealed, recurrent, or new ulcer) at the 4-week follow-up visit of 41.5% (22/53) as compared to a rate of 48.1% (13/27) among patients who were not eradicated of H. pylori when combining treatment groups.

Based on all randomized patients, of the 13 patients enrolled in this study who did not have an active DU at the baseline endoscopy, there was only 1 patient (8%) who developed an ulcer (either duodenal or gastric) at some time during the study period. This patient (AN 3186) enrolled in the HAC group did not have an active DU at Baseline, but developed a DU at some time during the study period.

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 56% 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 there was a significant difference between the treatment groups in the proportion of patients with none or mild nighttime epigastric pain or burning symptoms at the Day 11 Visit (50 of the 52 patients or 96% in the HAC group; 15 of the 19 patients or 79% in the H group). There was also a significant difference between the treatment groups in the proportion of patients with none or mild nausea symptoms at the Day 38 visit (37 of the 38 patients or 97% in the HAC group; 9 of the 12 patients or 75% in the H group). There were no other significant differences between the treatment groups in the proportion of patients with none or mild symptoms at the Day 11 or the Day 38 visits. Also, there were no significant differences between the treatment groups in the proportion of patients with improvement from Baseline to the Day 11 visit or the Day 38 visit for any of the symptoms assessed.

9. Susceptibility

The susceptibility of all available *H. pylori* isolates to amoxicillin and 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.

H. pylori susceptibility results are presented for both amoxicillin and clarithromycin. Only data from patients considered *H. pylori* infected at Baseline are included in the following tables.

Clarithromycin

For both treatment groups combined, a total of 15% of the patients (12 of 82 patients with known susceptibility results) had *H. pylori* isolates which were considered to be resistant to clarithromycin at Baseline, and 85% of the patients (70 of 82 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 alone.

Table 10 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, 8% of the patients (1 of 12 patients) had previously taken *H. pylori* eradication regimens containing clarithromycin while 92% of the patients (11 of 12 patients) had not taken such previous regimens.

TABLE 10
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 #193

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	1	(8%)	11	(92%)	12
Intermediate	0	---	0	---	0
Susceptible	0	---	70	(100%)	70
No Result [a]	0	---	16	(100%)	16
TOTAL	1	(1%)	97	(99%)	98

[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 11. Results are presented for each treatment group, as well as for both treatment groups combined.

In this study, of the 70 *H. pylori* isolates susceptible to clarithromycin at Baseline (54 patients in the HAC group and 16 in the H group), 2 patients had isolates that developed resistance to clarithromycin by the end of the study (1 patient in the HAC group and I patient in the H group.

TABLE 11
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 #193

	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 + A 1000 bid + C 500 bid								
Resistant	6	3	0	1	0	4	0	10
Intermediate	0	0	0	0	0	0	0	0
Susceptible	44	1	0	2	3	6	4	54
No Result [a]	8	1	0	0	0	1	1	10
Total	58	5	0	3	3	11	5	74
H 40 qd								
Resistant	0	2	0	0	0	2	0	2
Intermediate	0	0	0	0	0	0	0	0
Susceptible	0	1	0	10	4	15	1	16
No Result [a]	1	0	0	2	3	5	0	6
Total	1	3	0	12	7	22	1	24
Both Treatment Groups Combined								
Resistant	6	5	0	1	0	6	0	12
Intermediate	0	0	0	0	0	0	0	0
Susceptible	44	2	0	12	7	21	5	70
No Result [a]	9	1	0	2	3	6	1	16
Total	59	8	0	15	10	33	6	98

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

Amoxicillin

For both treatment groups combined, a total of 82 patients (64 patients in the HAC group and 18 patients in the H group) had *H. pylori* isolates that were considered to be susceptible to amoxicillin at Baseline.

A comparison of the baseline *H. pylori* amoxicillin 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.

TABLE 12
Baseline *H. pylori* Susceptibility Results vs. *H. pylori* Eradication Status at Day 38
Susceptibility to Amoxicillin Based on Agar Dilution
Number of Patients
All Available Data
Study #193

