TABLE 2
Number of Subjects by Dosing Regimen: Phase I Clinical Pharmacology Studies

Clinical Pharmacology Study	Dosing Period (Number of Subjects who Received at Least One Dose)				Total Enrolled [a]
	H*	HAC*	A	C	
SH-QBE-0034	19	18	18	18	20
SH-QBE-0040	20	19	19	20	20
Total	39	37	37	38	40

* H 199/18 was dosed 40 mg qd in the morning in Protocol SH-QBE-0034 and 20 mg bid in Protocol SH-QBE-0040

[a] All 40 subjects enrolled in these studies received at least one of the four regimens; however, some may have discontinued prior to receiving all four.

B. Pools of Studies and Presentation of Data in the ISS

Data for the three US Phase III studies (191, 192, and 193) were pooled and data for the two non-US Phase III studies (SH-QBE-0019 and SH-QBE-0020) were pooled. Because clinical pharmacology studies were conducted in healthy volunteers and utilized a crossover design, safety results for these studies are presented separately from the Phase III studies. Data for the two clinical pharmacology studies were not pooled.

A summary of demographic and baseline characteristics is presented for US and non-US Phase III studies in Table 3. In both the US and non-US studies, treatment groups were generally well balanced with respect to demographic characteristics.

TABLE 3
Demographic and Baseline Characteristics: Phase III Studies

Characteristic	Treatment Group [a]				
	US Studies (191, 192, and 193)			Non-US Studies (SH-QBE-0019 and -0020)	
	HAC (N=348)	HC (N=301)	H (N=45)	HAC (N=446)	OAC (N=446)
Gender, n (%)					
Male	214 (61.5)	185 (61.5)	26 (57.8)	290 (65.0)	272 (61.0)
Female	134 (38.5)	116 (38.5)	19 (42.2)	156 (35.0)	174 (39.0)
Race, n (%)					
Caucasian	256 (73.6)	202 (67.1)	26 (57.8)	435 (97.5)	444 (99.6)
Black	80 (23.0)	81 (26.9)	14 (31.1)	7 (1.6)	1 (0.2)
Asian	7 (2.0)	15 (5.0)	3 (6.7)	4 (0.9)	1 (0.2)
Other	5 (1.4)	3 (1.0)	2 (4.4)	0 (0.0)	0 (0.0)
Age (years), n (%)					
< 35	68 (19.5)	54 (17.9)	8 (17.8)	70 (15.7)	63 (14.1)
35 – 44	104 (29.9)	70 (23.3)	16 (35.6)	99 (22.2)	100 (22.4)
45 – 54	68 (19.5)	80 (26.6)	10 (22.2)	118 (26.5)	121 (27.1)
55 – 64	51 (14.7)	53 (17.6)	8 (17.8)	81 (18.2)	78 (17.5)
65 – 74	49 (14.1)	37 (12.3)	2 (4.4)	61 (13.7)	57 (12.8)
≥ 75	8 (2.3)	7 (2.3)	1 (2.2)	17 (3.8)	27 (6.1)
Mean (± SD)	47 (± 13.9)	48 (± 13.9)	45 (± 12.5)	49 (± 14.1	50 (± 14.9)
Median (Min – Max)	45 (20-79)	48 (19-80)	44 (22-77)	49 (18-86)	49 (18-91)
Baseline Duodenal Ulcer Status, n (%) [b]					
Active	278 (79.9)	225 (74.8)	40 (88.9)	222 (49.8)	224 (50.2)
Not active	70 (20.1)	76 (25.2)	5 (11.1)	224 (50.2)	222 (49.8)
Duration of DU disease, n (%)					
< 1 year	257 (73.9)	209 (69.4)	26 (57.8)	111 (24.9)	125 (28.0)
1-5 years	49 (14.1)	58 (19.3)	10 (22.2)	79 (17.7)	93 (20.9)
> 5 years	42 (12.1)	34 (11.3)	9 (20.0)	256 (57.4)	228 (51.1)

[a] In the US studies, H 199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days. In the non-US studies, H 199/18 was administered as 20 mg bid and the duration of eradication therapy was 7 days.

[b] The inclusion criterion for Baseline DU status varied for the five Phase III studies. In the three US studies, patients could have had an active DU or a history of DU to enter the study. In SH-QBE-0019, patients were not permitted to enter the study if they had one or more active DUs at Baseline. In SH-QBE-0020, patients must have had an active DU to enter the study.

In the US Phase III studies, an AE was defined as any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body, temporally associated with any use of the study drug whether or not considered related to the use of the study drug. Exacerbation or an increase in the severity, frequency, or duration of a pre-existing condition occurring during the use of any study drug also constituted an AE. In the non-US studies, the definition of what constituted an AE was essentially the same as that in the US studies, with the exception that symptoms associated

with the disease under study (epigastric pain and heartburn) were only to be reported as AEs if they were not in accordance with the patient's normal symptoms, as judged by the patient or investigator. If an episode of epigastric pain or heartburn was deemed serious, it was to be reported as an SAE.

Counts and proportions of patients who discontinued due to an AE are presented separately for the US Phase III studies pooled and for the non-US Phase III studies pooled. Data were handled differently in the US and non-US Phase III studies. In the US Phase III studies, patients were included in the counts for discontinuations if they discontinued from the study due to an AE at any time during the entire study (i.e., patients who discontinued from the study during the treatment period as well as patients who discontinued from the study at any time during the follow-up period). In contrast, in the non-US Phase III studies, patients were included in the counts for discontinuations if they stopped taking study drug due to an AE.

Clinical Reviewer's Comment: Of the demographic and baseline characteristics presented in Table 3, only baseline duodenal ulcer status and duration of DU disease (a function of DU status) differs between the US and non-US studies. This is a reflection of the inclusion criteria for the studies. See Table 3, footnote b. It is not expected that this difference in the proportion of patients with an active DU would effect the incidence of adverse events/discontinuations in the non-US versus US studies, except that adverse events associated with the GI body system may have been underreported in the non-US studies due to lack of active GI disease and more strict definition of what constitutes a GI AE.

C. Overview of Adverse Events: Phase III Studies

1. US Phase III Studies

An overview of AE data is presented for the US Phase III studies in Table 4 and for the non-US Phase III studies in Table 5. In the US Phase III studies, similar percentages of patients in the HAC and HC groups had at least one AE (54.3% and 55.5%, respectively). In contrast, a slightly lower percentage of patients in the H group had at least one AE (46.7%). The percentage of patients who had a drug-related AE was greatest in the HAC group (30.2%) compared to that observed in the HC (26.6%) and H (22.2%) groups. Across the three treatment groups, there the percentages of patients who discontinued from study due to an AE (2.2% to 3.7%), had an SAE (0.6% to 2.2%), or died during study (0% to 0.3%) were similar.

Clinical Reviewer's Comment: It is known from the two drug interaction studies (SH-QBE-0034 and –0040) that the AUC of H 199/18 approximately doubles during co-administration with amoxicillin and clarithromycin. This is thought to be due to competitive inhibition of metabolism of H 199/18 by clarithromycin. Therefore, the increased incidence of AEs in the HAC and HC groups, as compared to the H group, may be due to the increased exposure to H 199/18, although it is more likely to be a result of the antibiotic component(s) of these combination regimens.

TABLE 4
Overview of Adverse Events: US Phase III Studies

Number of Patients (%):	US Studies (191, 192, and 193) Treatment Group		
	HAC (N=348)	HC (N=301)	H (N=45)
With at least one AE	189 (54.3)	167 (55.5)	21 (46.7
With at least one drug-related AE [a]	105 (30.2)	80 (26.6)	10 (22.2
Who discontinued from study due to an AE	11 (3.2	11 (3.7)	1 (2.
With at least one SAE [c]	2 (0.6	3 (1.0)	1 (2.
Who died during study	0 (0.0	1 (0.3)	0 (0.

[a] In the US studies, H 199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.
[b] A drug-related AE was any AE believed by the investigator to be possibly or probably related to study drug.
[c] This count includes fatal and non-fatal SAEs.

2. Non-US Phase III Studies

In the non-US Phase III studies, the percentages of patients who had at least one AE (52.2% and 50.7%, respectively), discontinued study drug due to an AE (1.1% and 2.2%, respectively), had at least one SAE (2.0% and 1.6%, respectively), or died during study (0% to 0.2%) were similar.

TABLE 5
Overview of Adverse Events: Non-US Phase III Studies

Number of Patients (%):	Non-US Studies (SH-QBE-0019 and -0020) Treatment Group [a]	
	HAC (N=446)	OAC (N=446)
With at least one AE	233 (52.2)	226 (50.7)
Who discontinued from study drug due to an AE	5 (1.1)	10 (2.2)
With at least one SAE [b]	9 (2.0)	7 (1.6)
Who died during study	0 (0.0)	1 (0.2)

[a] In the non-US studies, H 199/18 was administered as 20 mg bid and the duration of eradication therapy was 7 days.
[b] This count includes fatal and non-fatal SAEs.

Reviewer's Comment: The overall incidence of AEs was similar between the HAC regimen in the US and non-US studies. This indicates that despite different definitions of what constitutes a GI AE, the two regimens behaved similarly.

D. Adverse Events by Body System and Preferred Term: Phase III Studies

The most common AEs (≥ 3 patients in any treatment group) by body system and preferred term are presented for US and non-US Phase III studies in Table 6. In these tables patients may have reported more than one of the individual AEs within each body system. These patients are included once in the count for each individual AE they reported, but are counted only once in the overall total by body system.

1. US Phase III Studies

In the US Phase III studies, gastrointestinal system disorders were the most frequently reported AEs in all three treatment groups. The percentage of patients with a GI system disorder in the HAC group was similar to that observed in the HC group (38.2% vs. 37.2%, respectively). In contrast, a lower percentage of patients in the H group experienced a GI system AE (31.1%). Within this body system, the most frequently reported AEs were abdominal pain, diarrhea, flatulence, nausea, and esophagitis. Each of these events occurred in a larger percentage of patients in the HAC and HC groups compared to the H group.

The percentage of patients who experienced an AE related to the central and peripheral nervous system was similar between the HAC (10.1%) and HC (12.0%) groups. However, a lower percentage of patients in the H group experienced AEs associated with this system (4.4%). This difference resulted from a greater incidence of dizziness and headache in the HAC group and the HC group compared to that observed in the H group.

There also appeared to be a difference among treatment groups in the body system of special senses/other disorders that resulted from a greater incidence of taste perversion in the HAC group (6.6%) and the HC group (10.3%) compared to that observed in the H group (0%).

Clinical Reviewer's Comments: According to the package insert for omeprazole and lansoprazole the following are the three most common adverse events associated with triple therapy regimens in the respectively H. pylori clinical trials. The US data on HAC has been added to the table for comparison. From this data it appears that the three regimens behave similarly.

Most Common AE's associated with PPI-based Triple Therapy

AE	*OAC (%) (n=274)*	*LAC (%) (n=138)*	*HAC (%) (n=348)*
Diarrhea	*14*	*7*	*10.1*
Taste perversion	*10*	*5*	*6.6*
Headache	*7*	*6*	*6.9*

The higher incidence of taste perversion in the HAC and HC groups is likely to be caused by the addition of clarithromycin to the regimen, since this is a previously documented side effect of clarithromycin.

Other adverse events of note in the HAC group include a 0.9% and 1.7% incidence of increased SGOT and SGPT. These results are similar to the HAC (1.3% and 3.4%) and OAC (1.6% and 3.6%) regimens in the non-US trials. Also, there was a 5.5% incidence of psychiatric disorders reported in the US studies, which is slightly higher than the 2.0% and 1.3% incidence for HAC and OAC, respectively, in the non-US trials.

2. Non-US Phase III Studies

In the non-US Phase III studies (see Table 6), patients also experienced AEs associated with the GI system most frequently. There were no clinically meaningful differences between the HAC group (33.0%) and the OAC group (30.5%) in the proportion of patients with a GI system AE. In addition, there were no clinically meaningful differences between the groups in the incidence of any other AEs by body system or by individual event.

Clinical Reviewer's Comment: Four patients in the HAC group (0.9%) and 5 in the OAC group (1.1%) experienced bilirubinemia. Since the applicant did not submit clinical lab data from the non-US Phase III studies, it is not possible to determine the relative increase in bilirubin that occurred.

TABLE 6
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System and Preferred Term: Phase III Studies

Body System Preferred Term	Treatment Group [a] [Number of Patients (%)]				
	US Studies (191, 192, and 193)			Non-US Studies (SH-QBE-0019 and 0020)	
	HAC (N=348)	HC (N=301)	H (N=45)	HAC (N=446)	OAC (N=446)
Body as a Whole	19 (5.5)	21 (7.0)	2 (4.4)	20 (4.5)	16 (3.6)
Accident and/or injury	3 (0.9)	3 (1.0)	0 (0.0)	2 (0.4)	3 (0.7)
Asthenia	0 (0.0)	4 (1.3)	0 (0.0)	2 (0.4)	0 (0.0)
Back pain	5 (1.4)	5 (1.7)	1 (2.2)	3 (0.7)	5 (1.1)
Oedema peripheral	3 (0.9)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Pain	1 (0.3)	2 (0.7)	0 (0.0)	3 (0.7)	4 (0.9)
Central and Peripheral Nervous System	35 (10.1)	36 (12.0)	2 (4.4)	22 (4.9)	16 (3.6)
Dizziness	11 (3.2)	10 (3.3)	0 (0.0)	2 (0.4)	2 (0.4)
Headache	24 (6.9)	26 (8.6)	2 (4.4)	18 (4.0)	13 (2.9)
Gastrointestinal System Disorders	133 (38.2)	112 (37.2)	14 (31.1)	147 (33.0)	136 (30.5)
Abdominal pain	17 (4.9)	15 (5.0)	1 (2.2)	5 (1.1)	6 (1.3)
Constipation	6 (1.7)	10 (3.3)	2 (4.4)	2 (0.4)	3 (0.7)
Diarrhoea	35 (10.1)	27 (9.0)	2 (4.4)	98 (22.0)	98 (22.0)
Duodenitis [b]	16 (4.6)	9 (3.0)	2 (4.4)	0 (0.0)	0 (0.0)
Dyspepsia	7 (2.0)	8 (2.7)	1 (2.2)	8 (1.8)	6 (1.3)
Epigastric pain	3 (0.9)	4 (1.3)	0 (0.0)	6 (1.3)	1 (0.2)
Flatulence	8 (2.3)	6 (2.0)	0 (0.0)	9 (2.0)	8 (1.8)
Gastritis [b]	44 (12.6)	31 (10.3)	6 (13.3)	0 (0.0)	0 (0.0)
Gastrointestinal system disorder, NOS	4 (1.1)	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gastroesophageal reflux	0 (0.0)	3 (1.0)	0 (0.0)	2 (0.4)	1 (0.2)
Mouth dry	4 (1.1)	7 (2.3)	0 (0.0)	15 (3.4)	6 (1.3)
Nausea	13 (3.7)	16 (5.3)	0 (0.0)	8 (1.8)	10 (2.2)
Oesophagitis [b]	23 (6.6)	19 (6.3)	1 (2.2)	1 (0.2)	0 (0.0)
Pharynx disorder	2 (0.6)	2 (0.7)	0 (0.0)	3 (0.7)	1 (0.2)
Stomatitis	1 (0.3)	1 (0.3)	0 (0.0)	6 (1.3)	5 (1.1)
Tongue disorder	0 (0.0)	2 (0.7)	0 (0.0)	3 (0.7)	4 (0.9)
Vomiting	6 (1.7)	2 (0.7)	0 (0.0)	6 (1.3)	6 (1.3)
Heart Rate and Rhythm Disorders	3 (0.9)	1 (0.3)	0 (0.0)	2 (0.4)	1 (0.2)
Tachycardia	3 (0.9)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)
Liver and Biliary System Disorders	9 (2.6)	1 (0.3)	0 (0.0)	20 (4.5)	21 (4.7)
Bilirubinaemia	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	5 (1.1)
Hepatic enzymes increased, NOS	3 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
SGOT increased	3 (0.9)	0 (0.0)	0 (0.0)	6 (1.3)	7 (1.6)
SGPT increased	6 (1.7)	0 (0.0)	0 (0.0)	15 (3.4)	16 (3.6)
Metabolic and Nutritional System Disorders	1 (0.3)	2 (0.7)	0 (0.0)	7 (1.6)	6 (1.3)
Phosphatase alkaline, increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	1 (0.2)

NOS =not otherwise specified

[a] In the US studies, H 199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days. In the non-US studies, H 199/18 was administered as 20 mg bid and the duration of eradication therapy was 7 days.

[b] AEs observed during EGD in the US studies only.

TABLE 6 (Continued)
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System and Preferred Term: Phase III Studies

Body System Preferred Term	Treatment Group [a] [Number of Patients (%)]				
	US Studies (191, 192, and 193)			Non-US Studies (SH-QBE-0019 and 0020)	
	HAC (N=348)	HC (N=301)	H (N=45)	HAC (N=446)	OAC (N=446)
Musculoskeletal System Disorders	14 (4.0)	6 (2.0)	0 (0.0)	2 (0.4)	4 (0.9)
Fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)
Hernia [c]	8 (2.3)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet Bleeding and Clotting	1 (0.3)	4 (1.3)	0 (0.0)	1 (0.2)	4 (0.9)
Purpura	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombocytopenia	1 (0.3)	1 (0.3)	0 (0.0)	1 (0.2)	3 (0.7)
Psychiatric Disorders	19 (5.5)	12 (4.0)	0 (0.0)	9 (2.0)	6 (1.3)
Anorexia	3 (0.9)	2 (0.7)	0 (0.0)	2 (0.4)	0 (0.0)
Anxiety	3 (0.9)	2 (0.7)	0 (0.0)	2 (0.4)	3 (0.7)
Insomnia	5 (1.4)	4 (1.3)	0 (0.0)	3 (0.7)	1 (0.2)
Somnolence	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
RBC Disorders	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	6 (1.3)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	6 (1.3)
Reproductive, Female	6 (1.7)	1 (0.3)	2 (4.4)	1 (0.2)	4 (0.9)
Vaginal fungal infection	3 (0.9)	0 (0.0)	1 (2.2)	1 (0.2)	1 (0.2)
Resistance Mechanism Disorders	7 (2.0)	2 (0.7)	1 (2.2)	2 (0.4)	8 (1.8)
Infection, viral	1 (0.3)	2 (0.7)	0 (0.0)	1 (0.2)	3 (0.7)
Moniliasis	4 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Respiratory System Disorders	17 (4.9)	17 (5.6)	2 (4.4)	18 (4.0)	7 (1.6)
Pharyngitis	2 (0.6)	3 (1.0)	0 (0.0)	9 (2.0)	4 (0.9)
Respiratory Infection	8 (2.3)	8 (2.7)	0 (0.0)	3 (0.7)	2 (0.4)
Rhinitis	6 (1.7)	1 (0.3)	0 (0.0)	2 (0.4)	0 (0.0)
Sinusitis	0 (0.0)	5 (1.7)	1 (2.2)	0 (0.0)	0 (0.0)
Skin and Appendages Disorders	10 (2.9)	15 (5.0)	0 (0.0)	22 (4.9)	17 (3.8)
Pruritus	1 (0.3)	3 (1.0)	0 (0.0)	2 (0.4)	4 (0.9)
Pruritus, ani	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.7)	2 (0.4)
Pruritus, genital	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.7)	2 (0.4)
Rash	4 (1.1)	3 (1.0)	0 (0.0)	1 (0.2)	4 (0.9)
Rash erythematous	1 (0.3)	0 (0.0)	0 (0.0)	5 (1.1)	4 (0.9)
Urticaria	1 (0.3)	1 (0.3)	0 (0.0)	4 (0.9)	2 (0.4)
Special Senses Other Disorders	24 (6.9)	31 (10.3)	0 (0.0)	58 (13.0)	68 (15.2)
Taste Perversion	23 (6.6)	31 (10.3)	0 (0.0)	56 (12.6)	68 (15.2)
Urinary System Disorders	8 (2.3)	4 (1.3)	1 (2.2)	9 (2.0)	11 (2.5)
Hematuria	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)	7 (1.6)
Urinary tract infection	4 (1.1)	2 (0.7)	1 (2.2)	0 (0.0)	1 (0.2)
WBC and Resistance Disorders	1 (0.3)	0 (0.0)	1 (2.2)	7 (1.6)	3 (0.7)
Leukopenia	1 (0.3)	0 (0.0)	1 (2.2)	5 (1.1)	2 (0.4)

[a] In the US studies, H 199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days. In the non-US studies, H 199/18 was administered as 20 mg bid and the duration of eradication therapy was 7 days.
[c] Hiatal hernia observed during EGD in the US studies only.