	Day 38 Visit *H. pylori* Eradication Status						
Baseline *H. pylori* Susceptibility to Amoxicillin	*H. pylori* Eradicated	*H. pylori* Not Eradicated				No *H. pylori* Eradication Result	Total
		Day 38 Visit Susceptibility to Amoxicillin					
		Not Def.	*Susc.*	*No Result*	*Total*		
H 40 qd + A 1000 bid + C 500 bid							
Not defined	0	0	0	0	0	0	0
Susceptible	50	0	7	3	10	4	64
No Result [a]	8	0	1	0	1	1	10
Total	58	0	8	3	11	5	74
H 40 qd							
Not defined	0	0	0	0	0	0	0
Susceptible	0	0	13	4	17	1	18
No Result [a]	1	0	2	3	5	0	6
Total	1	0	15	7	22	1	24
Both Treatment Groups Combined							
Not defined	0	0	0	0	0	0	0
Susceptible	50	0	20	7	27	5	82
No Result [a]	9	0	3	3	6	1	16
Total	59	0	23	10	33	6	98

[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 113 patients were randomized to one of the two treatment groups in this study. All 113 were 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 #193

	H 40 qd + A 1000 bid + C 500 bid (N=85)		H 40 qd (N=28)	
Number (%) of Patients:	n	(%)	n	(%)
With ≥1 AE	30	(35%)	11	(39%)
With a possibly or probably drug related AE	14	(16%)	5	(18%)
With a serious AE	0	(0%)	1	(4%)
Discontinued due to an AE	1	(1%)	1	(4%)

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 with at least one possibly or probably drug-related AE, the proportion of patients experiencing serious AEs, or the proportion of patients who discontinued from the study early due to an AE.

One patient in this study experienced an AE considered to be serious (H group). Also, 2 patients in this study discontinued from the study due to an AE (1 patient in the HAC group and 1 patient in the H group).

Clinical Reviewer's Comment: There were two patients listed as discontinuing from the study due to AE's, but neither was considered to be drug-related by either the investigator or the reviewer. A patient in the HAC group (321/002;3018) discontinued study drug on Day 5 due to constipation. This patient was determined not to be H. pylori positive by endoscopic tests at baseline and was therefore excluded from both efficacy analysis for lack of infection. One patient in the H group (324/007;3099) was withdrawn by the investigator after completing study medication. She developed a UTI and was treated with nitrofurantoin on Day 38. This patient was also determined to be pregnant on Day 38 and eventually developed a placenta previa on Day 229. This patient was not excluded from either efficacy analysis.

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 (with an incidence of ≥ 5% in both treatment groups combined) were diarrhea (8 of 113 patients or 7%) and gastritis (12 of 113 patients or 11%). Most of the other AEs were experienced by only one or two patients in either treatment group. There were no significant differences observed between the treatment groups in the proportions for any of the individual AEs ($p > 0.050$ by 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 #193

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.

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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 #193

Body System AE	H 40 qd + A 1000 bid + C 500 bid (N=85)			H 40 qd (N=28)		
	n	(%)		n	(%)	
Psychiatric Disorders						
anorexia	1	(1%)	[1]	0	(0%)	---
insomnia	1	(1%)	[1]	0	(0%)	---
Reproductive Female Disorders						
placental disorder	0	(0%)	---	1	(4%)	---
pregnancy unintended	0	(0%)	---	1	(4%)	---
vaginal fungal infection	1	(1%)	[1]	1	(4%)	[1]
Resistance Mechanism Disorders	0	(0%)	---	1	(4%)	---
ear infection external	1	(1%)	[1]	0	(0%)	---
infection fungal	1	(1%)	---	0	(0%)	---
infection viral						
Respiratory System Disorders						
coughing	1	(1%)	---	0	(0%)	---
respiratory infection	1	(1%)	---	0	(0%)	---
rhinitis	2	(2%)	---	0	(0%)	---
Skin and Appendages Disorders						
rash	1	(1%)	[1]	0	(0%)	---
rash erythematous	1	(1%)	[1]	0	(0%)	---
Special Senses Other Disorders						
taste perversion	3	(4%)	[3]	0	(0%)	---
Urinary System Disorders						
urinary tract infection	0	(0%)	---	1	(4%)	---

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

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Serious Adverse Events

Of the 513 patients enrolled into this study who took at least one dose of study medication, 1 patient experienced an AE considered to be serious (H group). This serious AE 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 #193

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									
No patients in this treatment group reported serious adverse events.									
H 40 qd group									
324/007	3099	F/34	> 150	Placenta disorder	50-81	Severe	Unlikely	None	Hospitalization

Clinical Reviewer's Comment: A narrative on Patient 324/007 (AN 3099) can be found in the Integrated Summary of Safety (ISS).