E. Adverse Events by Relationship to Treatment: US Phase III Studies

A summary of drug-related AEs is presented for the US Phase III studies in Table 7. In all three treatment groups, GI system disorders were the most frequent AEs evaluated as drug related by investigators. There were no clinically meaningful differences among the three treatment groups in the overall percentage of patients who experienced a drug-related AE associated with the GI system (HAC: 19.8%; HC: 17.6%; and H: 17.8%). However, within this body system, drug-related abdominal pain, diarrhea, and nausea were reported by a slightly greater percentage of patients in the HAC and/or the HC group compared to that observed in the H group. For all other drug-related AEs, the incidence was similar between the three treatment groups with the possible exception of drug-related taste perversion, which was reported by a greater percentage of patients in the combination therapy groups compared to those who received monotherapy (HAC: 6.6%; HC: 9.3%; and H: 0%).

Clinical Reviewer's Comment: As noted previously, GI-related AEs are known side effects of antibiotics and taste perversion is a known side effect of clarithromycin. Therefore, the higher incidence of these AEs in the HAC and HC groups is not unexpected.

TABLE 7
Most Common (≥ 3 Patients in Any Group) Possibly or Probably Drug-Related Adverse Events by Body System and Preferred Term: US Phase III Studies

Body System Preferred Term	US Studies (191, 192, and 193)[a] Treatment Group [Number of Patients (%)] HAC (N=348)	HC (N=301)	H (N=45)
Central and Peripheral Nervous System	17 (4.9)	21 (7.0)	1 (2.2)
Dizziness	8 (2.3)	6 (2.0)	0 (0.0)
Headache	11 (3.2)	14 (4.7)	1 (2.2)
Gastrointestinal System Disorders	69 (19.8)	53 (17.6)	8 (17.8)
Abdominal pain	13 (3.7)	6 (2.0)	0 (0.0)
Constipation	3 (0.9)	7 (2.3)	2 (4.4)
Diarrhea	32 (9.2)	21 (7.0)	2 (4.4)
Dyspepsia	2 (0.6)	3 (1.0)	1 (2.2)
Flatulence	7 (2.0)	4 (1.3)	0 (0.0)
Gastritis[b]	4 (1.1)	6 (2.0)	3 (6.7)
Mouth dry	3 (0.9)	6 (2.0)	0 (0.0)
Nausea	12 (3.4)	13 (4.3)	0 (0.0)
Oesophagitis[b]	3 (0.9)	5 (1.7)	0 (0.0)
Vomiting	5 (1.4)	2 (0.7)	0 (0.0)
Liver and Biliary System Disorders	7 (2.0)	1 (0.3)	0 (0.0)
SGOT increased	3 (0.9)	0 (0.0)	0 (0.0)
SGPT increased	5 (1.4)	0 (0.0)	0 (0.0)
Psychiatric Disorders	14 (4.0)	7 (2.3)	0 (0.0)
Anorexia	3 (0.9)	2 (0.7)	0 (0.0)
Insomnia	3 (0.9)	0 (0.0)	0 (0.0)
Somnolence	3 (0.9)	0 (0.0)	0 (0.0)
Resistance Mechanism Disorders	6 (1.7)	0 (0.0)	0 (0.0)
Moniliasis	4 (1.1)	0 (0.0)	0 (0.0)
Skin and Appendage Disorders	7 (2.0)	6 (2.0)	0 (0.0)
Pruritus	1 (0.3)	3 (1.0)	0 (0.0)
Rash	3 (0.9)	2 (0.7)	0 (0.0)
Special Senses Other Disorders	24 (6.9)	28 (9.3)	0 (0.0)
Taste perversion	23 (6.6)	28 (9.3)	0 (0.0)

[a] In the US Studies, H 199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.
[b] AEs observed during EGD.

F. Adverse Events by Age

1. US Phase III Studies

A summary of the most common AEs (≥ 3 patients in any treatment group) is presented by age groups for the US Phase III studies in Table 8. Within the HAC group, elderly patients (≥ 65 years) tended to report one or more AEs more frequently than those in the younger age groups (≤ 40 years: 51.9%; 41 years - 64 years: 53.2%; ≥ 65 years: 63.2%). Other AEs

that occurred at a higher frequency in the elderly patients within this treatment group include GI, musculoskeletal, and special senses/other (taste perversion) disorders.

When comparing the same age group between treatments, the percentage of patients with an AE in each of the age groups in the HAC treatment group was generally similar to or lower than that observed in the same age group in the HC group, with the possible exception of AEs patients in patients ≥ 65 years of age associated with the GI system, the musculoskeletal system, special/senses other disorders, and respiratory system.

Clinical Reviewer's Comments: The incidence of liver and biliary disorders (increased SGPT) was found entirely in the younger patients (< 65 years old).

There were too few patients in the H group to attempt any conclusions about potential age-related effects.

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TABLE 8
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Age Groups (Years): US Phase III Studies

Body System *Preferred Term*	US Studies (191, 192, and 193) Treatment Group [a] [Number of Patients (%)]								
	HAC			HC			H		
	≤ 40 (N=133)	41 – 64 (N=158)	≥ 65 (N=57)	≤ 40 (N=91)	41 – 64 (N=166)	≥ 65 (N=44)	≤ 40 (N=17)	41 – 64 (N=25)	≥ 65 (N=3)
Total Patients with at Least One AE	69 (51.9)	84 (53.2)	36 (63.2)	44 (48.4)	101 (60.8)	22 (50.0)	9 (52.9)	11 (44.0)	1 (33.3)
Body as a Whole	4 (3.0)	11 (7.0)	4 (7.0)	5 (5.5)	13 (7.8)	3 (6.8)	0 (0.0)	2 (8.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	2 (1.5)	3 (1.9)	0 (0.0)	1 (1.1)	3 (1.8)	1 (2.3)	0 (0.0)	1 (4.0)	0 (0.0)
Central and Peripheral Nervous System	13 (9.8)	18 (11.4)	4 (7.0)	10 (11.0)	22 (13.3)	4 (9.1)	1 (5.9)	1 (4.0)	0 (0.0)
Dizziness	4 (3.0)	6 (3.8)	1 (1.8)	4 (4.4)	4 (2.4)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	10 (7.5)	12 (7.6)	2 (3.5)	6 (6.6)	18 (10.8)	2 (4.5)	1 (5.9)	1 (4.0)	0 (0.0)
Gastrointestinal System Disorders	47 (35.3)	61 (38.6)	25 (43.9)	31 (34.1)	66 (39.8)	15 (34.1)	5 (29.4)	9 (36.0)	0 (0.0)
Abdominal pain	8 (6.0)	6 (3.8)	3 (5.3)	3 (3.3)	10 (6.0)	2 (4.5)	0 (0.0)	1 (4.0)	0 (0.0)
Constipation	2 (1.5)	3 (1.9)	1 (1.8)	3 (3.3)	6 (3.6)	1 (2.3)	1 (5.9)	1 (4.0)	0 (0.0)
Diarrhea	12 (9.0)	17 (10.8)	6 (10.5)	10 (11.0)	15 (9.0)	2 (4.5)	1 (5.9)	1 (4.0)	0 (0.0)
Duodenitis [b]	5 (3.8)	5 (3.2)	6 (10.5)	1 (1.1)	6 (3.6)	2 (4.5)	1 (5.9)	1 (4.0)	0 (0.0)
Dyspepsia	1 (0.8)	5 (3.2)	1 (1.8)	3 (3.3)	5 (3.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)
Epigastric pain	2 (1.5)	1 (0.6)	0 (0.0)	1 (1.1)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	4 (3.0)	1 (0.6)	3 (5.3)	2 (2.2)	3 (1.8)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis [b]	13 (9.8)	21 (13.3)	10 (17.5)	7 (7.7)	18 (10.8)	6 (13.6)	1 (5.9)	5 (20.0)	0 (0.0)
Gastrointestinal system disorder, NOS	2 (1.5)	1 (0.6)	1 (1.8)	0 (0.0)	5 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mouth dry	2 (1.5)	2 (1.3)	0 (0.0)	2 (2.2)	4 (2.4)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	5 (3.8)	3 (1.9)	5 (8.8)	8 (8.8)	7 (4.2)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Oesophagitis [b]	10 (7.5)	10 (6.3)	3 (5.3)	6 (6.6)	12 (7.2)	1 (2.3)	1 (5.9)	0 (0.0)	0 (0.0)
Vomiting	3 (2.3)	2 (1.3)	1 (1.8)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Liver and Biliary Disorders	6 (4.5)	3 (1.9)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SGPT increased	4 (3.0)	2 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOS = not otherwise specified

[a] In the US studies, H199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.

[b] AEs observed during EGD.

TABLE 8 (Continued)
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Age Groups (Years): US Phase III Studies

Body System Preferred Term	US Studies (191, 192, and 193) Treatment Group [a] [Number of Patients (%)]								
	HAC			HC			H		
	≤ 40 (N=133)	41 – 64 (N=158)	≥ 65 (N=57)	≤ 40 (N=91)	41 – 64 (N=166)	≥ 65 (N=44)	≤ 40 (N=17)	41 – 64 (N=25)	≥ 65 (N=3)
Musculoskeletal System Disorders	4 (3.0)	5 (3.2)	5 (8.8)	2 (2.2)	4 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hernia [c]	3 (2.3)	2 (1.3)	3 (5.3)	1 (1.1)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory System Disorders	5 (3.8)	8 (5.1)	4 (7.0)	6 (6.6)	10 (6.0)	1 (2.3)	0 (0.0)	1 (4.0)	1 (33.3)
Respiratory Infection	1 (0.8)	5 (3.2)	2 (3.5)	3 (3.3)	4 (2.4)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	3 (2.3)	3 (1.9)	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)
Skin and Appendage Disorders	4 (3.0)	3 (1.9)	3 (5.3)	6 (6.6)	7 (4.2)	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	3 (2.3)	0 (0.0)	1 (1.8)	2 (2.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Special Senses Other Disorders	8 (6.0)	9 (5.7)	7 (12.3)	6 (6.6)	24 (14.5)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Taste perversion	7 (5.3)	9 (5.7)	7 (12.3)	6 (6.6)	24 (14.5)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary System Disorders	3 (2.3)	4 (2.5)	1 (1.8)	2 (2.2)	1 (0.6)	1 (2.3)	1 (5.9)	0 (0.0)	0 (0.0)
Urinary tract infection	1 (0.8)	3 (1.9)	0 (0.0)	1 (1.1)	0 (0.0)	1 (2.3)	1 (5.9)	0 (0.0)	0 (0.0)

[a] In the US studies, H199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.
[c] Hiatal hernia observed during EGD.

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2. Non-US Phase III Studies

A summary of the most common AEs (≥ 3 patients in any treatment group) is presented by age groups for the non-US Phase III studies in Table 9. The percentage of elderly patients in the HAC group in the non-US Phase III studies who reported one or more AEs (55.1%) was similar to that observed in the 41 - 64 year age group (54.4%), but greater than that observed in the ≤ 40 year age group (45.8%).