A total of 2 of the 113 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 16 lists the 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 #193

Site/ Enroll-ment #	AN	Gende r/Age (yrs)	Rel. Day of Onset	AE	Dur. (Days)	Inten-sity	Drug Rel.	Seriou s	Last Day of Study Med.	Study Day Discon -tinued	Action Taken w/ Drug
H 40 qd + A 1000 bid + C 500 bid group											
321/002	3018	F/72	2	Constipation	3	Mod.	Prob.	No	2	4	Drug stopped
H 40 qd group											
324/007	3099	F/34	38	Pregnancy unintended	191	Mild	Unlik.	No	10	52	None

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 ——————————— 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 193

This was a well conducted, randomized, clinical trial which demonstrated the superiority of triple therapy (HAC) over monotherapy (H) 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 67%, which is above the 60% threshold as suggested by the Division.

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IX. Integrated Summary of Efficacy (ISE)

A. Overview

The three pivotal clinical trials included in this submission compare H 199/18 plus amoxicillin plus clarithromycin (HAC), H 199/18 plus clarithromycin (HC), and H 199/18 monotherapy (H) for *H. pylori* eradication in patients with an active duodenal ulcer or a history of duodenal ulcer disease. Comparing HAC to HC shows the contribution of amoxicillin to the triple therapy. The contributions of H 199/18 and clarithromycin can be demonstrated by making comparisons to other *H. pylori* eradication regimens using documented, published results. The contributions of each component in the triple therapy are presented using *H. pylori* eradication rates and discussions of treatment-emergent resistance to clarithromycin. A summary of duodenal ulcer healing rates is also provided for the three H 199/18 US studies.

In addition, two studies (Study SH-QBE-0019 and Study SH-QBE-0020) conducted outside of the US examined a different *H. pylori* eradication regimen with H 199/18, amoxicillin, and clarithromycin (HAC). These studies are considered supportive to the US clinical program.

B. *H. pylori* Eradication Results from US Studies

The *H. pylori* eradication rates at 4 weeks post-treatment in Studies 191, 192, and 193 individually and combined across studies are displayed for the per-protocol (PP) and intention-to-treat (ITT) analyses in Tables 1 and 2, respectively.

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: $p < 0.001$* 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, ($p = 0.932$), using logistic regression.

The *H. pylori* eradication rates for the HAC treatment group were significantly higher than both the HC and H treatment groups. This is true for each individual study and for the three studies combined. Results were consistent for both the PP population and the ITT populations. This demonstrates the superiority of HAC over the HC and H regimens for *H. pylori* eradication. It also demonstrates the positive contribution of amoxicillin to the HAC regimen.

In addition, the *H. pylori* eradication rates for the HAC treatment group satisfy the efficacy threshold recommended in the FDA draft guidance, Guidance for Industry: Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products, Draft, February 1997. The 95% confidence intervals for the ITT 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.

1. Eradication Rates - Special Populations

Eradication results by age, gender, and race for the PP analysis are shown in Table 3 for all three US studied combined. Covariate analyses using logistic regression were performed to determine whether age, gender, or race had a significant effect on the *H. pylori* eradication rates. None of these covariates had a significant effect on *H. pylori* eradication status.

Clinical Reviewer's Comment: Table 3 was created by the reviewer and not the applicant.

TABLE 3
***H. pylori* Eradication at Day 38 Visit - Subgroup Analysis**
Number (%) of Patients
Per-Protocol Analysis
US H 199/18 *H. pylori* Studies 191, 192, 193

Subgroup	n/N (%)		
	HAC	HC	H
Age			
≤ 65 years	194/232 (84%)	108/200 (54%)	1/35 (3%)
> 65 years	27/31 (87%)	17/31 (55%)	0/2 (0%)
Gender			
Males	145/163 (89%)	79/149 (53%)	1/19 (5%)
Females	76/100 (76%)	46/82 (56%)	0/18 (0%)
Race			
Caucasian	165/191 (86%)	82/151 (54%)	1/21 (5%)
Black	48/62 (77%)	35/65 (54%)	0/11 (0%)
Other	8/10 (80%)	8/15 (53%)	0/3 (0%)

C. Duodenal Ulcer Healing Results from US Studies

Tables 4 and 5 present the PP and ITT duodenal ulcer healing rates by Day 38, for those patients with a duodenal ulcer at Baseline, for each of the three studies.

TABLE 4
Duodenal Ulcer Healed Status by Day 38 Visit (4 Weeks Post-Treatment)
For Patients With An Active Duodenal Ulcer at Baseline
Per-Protocol Analysis
US H 199/18 *H. pylori* Studies 191, 192, 193

Duodenal Ulcer Healed by Day 38 Visit	HAC	HC	H	Pairwise Treatment Group Comparisons (Using Logistic Regression)
	n/N (%)	n/N (%)	n/N (%)	P-value
Study 191	117/156 (75%)	95/144 (66%)		HAC vs. HC: p = 0.087
Study 192		26/32 (81%)	5/11 (45%)	HC vs. H: p = 0.029*
Study 193	34/60 (57%)		12/22 (55%)	HAC vs. H: p = 0.864

* Significant difference observed between the treatment groups, ($p < 0.050$).

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TABLE 5
Duodenal Ulcer Healed Status by Day 38 Visit (4 Weeks Post-Treatment)
For Patients With An Active Duodenal Ulcer at Baseline
Intention-to-Treat Analysis
US H 199/18 *H. pylori* Studies 191, 192, 193

Duodenal Ulcer Healed by Day 38 Visit	HAC	HC	H	Pairwise Treatment Group Comparisons (Using Logistic Regression)
	n/N (%)	n/N (%)	n/N (%)	P-value
Study 191	127/185 (69%)	104/168 (62%)		HAC vs. HC: p = 0.184
Study 192		26/34 (76%)	6/12 (50%)	HC vs. H: p = 0.095
Study 193	35/66 (53%)		13/24 (54%)	HAC vs. H: p = 0.924

Note: There were no significant differences observed between the treatment groups for any of the three studies, (p > 0.050).

Clinical Reviewer's Comment: The incidence of ulcers (unhealed/recurrent/new) was determined for all three dosing regimens in relation to H. pylori status post-treatment. Overall, ulcer rates were lower for those eradicated of H. pylori versus those with persistent infection. This difference was statistically significant within the HC and HAC treatment regimens.

Incidence of Ulcers in Relation to H. pylori Status

Treatment Group	*H. pylori Eradicated*	*H. pylori Not Eradicated*	*Difference in Rates (95% CI)*	*Odds Ratio (95% CI)*	*P-value*
H	*0/1*	*16/32 (50.0%)*	--	--	--
HC	*25/99 (25.3%)*	*29/73 (39.7%)*	*-14.5%,(-30%, 0.8%)*	*0.513 (0.268,0.982)*	*0.044*
HAC	*50/184 (27.2%)*	*11/22 (50.0%)*	*-22.8% (-47.2%,1.6%)*	*0.373 (0.156, 0.894)*	*0.027*

D. Demonstration of the Contribution of Each Component to Eradication in the HAC Regimen

In order to demonstrate the contributions of each component, comparisons were made using the different sources, either data from specific studies, comparisons across studies, or data from published literature. To show the benefit of amoxicillin (A) in the triple therapy regimen, direct comparisons were made between the HAC and HC treatment groups within Study 191, and indirect comparisons were made between the HAC and HC groups across Study 192 and Study 193. To show the benefit of H to the HAC regimen, indirect comparisons were made between the combined results for the HAC treatment groups in Study 191 and Study 193 and the AC data from published literature (and NDA 20-916). The benefit of clarithromycin in triple therapy regimens has been proven in other *H. pylori* eradication programs and documented in the published data.

1. Demonstration of the Contribution of Amoxicillin (A) to the HAC Regimen

The contribution of amoxicillin to the HAC regimen was demonstrated in two ways: 1) comparisons of *H. pylori* eradication rates for the HAC and HC treatment groups within and across Studies 191, 192 and 193, and 2) an examination of the *H. pylori* susceptibility

results to clarithromycin for the HAC and HC treatment groups across Studies 191, 192, and 193. The results of these two analyses are summarized below in Tables 6 and 7.

The *H. pylori* eradication rates at 4 weeks post-treatment were significantly higher for the HAC group compared to the HC group. This was shown for both the PP and ITT populations for the comparison within Study 191, across Study 192 and Study 193, and for all three studies combined.

TABLE 6
***H. pylori* Eradication at Day 38 Visit (4 Weeks Post-Treatment)**
Per-Protocol Analysis
Comparison of HAC vs. HC
US H 199/18 *H. pylori* Studies 191, 192, 193

H. pylori Eradication at 4 Weeks Post-Treatment	HAC	HC	Pairwise Treatment Group Comparisons (Using Logistic Regression)
	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%]	
Study 193	57/67 (85%) [74%, 93%]		HAC in Study 193 vs. HC in Study 192: $p = 0.001$ *
All three studies combined[a]	221/263 (84%) [79%, 88%]	125/231 (54%) [48%, 61%]	HAC vs HC: $p < 0.001$ *

* Significant difference between HAC and HC, ($p < 0.050$).
[a] Test for study by treatment group interaction was not significant, ($p = 0.922$), using logistic regression.