In the HAC group, incidence of individual AEs was similar between the age groups, with the possible exceptions of GI system AEs (abdominal pain and flatulence).

When comparing the same age between treatments, the percentage of patients with an AE in each of the age groups in the HAC group was generally similar to or lower than that observed in the same age group in the OAC group, with the possible exceptions of AEs associated with the body as a whole, respiratory system disorders, central and peripheral nervous system disorders, and GI system disorders.

TABLE 9

Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Age Groups (Years): Non-US Phase III Studies

Body System Preferred Term	Non-US Studies (SH-QBE-0019 and 0020) Treatment Group [a] [Number of Patients (%)]					
	HAC			OAC		
	≤ 40 (N=118)	41 - 64 (N=250)	≥ 65 (N=78)	≤ 40 (N=103)	41 - 64 (N=259)	≥ 65 (N=84)
Total Patients with at Least One AE	54 (45.8)	136 (54.4)	43 (55.1)	45 (43.7)	137 (52.9)	44 (52.4)
Body as a Whole	2 (1.7)	12 (4.8)	6 (7.7)	1 (1.0)	13 (5.0)	2 (2.4)
Back pain	0 (0.0)	3 (1.2)	0 (0.0)	1 (1.0)	4 (1.5)	0 (0.0)
Pain	0 (0.0)	2 (0.8)	1 (1.3)	0 (0.0)	3 (1.2)	1 (1.2)
Central and Peripheral Nervous System	4 (3.4)	13 (5.2)	5 (6.4)	3 (2.9)	12 (4.6)	1 (1.2)
Headache	4 (3.4)	10 (4.0)	4 (5.1)	1 (1.0)	11 (4.2)	1 (1.2)
Gastrointestinal System Disorders	32 (27.1)	83 (33.2)	32 (41.0)	25 (24.3)	80 (30.9)	31 (36.9)
Abdominal pain	1 (0.8)	3 (1.2)	1 (1.3)	3 (2.9)	2 (0.8)	1 (1.2)
Diarrhea	21 (17.8)	55 (22.0)	22 (28.2)	16 (15.5)	57 (22.0)	25 (29.8)
Dyspepsia	3 (2.5)	3 (1.2)	2 (2.6)	1 (1.0)	4 (1.5)	1 (1.2)
Epigastric pain	1 (0.8)	5 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Flatulence	1 (0.8)	4 (1.6)	4 (5.1)	0 (0.0)	7 (2.7)	1 (1.2)
Mouth dry	4 (3.4)	9 (3.6)	2 (2.6)	1 (1.0)	4 (1.5)	1 (1.2)
Nausea	4 (3.4)	2 (0.8)	2 (2.6)	3 (2.9)	5 (1.9)	2 (2.4)
Stomatitis	0 (0.0)	5 (2.0)	1 (1.3)	0 (0.0)	4 (1.5)	1 (1.2)
Tongue disorder	1 (0.8)	2 (0.8)	0 (0.0)	0 (0.0)	4 (1.5)	0 (0.0)
Vomiting	1 (0.8)	4 (1.6)	1 (1.3)	3 (2.9)	3 (1.2)	0 (0.0)
Liver and Biliary System Disorders	5 (4.2)	11 (4.4)	4 (5.1)	11 (10.7)	7 (2.7)	3 (3.6)
Bilirubinemia	0 (0.0)	1 (0.4)	3 (3.8)	3 (2.9)	2 (0.8)	0 (0.0)
SGOT increased	0 (0.0)	5 (2.0)	1 (1.3)	3 (2.9)	2 (0.8)	2 (2.4)
SGPT increased	5 (4.2)	9 (3.6)	1 (1.3)	9 (8.7)	4 (1.5)	3 (3.6)
RBC Disorders	0 (0.0)	2 (0.8)	2 (2.6)	0 (0.0)	5 (1.9)	1 (1.2)
Anemia	0 (0.0)	2 (0.8)	2 (2.6)	0 (0.0)	5 (1.9)	1 (1.2)
Respiratory System Disorders	7 (5.9)	11 (4.4)	0 (0.0)	1 (1.0)	3 (1.2)	3 (3.6)
Pharyngitis	2 (1.7)	7 (2.8)	0 (0.0)	1 (1.0)	2 (0.8)	1 (1.2)

[a] In the non-US studies, H 199/18 was administered as 20 mg bid and eradication therapy was 7 days.

Table 9 (Continued)
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Age Groups (Years): Non-US Phase III Studies

Body System Preferred Term	Non-US Studies (SH-QBE-0019 and 0020) Treatment Group [a] [Number of Patients (%)]					
	HAC			OAC		
	≤ 40 (N=118)	41 - 64 (N=250)	≥ 65 (N=78)	≤ 40 (N=103)	41 - 64 ((n=259)	≥ 65 (N=84)
Skin and Appendage Disorders	2 (1.7)	14 (5.6)	6 (7.7)	0 (0.0)	12 (4.6)	5 (6.0)
Pruritus	0 (0.0)	1 (0.4)	1 (1.3)	0 (0.0)	3 (1.2)	1 (1.2)
Pruritus, ani	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.2)
Rash	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.2)	1 (1.2)
Rash erythematous	0 (0.0)	3 (1.2)	2 (2.6)	0 (0.0)	2 (0.8)	2 (2.4)
Special Senses Other Disorders	11 (9.3)	36 (14.4)	11 (14.1)	15 (14.6)	37 (14.3)	16 (19.0)
Taste perversion	11 (9.3)	35 (14.0)	10 (12.8)	15 (14.6)	37 (14.3)	16 (19.0)
Urinary System Disorders	2 (1.7)	7 (2.8)	0 (0.0)	3 (2.9)	7 (2.7)	1 (1.2)
Haematuria	2 (1.7)	3 (1.2)	0 (0.0)	2 (1.9)	5 (1.9)	0 (0.0)
WBC & Resistance Disorders	2 (1.7)	5 (2.0)	0 (0.0)	2 (1.9)	1 (0.4)	0 (0.0)
Leukopenia	1 (0.8)	4 (1.6)	0 (0.0)	1 (1.0)	1 (0.4)	0 (0.0)

[a] In the non-US studies, H 199/18 was administered as 20 mg bid and eradication therapy was 7 days.

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G. Gender

1. US Phase III Studies

A summary of the most common AEs (≥ 3 patients in any treatment group) is presented by gender for the US Phase III studies in Table 10.

In the HAC group, females reported one or more AEs more frequently than males (62.7% vs 49.1%). Notable differences between males and females were observed in AEs associated with the body as a whole, GI system disorders, musculoskeletal system disorders, psychiatric disorders, special senses/other disorders (taste perversion), liver and biliary system disorders, and urinary system disorders. For all of these body systems, all percentages were greater for females compared to males except disorders of the liver and biliary system (all increases in SGOT/SGPT occurred in males).

When comparing the same gender between the HAC and HC groups, a greater percentage of males who received HC reported one or more AEs (57.8%) compared to males who received HAC (49.1%). In general, the percentage of males in the HAC group who reported AEs, both by body system and by individual AE, was similar to or lower than that observed among males in the HC group, with the possible exception of liver and biliary system disorders. These events were reported more frequently by males in the HAC group (4.2% vs. 0.5%).

When comparing females between treatment groups, a greater percentage of females who received HAC reported one or more AEs (62.7%) compared to females who received HC (51.7%). When examined by body system, the most notable differences between females in the two groups occurred in AEs associated with the GI system (42.5% vs. 31.0%).

Clinical Reviewer's Comment: There were too few patients in the H group to attempt any conclusions about potential gender-related adverse events.

TABLE 10
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Gender: US Phase III Studies

Body System Preferred Term	US Studies (191, 192, and 193) Treatment Group [a] [Number of Patients (%)]					
	HAC		HC		H	
	Male (N=214)	Female (N=134)	Male (N=185)	Female (N=116)	Male (N=26)	Female (N=19)
Total Patients with at Least One AE	105 (49.1)	84 (62.7)	107 (57.8)	60 (51.7)	13 (50.0)	8 (42.1)
Body as a Whole	6 (2.8)	13 (9.7)	13 (7.0)	8 (6.9)	0 (0.0)	2 (10.5)
Back pain	2 (0.9)	3 (2.2)	2 (1.1)	3 (2.6)	0 (0.0)	1 (5.3)
Oedema peripheral	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Central and Peripheral Nervous System	19 (8.9)	16 (11.9)	23 (12.4)	13 (11.2)	1 (3.8)	1 (5.3)
Dizziness	5 (2.3)	6 (4.5)	7 (3.8)	3 (2.6)	0 (0.0)	0 (0.0)
Headache	14 (6.5)	10 (7.5)	17 (9.2)	9 (7.8)	1 (3.8)	1 (5.3)
Gastrointestinal System Disorders	76 (35.5)	57 (42.5)	76 (41.1)	36 (31.0)	9 (34.6)	5 (26.3)
Abdominal pain	6 (2.8)	11 (8.2)	10 (5.4)	5 (4.3)	0 (0.0)	1 (5.3)
Constipation	2 (0.9)	4 (3.0)	9 (4.9)	1 (0.9)	2 (7.7)	0 (0.0)
Diarrhea	20 (9.3)	15 (11.2)	23 (12.4)	4 (3.4)	0 (0.0)	2 (10.5)
Duodenitis [b]	9 (4.2)	7 (5.2)	9 (4.9)	0 (0.0)	2 (7.7)	0 (0.0)
Dyspepsia	5 (2.3)	2 (1.5)	4 (2.2)	4 (3.4)	1 (3.8)	0 (0.0)
Epigastric pain	1 (0.5)	2 (1.5)	3 (1.6)	1 (0.9)	0 (0.0)	0 (0.0)
Flatulence	2 (0.9)	6 (4.5)	5 (2.7)	1 (0.9)	0 (0.0)	0 (0.0)
Gastritis [b]	22 (10.3)	22 (16.4)	20 (10.8)	11 (9.5)	4 (15.4)	2 (10.5)
Gastrointestinal System Disorder, NOS	2 (0.9)	2 (1.5)	3 (1.6)	2 (1.7)	0 (0.0)	0 (0.0)
Mouth dry	2 (0.9)	2 (1.5)	6 (3.2)	1 (0.9)	0 (0.0)	0 (0.0)
Nausea	1 (0.5)	12 (9.0)	9 (4.9)	7 (6.0)	0 (0.0)	0 (0.0)
Esophagitis [b]	20 (9.3)	3 (2.2)	17 (9.2)	2 (1.7)	1 (3.8)	0 (0.0)
Vomiting	0 (0.0)	6 (4.5)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Liver and Biliary System Disorders	9 (4.2)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzymes increased, NOS	3 (1.4)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
SGOT increased	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SGPT increased	6 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

NOS = not otherwise specified

[a] In the US studies, H199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.