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TABLE 7
***H. pylori* Eradication at Day 38 Visit (4 Weeks Post-Treatment)**
Intention-to-Treat Analysis
Comparison of HAC vs. HC
US H 199/18 *H. pylori* Studies 191, 192, 193

H. pylori Eradication at 4 Weeks Post-Treatment	HAC	HC	Pairwise Treatment Group Comparisons (Using Logistic Regression)
	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%]	
Study 193	58/74 (78%) [67%, 87%]		HAC in Study 193 vs. HC in Study 192: $p = 0.001$ *
All three studies combined [a]	237/307 (77%) [72%, 82%]	135/265 (51%) [45%, 57%]	HAC vs HC: $p < 0.001$ *

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

Table 8 presents the clarithromycin susceptibility results at the Baseline and Day 38 visits by *H. pylori* eradication status for the HAC and HC treatment groups.

Clinical Reviewer's Comment: Table 8 has been modified from the applicant's original table for clarity.

TABLE 8
Baseline *H. pylori* Susceptibility Results vs. *H. pylori* Eradication Status
Susceptibility to Clarithromycin, HAC and HC
All Patients with Clarithromycin Susceptibility Results at Baseline
US H 199/18 *H. pylori* Studies 191, 192, 193 Combined

	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	GRAND TOTAL
		Day 38 Visit Susceptibility to Clarithromycin						
		Res.	*Int.*	*Susc.*	*No Result*	*Total*		
HAC (Studies 191 and 193 combined)								
Resistant [n = 31]	13	13	0	1	2	16	2	31
Intermediate [n =1]	1	0	0	0	0	0	0	1
Susceptible [n =197]	162	2	0	4	14	20	15	197
TOTAL [n = 229]	176	15	0	5	16	36	17	229
HC (Studies 191 and 192 combined)								
Resistant [n = 30]	4	22	0	0	4	26	0	30
Intermediate [n = 1]	0	0	1	0	0	1	0	1
Susceptible [n = 153]	88	23	1	3	29	56	9	153
TOTAL [n = 184]	92	45	2	3	33	83	9	184

The rate of emerging resistance to clarithromycin appears to be lower for patients who received HAC (2/197 or 1.0%) versus patients who received HC (23/153 or 15.0%). A test for the comparison between the two treatment groups for treatment-emergent resistance is significant (p-value < 0.001) using Fisher's Exact Test.

Clinical Reviewer's Comment: See discussion on emerging resistance, immediately following Table 11.

2. Demonstration of the Contribution of H 199/18 (H) to the HAC Regimen

H 199/18 with amoxicillin and clarithromycin (HAC) provides significantly higher eradication rates than treatment with amoxicillin and clarithromycin (AC) alone. Comparisons of the *H. pylori* eradication rates at 4 to 6 weeks post-treatment were made between the combined results for the HAC treatment group and the combined results for the AC treatment group as shown for the PP and ITT populations in Table 9.

Clinical Reviewer's Comment: Studies 126 and 127 are Astra Merck studies and Study M96-446 is an ——— study. All were reviewed and supported approval of NDA 20-916 (OAC therapy). All three studies had similarly designed protocols and evaluability criteria for the eradication analyses; therefore it is appropriate to combine eradication rates across studies.

TABLE 9
***H. pylori* Eradication at 4 to 6 Weeks Post-Treatment**
Per-Protocol and Intention-to-Treat Analyses
Comparison of HAC (Studies 191, 193) vs. AC (Studies 126, 127, M96-446)

H. pylori Eradication at 4-6 Weeks Post-Treatment	HAC	AC	Treatment Group Comparisons (Using Logistic Regression)
	n/N (%) [95% CI]	n/N (%) [95% CI]	HAC vs. AC p-value
Per-Protocol results	221/263 (84%) [79%, 88%]	88/224 (39%) [33%, 46%]	p < 0.001*
Intention-to-Treat results	237/307 (77%) [72%, 82%]	93/266 (35%) [29%, 41%]	p < 0.001*

Note: Results are combined across studies: HAC - Studies 191 and 193 combined, AC - Studies 126, 127, and M96-446 combined.
* Significant difference between treatment groups, (p < 0.050), using logistic regression.

The *H. pylori* eradication rates were significantly higher in the HAC group than the AC group for both the PP and ITT analyses. The higher eradication rates in the HAC group when compared to the AC group demonstrate the contribution of H to the HAC triple therapy regimen.

3. Indirect Comparison of the Clarithromycin Susceptibility Results for HAC vs. AC

Testing for *H. pylori* susceptibility to clarithromycin was performed for all available isolates using agar dilution for the H 199/18 *H. pylori* eradication studies 191, 192, and 193 and Etest for the Astra Merck and ———studies (Studies 126, 127, and M96-446). For all studies, when more than one isolate was available for a patient, the isolate with the higher MIC was used in the analysis of susceptibility. However, the HAC studies used slightly different breakpoints than the AC studies to determine the susceptibility categories. Table 10 below outlines the MIC value ranges for the susceptibility categories. The resistant category starts at a lower MIC value for the HAC studies than the AC studies making it easier to declare an isolate resistant to clarithromycin in the HAC treatment group. This effect would tend to favor the AC group when comparing the results for the two treatment groups.

TABLE 10
Minimum Inhibitory Concentration (MIC) Breakpoints for Clarithromycin Susceptibility Status
Comparison of HAC (Studies 191, 193) to AC (Studies 126, 127, M96-446)

Susceptibility Category	HAC Studies (Studies 191, 193)	AC Studies (Studies 126, 127, M96-446)
Resistant	MIC > 0.5 mcg/mL	MIC > 2 mcg/mL
Intermediate	MIC = 0.5 mcg/mL	0.125 mcg/ml < MIC ≤ 2 mcg/mL
Susceptible	MIC ≤ 0.25 mcg/mL	MIC ≤ 0.125 mcg/mL

A summary of the clarithromycin susceptibility findings for the two treatment groups is presented in Table 11.

Clinical Reviewer's Comment: Table 11 has been modified from the applicant's original table for clarity.

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TABLE 11
Comparison of Baseline and Post-Treatment *H. pylori* Susceptibility Results
Susceptibility to Clarithromycin
All Patients with Clarithromycin Susceptibility Results at Baseline
Comparison of HAC (Studies 191, 193) vs. AC (Studies 126, 127, M96-446)

		Day 38 Visit to *H. pylori* Eradication Status						
Baseline Clarithromycin Susceptibility Results	*H. pylori* Eradicated	*H. pylori* Not Eradicated					No *H. pylori* Eradication Results	GRAND TOTAL
		Day 38 Visit Susceptibility to Clarithromycin						
		Res.	*Int.*	*Susc.*	*No Result*	*Total*		
HAC (Studies 191 and 193 combined)								
Resistant [n = 31]	13	13	0	1	2	16	2	31
Intermediate [n = 1]	1	0	0	0	0	0	0	1
Susceptible [n = 197]	162	2	0	4	14	20	15	197
TOTAL [n = 229]	176	15	0	5	16	36	17	229
AC (Studies 126, 127, and M96-446 combined)								
Resistant [n = 26]	2	21	0	0	1	22	2	26
Intermediate [n = 3]	0	2	0	0	1	3	0	3
Susceptible [n = 205]	73	10	8	73	20	111	21	205
TOTAL [n = 234]	75	33	8	73	22	136	23	234

The rate of emerging resistance to clarithromycin appears to be lower for patients who received HAC (2 out of 197 patients) versus patients who received AC (10 out of 205 patients) despite the difference in the MIC value breakpoints. A test for comparison of the two proportions for treatment-emergent resistance is significant, p-value = 0.036, using Fisher's Exact Test.

Clinical Reviewer's Comment: The rates of emerging resistance to clarithromycin in patients with susceptible isolates at baseline (MIC ≤ 0.25 µg/mL) were calculated in three different ways. The percent of resistant isolates was determined using different populations: (1) patients with susceptibility test results post-treatment, (2) all patients who had susceptibility testing post-treatment (including those who eradicated H. pylori), and (3) all patients regardless of whether or not they had susceptibility testing or results post-treatment. In the third analysis a "worst case" approach was taken in which patients who did not have susceptibility or eradication results post-treatment were considered to have failed therapy and to have resistant isolates.

Emerging Resistance Rates (%) in Patients with Clarithromycin Susceptible Isolates at Baseline

Treatment	*Post-Treatment Results*	*All With Post-Treatment Results*	*All Patients**
HC	*23/27*	*23/115 (20.0)*	*61/153 (40.0)*
HAC	*2/6*	*2/168 (1.2)*	*3/197 (15.7)*
AC	*10/91*	*10/164 (6.1)*	*51/205 (24.9)*

**patients without Day 38 testing and those in whom testing was performed, but no result was available, were considered failures with resistant isolates*

Treatment failures in patients with clarithromycin susceptible isolates at baseline (MIC ≤ 0.25 µg/mL) were also determined. The percent of treatment failures was determined using different populations: (1) patients with an isolate obtained at post-treatment testing (regardless of whether or not an MIC value was determined) and (2) all patients regardless of whether or not they had susceptibility testing performed post-treatment. The second analysis is a "worst case" scenario, in which patients who did not have susceptibility or eradication results post-treatment were included and considered to have failed therapy.