[b] AEs observed during EGD.

TABLE 10 (Continued)
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Gender: US Phase III Studies

Body System Preferred Term	US Studies (191, 192, and 193) Treatment Group [a] [Number of Patients (%)]					
	HAC		HC		H	
	Male (N=214)	Female (N=134)	Male (N=185)	Female (N=116)	Male (N=26)	Female (N=19)
Musculoskeletal System Disorders	6 (2.8)	8 (6.0)	4 (2.2)	2 (1.7)	0 (0.0)	0 (0.0)
Hernia [c]	4 (1.9)	4 (3.0)	3 (1.6)	1 (0.9)	0 (0.0)	0 (0.0)
Psychiatric Disorders	7 (3.3)	12 (9.0)	7 (3.8)	5 (4.3)	0 (0.0)	0 (0.0)
Insomnia	2 (0.9)	3 (2.2)	3 (1.6)	1 (0.9)	0 (0.0)	0 (0.0)
Reproductive Female	0 (0.0)	6 (4.5)	0 (0.0)	1 (0.9)	0 (0.0)	2 (10.5)
Vaginal fungal infection	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Resistance Mechanism Disorders	2 (0.9)	5 (3.7)	2 (1.1)	0 (0.0)	1 (3.8)	0 (0.0)
Moniliasis	1 (0.5)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory System Disorders	11 (5.1)	6 (4.5)	14 (7.6)	3 (2.6)	2 (7.7)	0 (0.0)
Respiratory infection	5 (2.3)	3 (2.2)	6 (3.2)	2 (1.7)	0 (0.0)	0 (0.0)
Rhinitis	4 (1.9)	2 (1.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	5 (2.7)	0 (0.0)	1 (3.8)	0 (0.0)
Skin and Appendage Disorders	7 (3.3)	3 (2.2)	6 (3.2)	9 (7.8)	0 (0.0)	0 (0.0)
Rash	4 (1.9)	0 (0.0)	1 (0.5)	2 (1.7)	0 (0.0)	0 (0.0)
Special Senses Other Disorders	6 (2.8)	18 (13.4)	15 (8.1)	16 (13.8)	0 (0.0)	0 (0.0)
Taste perversion	5 (2.3)	18 (13.4)	15 (8.1)	16 (13.8)	0 (0.0)	0 (0.0)
Urinary System Disorders	1 (0.5)	7 (5.2)	0 (0.0)	4 (3.4)	0 (0.0)	1 (5.3)
Urinary Tract Infection	0 (0.0)	4 (3.0)	0 (0.0)	2 (1.7)	0 (0.0)	1 (5.3)

[a] In the US studies, H199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.
[c] *Hiatal hernia observed during EGD.*

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2. Non-US Phase III Studies

A summary of the most common AEs (≥ 3 patients in any treatment group) is presented by gender for the non-US Phase III studies in Table 11.

In the HAC group, a slightly greater percentage of females reported one or more AEs compared to males (55.8% vs. 50.3%). Overall, the only clinically meaningful differences between males and females in the HAC group occurred in AEs associated with the liver and biliary system and special senses/other disorders (taste perversion).

When comparing the same gender between the two treatment groups, the percentage of males in the HAC group who reported one or more AEs was slightly greater than that for males in the OAC group (50.3% vs. 46.0%). Overall, the percentage of males in the HAC group who reported AEs, both by body system and by individual event, was generally similar to that reported by males in the OAC group, with the possible exception of GI system disorders.

There were no apparent differences between the percentage of females in the HAC group and females in the OAC group who reported one or more AEs.

TABLE 11
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Gender: Non-US Phase III Studies

Body System Preferred Term	Non-US Studies (SH-QBE-0019 and 0020) Treatment Group [a] [Number of Patients (%)]			
	HAC		OAC	
	Male (N=290)	Female (N=156)	Male (N=272)	Female (N=174)
Total Patients with at Least One AE	146 (50.3)	87 (55.8)	125 (46.0)	101 (58.0)
Body as a Whole	10 (3.4)	10 (6.4)	9 (3.3)	7 (4.0)
Back pain	1 (0.3)	2 (1.3)	3 (1.1)	2 (1.1)
Pain	2 (0.7)	1 (0.6)	4 (1.5)	0 (0.0)
Central and Peripheral Nervous System	13 (4.5)	9 (5.8)	8 (2.9)	8 (4.6)
Headache	11 (3.8)	7 (4.5)	8 (2.9)	5 (2.9)
Gastrointestinal System Disorders	94 (32.4)	53 (34.0)	74 (27.2)	62 (35.6)
Abdominal pain	4 (1.4)	1 (0.6)	3 (1.1)	3 (1.7)
Diarrhea	66 (22.8)	32 (20.5)	56 (20.6)	42 (24.1)
Dyspepsia	6 (2.1)	2 (1.3)	4 (1.5)	2 (1.1)
Epigastric pain	6 (2.1)	0 (0.0)	1 (0.4)	0 (0.0)
Flatulence	7 (2.4)	2 (1.3)	4 (1.5)	4 (2.3)
Mouth dry	11 (3.8)	4 (2.6)	4 (1.5)	2 (1.1)
Nausea	3 (1.0)	5 (3.2)	4 (1.5)	6 (3.4)
Stomatitis	2 (0.7)	4 (2.6)	2 (0.7)	3 (1.7)
Tongue disorder	3 (1.0)	0 (0.0)	2 (0.7)	2 (1.1)
Vomiting	0 (0.0)	6 (3.8)	3 (1.1)	3 (1.7)
Liver and Biliary System Disorders	19 (6.6)	1 (0.6)	15 (5.5)	6 (3.4)
Bilirubinaemia	4 (1.4)	0 (0.0)	4 (1.5)	1 (0.6)
SGOT increased	5 (1.7)	1 (0.6)	6 (2.2)	1 (0.6)
SGPT increased	14 (4.8)	1 (0.6)	12 (4.4)	4 (2.3)
Metabolic and Nutritional System Disorders	6 (2.1)	1 (0.6)	5 (1.8)	1 (0.6)
Phosphatase alkaline increased	3 (1.0)	0 (0.0)	1 (0.4)	0 (0.0)
Platelet Bleeding and Clotting	0 (0.0)	1 (0.6)	3 (1.1)	1 (0.6)
Thrombocytopenia	0 (0.0)	1 (0.6)	3 (1.1)	0 (0.0)
RBC Disorders	4 (1.4)	0 (0.0)	4 (1.5)	2 (1.1)
Anaemia	4 (1.4)	0 (0.0)	4 (1.5)	2 (1.1)

[a] In the non-US studies, H 199/18 was administered as 20 mg bid and eradication therapy was 7 days.

TABLE 11 (Continued)
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Gender: Non-US Phase III Studies

Body System *Preferred Term*	Non-US Studies (SH-QBE-0019 and 0020) Treatment Group [a] [Number of Patients (%)]			
	HAC		OAC	
	Male (N=290)	Female (N=156)	Male (N=272)	Female (N=174)
Respiratory System Disorders	15 (5.2)	3 (1.9)	6 (2.2)	1 (0.6)
Pharyngitis	6 (2.1)	3 (1.9)	3 (1.1)	1 (0.6)
Respiratory infection	3 (1.0)	0 (0.0)	2 (0.7)	0 (0.0)
Skin and Appendage Disorders	10 (3.4)	12 (7.7)	3 (1.1)	14 (8.0)
Pruritus	1 (0.3)	1 (0.6)	1 (0.4)	3 (1.7)
Pruritus genital	0 (0.0)	3 (1.9)	0 (0.0)	2 (1.1)
Rash	0 (0.0)	1 (0.6)	0 (0.0)	4 (2.3)
Rash erythematous	2 (0.7)	3 (1.9)	0 (0.0)	4 (2.3)
Special Senses Other Disorders	26 (9.0)	32 (20.5)	34 (12.5)	34 (19.5)
Taste Perversion	25 (8.6)	31 (19.9)	34 (12.5)	34 (19.5)
Urinary System Disorders	7 (2.4)	2 (1.3)	6 (2.2)	5 (2.9)
Haematuria	5 (1.7)	0 (0.0)	6 (2.2)	1 (0.6)
WBC & Resistance Disorders	4 (1.4)	3 (1.9)	2 (0.7)	1 (0.6)
Leukopenia	3 (1.0)	2 (1.3)	1 (0.4)	1 (0.6)

[a] In the non-US studies, H 199/18 was administered as 20 mg bid and eradication therapy was 7 days.

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H. Race

1. US Phase III Studies

A summary of the most common AEs (≥ 3 patients in any treatment group) is presented by race for the US Phase III studies in Table 12. In the US Phase III studies, the following discussion focuses on Caucasian and Black patients in the HAC and HC groups since there were too few patients in any of the other groups to draw any meaningful conclusions.

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

Clinical Reviewer's Comment: There are too few patients in the Asian and Other subgroups to attempt any conclusions about race-related adverse events.