Treatment Failures (%) in Patients with Clarithromycin Susceptible Isolates at Baseline

Treatment	*Post-Treatment Results*	*All Patients**
HC	*56/144 (38.9)*	*65/153 (42.5)*
HAC	*20/182 (11.0)*	*35/197 (17.8)*
AC	*111/184 (60.3)*	*132/226 (64.4)*

**patients without Day 38 testing and those in whom testing was performed, but no result was available, were considered failures with resistant isolates*

A combination of lansoprazole and amoxicillin (LA) yielded higher eradication rates — TAP Pharmaceuticals, Inc. studied two different dosing regimens of LA for 14 days: L 30 mg TID + A 1 gm TID (LA tid/tid) and L 30 mg bid + A 1 gm TID (LA bid/tid). Triple therapies with lansoprazole plus amoxicillin and clarithromycin (LAC) yielded significantly higher *H. pylori* eradication rates than LA dual therapy.

Clinical Reviewer's Comment: The eradication rates for LAC vs. LA are shown in the table below. Lansoprazole and antibiotic(s) were given for a total of 14 days.

H. pylori Eradication at 4 to 6 Weeks Post-Treatment
Per-Protocol and Intention-to-Treat Analyses
Comparison of LAC (Studies M93-131, M95-392, and M95-399)
vs. LA (Studies M93-131, M93-125)

H. pylori Eradication at 4-6 Weeks Post-Treatment	*n/N (%) [95% CI]*	*n/N (%) [95% CI]*	*Treatment Group Comparisons (Using Logistic Regression)*
	LAC	*LA*	*LAC vs. LA p-value*
Per-Protocol results	*195/227 (86%) [81%,90%]*	*77/109 (71%) [62%,79%]*	*0.001*
Intention-to-Treat results	*220/251 (88%) [84%,92%I]*	*83/127 (65%) [57%, 73%]*	*0.001*

H 199/18 is an enantiomer of omeprazole, and the H 199/18 triple therapy regimen uses the same dosages of antimicrobials as the approved regimens of OAC and LAC. Therefore, it is expected that the contribution of clarithromycin (C) in the HAC regimen would be comparable to the contributions already demonstrated with other PPI + amoxicillin + clarithromycin therapies.

E. Brief Summary of Non-US Supportive Studies

1. Astra Hässle AB Study SH-QBE-0019

51 sites in Canada, Denmark, France, Germany, Spain, and Sweden enrolled patients.

Study Design: Double blind, randomized, active-controlled *H. pylori* eradication study in patients with a history of duodenal ulcer disease.

Primary Objective:
--To estimate the *H. pylori* eradication rates for the two treatment groups.

Secondary Objectives:
--To compare the eradication rates for the two treatment groups.
--To evaluate the tolerability of H 199/18 in combination with clarithromycin and amoxicillin.

Daily dose, Days 1 to 7:
H 20 mg bid + A 1000 mg bid + C 500 mg bid (224 enrolled)
20 mg bid + A 1000 mg bid + C 500 mg bid (224 enrolled)

Eradication Results: Table 12

TABLE 12
***H. pylori* Eradication at 4 to 8 Weeks Post-Treatment**
AstraZeneca Non-US Study SH-QBE-0019

	H 20 bid + A 1000 bid + C 500 bid for 7 days	O 20 bid + A 1000 bid + C 500 bid for 7 days	Difference in *H. pylori* Eradication Rates: HAC - OAC
H. pylori Eradication at 4 to 8 Weeks Post-Treatment	n/N (%) [95% CI]	n/N (%) [95% CI]	Estimate [95% CI]
Per-protocol	174/192 (91%) [86%, 94%]	169/185 (91%) [86%, 95%]	-1% [-7%, 5%]
Intention-to-treat	183/202 (90%) [85%, 94%]	172/200 (88%) [82%, 92%]	2% [-4%, 8%]

2. Astra Hässle AB Study SH-QBE-0020

28 sites in the Czech Republic, Hungary, and Poland

Study Design: Double blind, randomized, active-controlled *H. pylori* eradication and duodenal ulcer healing study in patients with a duodenal ulcer.

Primary Objective:
--To estimate the duodenal ulcer healing rates for the two treatment groups.

Secondary Objectives:
--To estimate the *H. pylori* eradication rates for the two treatment groups.
--To compare the healing rates between the two treatment groups.