TABLE 12
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Race: US Phase III Studies

Body System Preferred Term	US Studies (191, 192, and 193) Treatment Group [a] [Number of Patients (%)]											
	HAC				HC				H			
	C (N=256)	B (N=80)	A (N=7)	O (N=5)	C (N=202)	B (N=81)	A (N=15)	O (N=3)	C (N=26)	B (N=14)	A (N=3)	O (N=2)
Total Patients with at Least One AE	151 (59.0)	33 (41.3)	2 (28.6)	3 (60.0)	114 (56.4)	42 (51.9)	9 (60.0)	2 (66.7)	11 (42.3)	8 (57.1)	0 (0.0)	2 (100)
Body as a Whole	15 (5.9)	4 (5.0)	0 (0.0)	0 (0.0)	15 (7.4)	5 (6.2)	0 (0.0)	1 (33.3)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)
Accident and/or injury	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	4 (1.6)	1 (1.3)	0 (0.0)	0 (0.0)	4 (2.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)
Central and Peripheral Nervous System	27 (10.5)	6 (7.5)	1 (14.3)	1 (20.0)	22 (10.9)	10 (12.3)	3 (20.0)	1 (33.3)	0 (0.0)	1 (7.1)	0 (0.0)	1 (50.0)
Dizziness	10 (3.9)	0 (0.0)	0 (0.0)	1 (20.0)	8 (4.0)	1 (1.2)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	18 (7.0)	4 (5.0)	1 (14.3)	1 (20.0)	14 (6.9)	9 (11.1)	3 (20.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (50.0)
Gastrointestinal System Disorders	110 (43.0)	19 (23.8)	2 (28.6)	2 (40.0)	75 (37.1)	28 (34.6)	7 (46.7)	2 (66.7)	9 (34.6)	4 (28.6)	0 (0.0)	1 (50.0)
Abdominal pain	14 (5.5)	2 (2.5)	0 (0.0)	1 (20.0)	9 (4.5)	3 (3.7)	2 (13.3)	1 (33.3)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)
Constipation	5 (2.0)	1 (1.3)	0 (0.0)	0 (0.0)	8 (4.0)	0 (0.0)	2 (13.3)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	1 (50.0)
Diarrhea	27 (10.5)	6 (7.5)	1 (14.3)	1 (20.0)	16 (7.9)	5 (6.2)	5 (33.3)	1 (33.3)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)
Duodenitis [b]	12 (4.7)	4 (5.0)	0 (0.0)	0 (0.0)	6 (3.0)	3 (3.7)	0 (0.0)	0 (0.0)	1 (3.8)	1 (7.1)	0 (0.0)	0 (0.0)
Dyspepsia	7 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.0)	2 (2.5)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Epigastric pain	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	7 (2.7)	1 (1.3)	0 (0.0)	0 (0.0)	3 (1.5)	3 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis [b]	36 (14.1)	8 (10.0)	0 (0.0)	0 (0.0)	22 (10.9)	9 (11.1)	0 (0.0)	0 (0.0)	6 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal system disorders, NOS	2 (0.8)	2 (2.5)	0 (0.0)	0 (0.0)	1 (0.5)	3 (3.7)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mouth dry	3 (1.2)	1 (1.3)	0 (0.0)	0 (0.0)	5 (2.5)	2 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	10 (3.9)	3 (3.8)	0 (0.0)	0 (0.0)	9 (4.5)	7 (8.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophagitis [b]	22 (8.6)	0 (0.0)	1 (14.3)	0 (0.0)	16 (7.9)	3 (3.7)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	5 (2.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

C = Caucasian, B = Black; A = Asian; O = Other

[a] In the US studies, H199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.

[b] AEs observed during EGD.

TABLE 12 (Continued)
Most Common (≥ 3 Patients in Any Group) Adverse Events by Body System, Preferred Term, and Race: US Phase III Studies

Body System Preferred Term	US Studies (191, 192, and 193) Treatment Group [a] [Number of Patients (%)]											
	HAC				HC				H			
	C (N=256)	B (N=80)	A (N=7)	O (N=5)	C (N=202)	B (N=81)	A (N=15)	O (N=3)	C (N=26)	B (N=14)	A (N=3)	O (N=2)
Liver and Biliary System Disorders	8 (3.1)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzymes increased, NOS	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SGPT increased	5 (2.0)	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal System Disorders	12 (4.7)	2 (2.5)	0 (0.0)	0 (0.0)	5 (2.5)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hernia [c]	7 (2.7)	1 (1.3)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric Disorders	14 (5.5)	4 (5.0)	0 (0.0)	1 (20.0)	10 (5.0)	1 (1.2)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resistance Mechanism Disorders	7 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (1.2)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Moniliasis	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory System Disorders	14 (5.5)	1 (1.3)	0 (0.0)	2 (40.0)	13 (6.4)	3 (3.7)	1 (6.7)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (50.0)
Respiratory infection	8 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	3 (3.7)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinitis	5 (2.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)
Skin and Appendage Disorders	8 (3.1)	1 (1.3)	0 (0.0)	1 (20.0)	12 (5.9)	3 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	3 (1.2)	1 (1.3)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Special Senses Other Disorders	19 (7.4)	4 (5.0)	0 (0.0)	1 (20.0)	17 (8.4)	9 (11.1)	4 (26.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taste perversion	18 (7.0)	4 (5.0)	0 (0.0)	1 (20.0)	17 (8.4)	9 (11.1)	4 (26.7)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary System Disorders	8 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	1 (1.2)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)

C = Caucasian, B = Black; A = Asian; O = Other

[a] In the US studies, H199/18 was administered as 40 mg qd and the duration of eradication therapy was 10 days.

[c] Hiatal hernia observed during EGD.

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2. Non-US Phase III Studies

Clinical Reviewer's Comment: In the non-US Phase III studies, there were too few patients in race categories of Black (n= 7) and Asian (n=4) to draw any meaningful conclusions about potential race-related effects. No subjects were enrolled in the Other category. Therefore, the non-US adverse event data by race is not included in this review.

I. Summary of Subgroup Analyses

Overall, results of the subgroup analyses of AEs by age in both the US and non-US studies generally indicated that elderly patients who receive HAC therapy may be more likely to report GI system AEs than younger patients.

Results of the subgroup analyses for gender indicated that females who received HAC tended to report AEs more frequently than males. In the US Phase III studies, this difference was greatest for GI system AEs and special senses/other disorders. These results suggest that female patients who receive HAC may be more likely to report GI system AEs and special senses/other disorders than male patients. In addition, in both the US and non-US Phase III studies, male patients who received HAC tended to have an increased incidence of liver and biliary system disorders compared to female patients, although the overall incidence was relatively low.

In the subgroup analyses by race, some differences were observed between Caucasian and Black patients in the US Phase III studies; however, these differences are not likely to be clinically relevant.

J. Discontinuations from Study Due to Adverse Events: US Phase III Studies

A summary of the most frequent AEs resulting in discontinuation from study is presented by body system and preferred term for the US Phase III Studies in Table 13. Due to the low number of discontinuations, the criterion for most frequent was lowered from ≥ 3 patients to ≥ 2 patients in any treatment group. In the US Phase III studies, the overall percentage of patients who discontinued from study due to one or more AEs was low, and was generally similar between the HAC and HC groups. Only one patient total discontinued in the H group.

Of the 348 patients in the HAC group, 11 (3.2%) discontinued from study due to one or more AEs. Within this treatment group, the only AEs that led to discontinuation from study for two or more patients included abdominal pain (n=4, 1.1%), nausea (n=3, 0.9%), diarrhea (n=2, 0.6%), and dizziness (n=2, 0.6%).

TABLE 13
Most Frequent (≥ 2 Patients in Any Group) Adverse Events Resulting in Discontinuation From Study by Body System and Preferred Term: US Phase III Studies

Body System [b] Preferred Term	US Studies (191, 192, and 193) Treatment Group [a] [Number of Patients (%)]		
	HAC (N=348)	HC (N=301)	H (N=45)
Total Number of Patients Who Discontinued From Study	11 (3.2)	11 (3.7)	1 (2.2)
Central and Peripheral Nervous System	3 (0.9)	4 (1.3)	0 (0.0)
Dizziness	2 (0.6)	1 (0.3)	0 (0.0)
Headache	1 (0.3)	2 (0.7)	0 (0.0)
Gastrointestinal System Disorders	11 (3.2)	8 (2.7)	0 (0.0)
Abdominal pain	4 (1.1)	1 (0.3)	0 (0.0)
Diarrhea	2 (0.6)	1 (0.3)	0 (0.0)
Dyspepsia	0 (0.0)	3 (1.0)	0 (0.0)
Nausea	3 (0.9)	1 (0.3)	0 (0.0)

[a] In the US studies, H 199/18 was administered as 40 mg qd and eradication therapy was 10 days.
[b] Patients may have discontinued for more than one of the individual AEs within each body system. These patients are included once in the count for each individual AE they reported, but are counted only once in the overall total by body system.

K. Discontinuations from Study Drug Due to Adverse Events: Non-US Phase III Studies

A listing of patients who discontinued study drug in the non-US Phase III studies is presented below in Table 14. In the non-US Phase III studies, the percentage of patients who discontinued from study drug due to an AE was 5/446 (1.1%) in the HAC group. Three of the 446 patients (0.7%) discontinued due to diarrhea.

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TABLE 14
All Patients Discontinued from Study Drug Due to Adverse Events: Non-US Phase III Studies

Study No./Site/ Patient No.	Gender/Age (yrs.)	Rel. Day of Onset	Adverse Event	Dur. (Days)	Intensity	Drug Rel.[a]	Serious	Last Day of Study Med.
Non-US Phase III Studies (SH-QBE-0019 and 0020)								
HAC								
0019/003/566	F/57	6	Rash	> 1	Mod.	NA	No	6
0019/005/543	M/42	3	Diarrhea	> 3	Mod.	NA	No	5
0019/021/175	F/52	2 3	Dizziness Diarrhea	> 1 Unk.	Sev. Sev.	NA NA	No No	2 2
0019/050/262	M/28	2	Diarrhea	> 1	Mild	NA	No	2
0020/030/279	F/49	1 1	Vomiting Taste perversion	3 3	Sev. Mod.	NA NA	No No	2 2
OAC								
0019/021/169	F/60	3 3	Diarrhea Taste Perversion	> 2 > 2	Mod. Mod.	NA NA	No No	4 4
0019/043/118	F/58	1 1 1	Anxiety Palpitation Tinnitus	3 3 3	Mild Mild Mild	NA NA NA	No No No	3 3 3
0019/061/342	F/79	2	Rash erythematous	> 1	Sev.	NA	No	2
0019/076/427	M/42	4	Headache	> 2	Sev.	NA	No	5
0020/010/011	F/49	3	Rash	3	Mild	NA	No	3
0020/012/056	F/50	2	Dysmenorrhea	4	Mod.	NA	No	4
0020/015/127	F/50	1	Allergic reaction	5	Mod.	NA	No	3
0020/025/532	M/68	1	Cerebrovascular disorder	1	Sev.	Unlike.	Yes	1
0020/010/018	M/55	16	Hematuria	> 1	Mild	Unlike.	Yes	9
0020/038/300	M/47	27	Appendicitis	> 1	Sev.	Unlike.	Yes	20

[a] Drug relationship was determined only for SAEs in the non-US studies.

L. Deaths

Of the 1,586 patients who participated in the Phase III studies, two deaths occurred (0.1%). The following are narratives for these two patients.

Patient Number 200/001 (AN 2045): An 80 year old female was randomized to HC for 10 days in Study 192. On Study Day 8, the patient experienced cardiac arrest and expired. The investigator indicated that "apparently she died in her sleep as a result of cardiac arrest". An autopsy was not performed. The patient had a history of arteriosclerosis, hypertension and right hip replacement. Concomitant medications included nifedipine, potassium chloride, and hydrochlorothiazide 25mg/triamterene 37.5mg. The investigator indicated that the patient's death was unlikely to be related to the study drug.