--To compare the eradication rates for the two treatment groups.
--To evaluate the tolerability of H 199/18 in combination with clarithromycin and amoxicillin.

Daily dose, Days 1 to 7:

H 20 mg bid + A 1000 mg bid + C 500 mg bid (enrolled 222)
O 20 mg bid + A 1000 mg bid + C 500 mg bid (enrolled 224)

Followed by an additional 21 days of placebo (Group 1) or O 20 mg qd (Group 2)

Eradication Results: Table 13

Duodenal Ulcer Healing Results: Table 14

TABLE 13
***H. pylori* Eradication at 4 Weeks Post-Treatment**
AstraZeneca Non-US H 199/18 *H. pylori* Study SH-QBE-0020

	H 20 bid + A 1000 bid + C 500 bid for 7 days followed by placebo for 21 days	O 20 bid + A 1000 bid + C 500 bid for 7 days followed by omeprazole for 21 days	Difference in *H. pylori* Eradication Rates: HAC - OAC
H. pylori Eradication at 4 to 8 Weeks Post-Treatment	n/N (%) [95% CI]	n/N (%) [95% CI]	Estimate [95% CI]
Per-protocol	176/198 (89%) [84%, 93%]	180/201 (90%) [85%, 93%]	-1% [-7%, 5%]
Intention-to-treat	184/214 (86%) [81%, 90%]	192/219 (88%) [83%, 92%]	-2% [-8%, 5%]

TABLE 14
Duodenal Ulcer Healing at 4 Weeks Post-Treatment
AstraZeneca Non-US H 199/18 *H. pylori* Study SH-QBE-0020

	H 20 bid + A 1000 bid + C 500 bid for 7 days followed by placebo for 21 days	O 20 bid + A 1000 bid + C 500 bid for 7 days followed by omeprazole for 21 days	Difference in Duodenal Ulcer Healing Rates: HAC - OAC
Duodenal Ulcer Healing at 4 Weeks Post-Treatment	n/N (%) [95% CI]	n/N (%) [95% CI]	Estimate [95% CI]
Per-protocol	190/202 (94%) [90%, 97%]	194/203 (96%) [92%, 98%]	-2% [-6%, 3%]
Intention-to-treat	195/214 (91%) [86%, 95%]	202/219 (92%) [88%, 95%]	-1% [-6%, 4%]

F. Summary

Based on the results summarized here, HAC triple therapy is an effective regimen for the eradication of *H. pylori*. Each of the individual medications used in the combination contributes to the overall effectiveness of the regimen.

X. Integrated Summary of Safety (ISS)

A. Overview

The global clinical program for eradication of *H. pylori* in patients with DU disease consisted of seven studies: five Phase III studies and two Phase I clinical pharmacology studies. A total of 1,626 patients/healthy subjects were treated in these studies (1,586 patients in the Phase III studies and 40 subjects in the two Phase I clinical pharmacology studies).

A total of 1,586 patients were enrolled in the Phase III studies and received at least one dose of study medication. Table 1 displays the treatment regimens and the number of patients who received at least one dose of study drug in these five Phase III studies. Table 2 displays the dosing regimens and the number of subjects who received each regimen in the two Phase I studies.

TABLE 1
Number of Patients by Treatment Regimen: Phase III Studies

	Treatment Regimen (Number of Patients who Received at Least One Dose)				
	HAC*	HC*	H*	OAC	Total
US Study (10-day treatment period)					
191	263[a]	250[a]	---	---	513
192	---	51	17	---	68
193	85	---	28	---	113
Subtotal	348	301	45	---	694
Non-US Study (7-day treatment period)					
SH-QBE-0019	222	---	---	224[b]	446
SH-QBE-0020b	222	---	---	224	446
Subtotal	446	---	---	446	892
Total	794	301	45	446	1586

* H199/18 was dosed 40 mg qd in the US studies and 20 mg bid in non-US studies.
[a] This count does not include patients who were randomized but did not receive treatment: two patients in Study 191 (one in the HAC group and one in the HC group) and two patients in SH-QBE-0019 (both in the OAC group).
[b] In this study, patients received an additional 3 weeks of treatment after completing the 7-day treatment period. Of the 222 patients who received HAC, 219 went on to receive placebo and of the 224 who received OAC, 218 went on to receive omeprazole 20 mg qd.

Clinical Reviewer's Comment: It is not believed that dosing H 199/18 40 mg once daily would lead to a different safety profile than 20 mg twice daily. In addition, 10 days versus 7 days of dosing is also not believed to lead to clinically significant differences in the incidence of adverse events.