Patient Number 002/581 (SH-QBE-0019): An 82 year old male received OAC for 7 days. The patient entered the study with a history of congestive heart failure, ischemic heart

disease, pacemaker, renal failure, and generalized edema. The patient was hospitalized for chest discomfort 32 days after completing treatment. Emergency blood results revealed markedly low postassium (2.8 mmol/L). The patient failed to respond to intravenous therapy and was admitted for further treatment of hypokalemia. The patient recovered after 4 days. Concomitant medication included allopurinol, codeine phosphate, ethacrynic acid, metolazone, and cefuroxime axetil. Fifty days after last intake of study drug, the patient died unexpectedly at home. No autopsy was performed. Concomitant medication was allopurinol, codein phosphate, ethacrynic acid, potassium chloride, and metolazone. The investigator assessed causal relationship to study drug as unlikely.

Clinical Reviewer's Comment: Agree with the investigators' assessments. It is unlikely that these two deaths were related to study drug.

M. Non-Fatal Serious Adverse Events

In the US Phase III studies, the incidence of non-fatal SAEs was low (see Table 15) and was generally similar across the three treatment groups (HAC: 2 of 348, 0.6%; HC: 2 of 301, 0.7%; and H: 1 of 45, 2.2%). All SAEs in the US Phase III studies were evaluated as unlikely to be related to study drug according to the investigators.

In the non-US Phase III studies, 9 of 446 (2.0%) patients in the HAC group and 7 of 446 (1.6%) patients in the OAC group experienced a non-fatal SAE (see Table 16). All of the SAEs in the non-US Phase III studies were evaluated as unlikely to be related to study drug by the investigator or applicant with the exception of one patient in the HAC group who experienced transient and non-symptomatic elevations in liver enzymes (SGPT, SGOT, and alkaline phosphatase) 68 days after the last dose of study drug had been taken. The investigator assessed a causal relationship to study drug as possible, as he would not exclude a possible delayed hepatic reaction to study drug.

Clinical Reviewer's Comment: Table 15 has been condensed by the reviewer from a similar table submitted by the applicant in the NDA.

TABLE 15
Patients with Non-Fatal Serious Adverse Events: US Phase III Studies

Study No./Site/ Patient No./ AN	Gender/ Age (yrs)	Adverse Event	Drug Rel.	Comment
HAC				
191/040/003/1607	F/43	Renal dysfunction (aggravated)	Unlikely	On Day -2, the baseline creatinine level was 2.8 mg/dL and the BUN level was 18 mg/dL. On Day 12, the creatinine level was 4.0 mg/dL and the BUN level was 38 mg/dL. On Day 13, the patient was seen in a renal clinic where she was diagnosed with diabetic nephropathy attributed to having diabetes for 20 years.
191/053/006/1858	M/67	Anxiety Dementia	Unlikely Unlikely	On Day 9, study medication was discontinued when the patient was hospitalized for generalized anxiety disorder and vascular dementia. Magnetic resonance imaging (MRI) of the brain was performed on Day 12 to evaluate the mental status of the patient. Results of the MRI showed periventricular white matter disease and vessel disease but no acute stroke.
HC				
191/025/001/1253	F/71	Gastric carcinoma	Unlikely	The patient had completed the study on Day 37 after taking all doses of study medication. On Day 37, the patient underwent an endoscopy per protocol with gastric biopsies containing fragments from the gastric mucosa. The endoscopy revealed one abnormal fold in the antrum and the persistence of an active DU. Results from the gastric biopsies were received on Day 56 and revealed a moderately to poorly differentiated adenocarcinoma, however, this was not clinically consistent with endoscopic appearance or the patient's clinical signs or symptoms. On Day 119, an endoscopic ultrasound was performed and biopsies of the DU and the antrum of the stomach revealed fragments of well-differentiated adenocarcinoma.
191/075/006/1518	M/55	Cellulitis skin	Unlikely	On Day 25, the patient experienced cellulitis of the right hand secondary to a scratch received from a cat on Day 20 of the study. On Day 26, the patient's condition worsened and he was admitted to the hospital. The patient received treatment and was discharged from the hospital on Day 28 of the study.
H				
193/324/007/3099	F/34	Placenta disorder	Unlikely	On Day 38, the patient tested positive to a urine pregnancy test. On Day 52, the pregnancy was confirmed by a serum pregnancy test at the study site. The patient discontinued the study on Day 52 due to the pregnancy. During the patient's seventh month of pregnancy, she was diagnosed with the serious adverse event of placenta previa. On 20 December 1998 (Day 229), she delivered an infant male via Cesarean section due to placenta previa.

TABLE 16
Patients with Non-Fatal Serious Adverse Events: Non-US Phase III Studies

Study No./Site/ Patient No./ AN	Gender/ Age (yrs)	Adverse Event	Drug Rel.	Comment
		HAC		
0019/022/188	M/84	Arthralgia	Unknown	The patient entered the study with a history of arthritis and was hospitalized due to deterioration of hip pain 48 days after completing treatment. A causal relationship to previous study medication was assessed as unlikely by the sponsor's medical advisor. There was no causality assessment by the investigator.
0019/031/001	M/48	Haemorrhage rectum SGOT increased SGPT increased	Unlikely Unlikely Unlikely	The patient was hospitalized due to rectorrhagia and elevated ASAT and ALAT values 47 days after completing treatment. The patient had moderate rectorrhagia preceded by spontaneously regressive diarrhea. Total colonoscopy was normal and anoscopy showed hemorrhoids. Test results on the day of onset were ASAT = 310 IU/L (reference range 5 - 40) and ALAT = 254 IU/L (ref. range 5 - 45). The rectal bleeding resolved after 2 days and the ASAT and ALAT values were normalized after 5 and 12 days, respectively.
0019/036/024	M/52	Polyneuritis aggravated	Unlikely	The patient entered the study with a history of polyneuritis in legs. The patient was hospitalized for a check-up due to aggravation of polyneuritis 11 days after completing treatment.
0019/047/138	F/33	Psychosis	Unlikely	The patient was hospitalized due to acute symptomatic psychosis 3 days after completing treatment. The patient had symptoms of confusion, restlessness, and delusional ideas. She was completely recovered after 27 days.
0019/047/143	M/40	Angina pectoris	Unlikely	The patient entered the study with a history of myocardial infarction, PTCA, and coronary insufficiency. The patient experienced angina pectoris of moderate intensity on 19 days after completing treatment. The patient was hospitalized the same day. An ECG ruled out myocardial infarction. The patient was completely recovered after 11 days.
0019/047/145	M/72	Tachycardia	Unlikely	The patient experienced tachycardia 31 days after completing treatment. The patient was hospitalized the same day with a heart rate of 198 beats/min and was completely recovered 2 days later.
0019/065/363	M/61	Pneumonia	Unlikely	The patient was hospitalized for pneumonia 9 days after completing treatment with H 20 bid + A + C. X- ray examination was performed. The patient was completely recovered after 20 days.
0019/067/374	F/66	Angioedema	Unlikely	She was hospitalized for Quincke's edema with swollen lip and tongue 60 days after completing treatment. The patient was observed over one night and the symptoms disappeared. Two days later, mild identical symptoms recurred, and then resolved spontaneously after one day.

TABLE 16 (continued)
Patients with Non-Fatal Serious Adverse Events: Non-US Phase III Studies

Study No./Site/ Patient No./ AN	Gender/ Age (yrs)	Adverse Event	Drug Rel.	Comment
HAC (continued)				
0019/072/403	M/77	SGOT increased SGPT increased Phosphatase alkaline increased	Possible Possible Possible	The patient was found to have abnormal liver enzyme values 68 days after completing treatment with H 20 bid + A + C (Visit 4). At this time, the values were ASAT = 386 U/ L (ref. range < 39 U/L); ALAT = 779 U/L (ref. range < 39 U/L); and alkaline phosphatase (ALP) = 138 U/L (ref. range 31 - 121 U/L). The values were all within normal ranges at Baseline (Visit 1) and on follow-up (Visit 3) one month after completion of H 20 bid + A + C. (No assessments were available from Visit 2.) On repeat assessment 8 days later, the values had gone down but were still above normal ranges (ASAT = 90 U/L, ALAT = 261 U/L and ALP = 134 U/L). An ultrasound of the liver and gallbladder was done and was found to be normal. Another 5 weeks later, the patient was reported to be recovered. According to the investigator the patient had been feeling well during the whole study and afterwards. The investigator assessed causal relationship to study drug as possible, as he would not exclude a possible delayed hepatic reaction to previous study medication.
OAC				
0019/002/581	M/82	Hypokalemia	Unlikely	The patient entered the study with a history of congestive heart failure, ischemic heart disease, pacemaker, renal failure, and generalized edema. The patient was hospitalized for chest discomfort 32 days after completing treatment. Emergency blood results revealed markedly low postassium (2.8 mmol/L). The patient failed to respond to intravenous therapy and was admitted for further treatment of hypokalemia. The patient recovered after 4 days. However, Fifty days after last intake of study drug, the patient died unexpectedly at home. No autopsy was performed.
0019/065/459	M/78	Cerebrovascular Disorder	Unlikely	The patient experienced dizziness and temporarily reduced vision in the left eye, on the third day of treatment. The patient was hospitalized and the symptoms resolved after 6 days. The final diagnosis of the event was stroke.
0019/065/488	F/54	Anxiety	Unlikely	The patient entered the study with current anxiety. The patient was hospitalized 14 days after completing treatment, due to exacerbation of anxiety caused by the death of a relative. The patient's condition stabilized during the hospital stay without extra medical treatment and she was discharged recovered after 3 weeks.

TABLE 16 (continued)
Patients with Non-Fatal Serious Adverse Events: Non-US Phase III Studies

Study No./Site/ Patient No./ AN	Gender/ Age (yrs)	Adverse Event	Drug Rel.	Comment
OAC (continued)				
0020/010/018	M/55	Hematuria	Unlikely	The patient entered the study with a medical history of chronic active hepatitis, jaundice, mild ascites, cholelithiasis, nephrolithiasis, and hypertension. The patient was hospitalized 9 days after completing treatment with OAC (at this time the patient was receiving omeprazole 20 mg qd). The patient experienced dizziness and overt hematuria. Abdominal ultrasonography revealed nephrolithiasis and lithiasis of the urinary bladder. The patient probably had cirrhosis of the liver that could be controlled conservatively. No operation was contemplated. The study drug was stopped when the AE occurred and commercial omeprazole was started. The patient was completely recovered after 5 days.
0020/022/433	F/50	Uterine Fibroid	Unlikely	The patient was admitted to the gynecology ward due to symptoms of vaginal bleeding and fever diagnosed as uterine myomata and urinary tract infection 11 days after completing treatment. After excochleation of the uterine cavity and conservative treatment, the symptoms disappeared.
0020/025/532	M/68	Cerebrovascular disorder	Unlikely	The patient experienced an episode of cerebral ischemia on the afternoon of his first day of treatment. The patient was admitted to the neurology ward. Examinations including a CT scan of the brain indicated an acute episode of cerebral ischemia. The following day, echocardiography was performed, revealing a pedunculated mural thrombus in the left ventricle. Electrocardiograph showed irregular sinus rhythm with traits of past infarction of the anterior wall. Due to pending risk of the thrombus dislodging from the wall, the patient was transferred to the cardiology ward where anticoagulative treatment was administered under constant monitoring. On repeat echocardiography 12 days later, no mural thrombus was seen and the patient was discharged in good general condition, without neurological symptoms and with efficient circulation.
0020/038/300	M/47	Appendicitis	Unlikely	The patient experienced abdominal pain after 19 days on omeprazole 20 mg qd preceded by 7 days treatment with OAC. The following day, the patient had a surgical examination in the morning but was not admitted to hospital since the pain was mild. In the afternoon, a second exam was performed and in the evening the patient was admitted with acute appendicitis and an appendectomy was performed. The patient made a complete recovery. The study drug was stopped when the AE occurred.

N. Pregnancy

One patient was found to be pregnant while participating in Study 193. There were no other known pregnancies in the clinical program for eradication of *H. pylori* in patients with DU disease.

Patient 324/007 (AN 3099): A 34 year old female with an active DU was randomized to H 40 qd for 10 days. The subject completed all doses of study medication. On Day 38, the subject tested positive to a urine pregnancy test. On Day 52, the pregnancy was confirmed by a serum pregnancy test at the study site. The subject discontinued the study on day 52 due to the pregnancy.

During the subject's seventh month of pregnancy, she was diagnosed with the serious adverse event of placenta previa. On [redacted] (Day 229), she delivered an infant male via Cesarean section due to placenta previa. The baby's due date for delivery was [redacted] The baby remained in the hospital until [redacted] (Day 238) due to his low birth weight of 3.62 lbs.

The mother's medical history included a recent urinary tract infection, a history of allergy to milk products, heartburn, and endometriosis that required surgical scrapping. Concomitant therapy during the study included Nitrofurantoin, and pre-natal vitamins. The investigator considered both events to be unlikely related to the study medication.

No further information is available for this patient.

O. Clinical Laboratory Evaluations

Clinical Reviewer's Comment: Clinical laboratory evaluations were conducted in all five Phase III studies; however, only the data from the US Phase III studies are summarized in the applicant's ISS.

1. Laboratory Values Over Time

In the US Phase III studies, there were no clinically meaningful changes from Baseline to the Day 11 visit within or between treatment groups in any of the laboratory parameters analyzed.

In the US Phase III studies, there were no clinically meaningful differences within or between treatment groups in the percentage of patients who experienced abnormal shifts from Baseline to the Day 11 visit, with the possible exceptions of ALAT/SGPT and ASAT/SGOT.

For ALAT/SGPT, a slightly greater percentage of patients in the HAC group shifted from normal at Baseline to above normal at the Day 11 Visit (16 of 301, 5.3%) compared to that observed in the HC (9 of 265, 3.4%) and H (1 of 42, 2.4%) groups.

Clinical Reviewer's Comments: All increases in patients with normal Baseline values returned to the normal range by the Day 38 visit for all treatment groups, except for 4 patients in the HAC group. All increases in ALAT/SGPT were minor (< 1.5x ULN) and not felt to be clinically significant.

In Study 191, eighteen patients who received HAC had elevated ALAT/SGPT values at Baseline (all but one were < 3x ULN). These values did not increase on study drug, with the exception of one patient (Patient 083/002 AN 1313) who had a Baseline ALAT/SGPT value of 130 which increased to 372 at Day 11 and went down slightly to 297 at Day 38.

For ASAT/SGOT, a slightly greater percentage of patients in the HAC group shifted from normal at Baseline to above normal at the Day 11 visit (12 of 314, 3.8%), compared to that in the HC group (3 of 279, 1.1%). In the H group, the percentage of patients who experienced a similar shift (2 of 43, 4.7%) was greater than that observed in the HAC group; however, there were a relatively low number of patients in this group.

Clinical Reviewer's Comments: All increases in patients with normal Baseline values returned to the normal range by the Day 38 visit for all treatment groups.

In Study 191, five patients who received HAC had elevated ASAT/SGOT values at Baseline (all were < 2.5x ULN). These values did not increase on study drug, with the exception of one patient (Patient 083/002 AN 1313) who had a Baseline ASAT/SGOT value of 75 which increased to 228 at Day 11 and went down slightly to 216 at Day 38.

The increased incidence of ASAT/SGOT in the HAC group may have resulted from the amoxicillin component of combination therapy, since a moderate rise in ASAT/SGOT has been previously documented with this antibiotic. The clinical relevance of this increase with amoxicillin therapy is not known.

P. Vital Sign And Physical Findings Related to Safety

In the US Phase III studies, there were no clinically meaningful changes in vital sign parameters over time.

Q. Clinical Pharmacology Studies

In both clinical pharmacology studies, the definition of what constituted an AE and coding of AEs were similar to that used for the non-US Phase III studies. An overview of AEs during the study periods and the washouts following each study period is displayed for each clinical pharmacology study in Table 17.

In SH-QBE-0034, the number of subjects with AEs, as well as the number of AEs, were highest during the triple therapy combination and the amoxicillin regimens. Most AEs were of mild or moderate intensity. Two subjects discontinued from the study due to AEs during a washout period and another subject had a non-fatal SAE.

In SH-QBE-0040, the number of subjects who reported AEs was generally similar across the regimens; however, the number of AEs reported was highest during the triple therapy combination regimen. Most AEs were of mild or moderate intensity. None of the subjects discontinued due to an AE, had a non-fatal SAE, or died during the study.

TABLE 17
Overview of Adverse Events: Phase I Clinical Pharmacology Studies

	Study Period Number of subjects during study period [number of subjects during washout period following the study period]							
	H[a]	[WO]	HAC[a]	[WO]	A	[WO]	C	[WO]
SH-QBE-0034								
N	19	[19]	18	[18]	18	[18]	18	[18]
With at least one AE	11	[10]	18	[14]	13	[12]	12	[6]
With a fatal SAE	0	[0]	0	[0]	0	[0]	0	[0]
With a nonfatal SAE	1	[0]	0	[0]	0	[0]	0	[0]
Who stopped drug due to an AE	0	[0]	0	[1]	0	[1]	0	[0]
With AE of severe intensity	1	[1]	3	[1]	1	[1]	0	[1]
Number of AEs recorded	19	[12]	38	[23]	32	[27]	23	[12]
SH-QBE-0040								
N	20	[20]	19	[19]	19	[19]	20	[20]
With at least one AE	12	[5]	12	[11]	10	[8]	9	[9]
With a fatal SAE	0	[0]	0	[0]	0	[0]	0	[0]
With a nonfatal SAE	0	[0]	0	[0]	0	[0]	0	[0]
Who stopped drug due to an AE	0	[0]	0	[0]	0	[0]	0	[0]
With AE of severe intensity	2	[2]	1	[0]	0	[2]	3	[1]
Number of AEs recorded	13	[6]	24	[18]	13	[10]	11	[12]

WO = washout period
[a] H 199/18 was administered as 40 mg qd in SH-QBE-0034 and as 20 mg bid in SH-QBE-0040.

1. Adverse Events by Preferred Term

A summary of the most common AEs (reported by more than one subject in any study period or washout period) is presented for the clinical pharmacology studies in Table 18. In this table, AEs are ordered from most to least frequent in the triple therapy combination regimen for each study.

In both clinical pharmacology studies, diarrhea, taste perversion, flatulence, and headache were the most frequently reported AEs. In general, these AEs occurred most frequently during the triple therapy combination, amoxicillin, and/or clarithromycin regimens, and are known side effects of antibiotics.

In SH-QBE-0034, severe AEs were reported for three subjects during active treatment. One subject (Subject 12) experienced a severe and serious anal abscess during the H 40 qd regimen. Subject 1 experienced a severe vasovagal reaction lasting for 3 minutes during triple therapy combination, and Subject 17 reported severe vomiting during the amoxicillin regimen.

In SH-QBE-0040, six subjects had severe AEs during active treatment. Two subjects (Subjects 19 and 20) reported severe headache during the H regimen, and one subject

(Subject 2) reported severe vomiting during triple therapy combination. During the clarithromycin period, a fractured clavicle, headache, and taste perversion were reported as severe (Subjects 4, 8, and 13, respectively).

TABLE 18
Most Common (Reported by ≥ 2 Subjects) Adverse Events by Preferred Term: Phase I Clinical Pharmacology Studies

Study	Study Period Number of subjects with an AE during study period [number of subjects with an AE during the washout period following the study period]							
Adverse Event (Preferred Term)	H[a]	[WO]	HAC[a]	[WO]	A	[WO]	C	[WO]
SH-QBE-0034								
N	19	[19]	18	[18]	18	[18]	18	[18]
Diarrhoea	0	[1]	10	[5]	5	[2]	2	[1]
Taste perversion	0	[0]	6	[3]	1	[1]	4	[2]
Flatulence	1	[0]	4	[1]	4	[1]	2	[0]
Headache	2	[1]	2	[2]	5	[6]	3	[1]
Fatigue	1	[1]	2	[1]	1	[1]	1	[0]
Intestinal hypermotility	0	[0]	2	[0]	0	[0]	1	[0]
Anemia	1	[1]	2	[2]	1	[1]	1	[1]
Nausea	2	[0]	2	[0]	2	[2]	0	[0]
Abdominal pain	2	[0]	1	[1]	1	[1]	1	[0]
Respiratory infection	1	[2]	0	[1]	0	[1]	1	[0]
Dizziness	1	[0]	0	[0]	1	[0]	2	[0]
SH-QBE-0040								
N	20	[20]	19	[19]	19	[19]	20	[20]
Diarrhoea	0	[1]	5	[4]	2	[2]	1	[1]
Taste perversion	0	[0]	5	[1]	0	[0]	4	[1]
Flatulence	2	[0]	3	[1]	1	[1]	1	[1]
Headache	6	[0]	2	[2]	3	[1]	1	[2]
ALAT (SGPT) increased	0	[0]	2	[2]	1	[0]	2	[2]
Thrombocytopenia	2	[1]	1	[1]	0	[0]	0	[0]
Respiratory infection	0	[0]	0	[0]	2	[2]	0	[1]
Dysmenorrhea	0	[1]	0	[0]	0	[0]	0	[2]
Rash	0	[0]	0	[2]	0	[0]	0	[0]

WO = washout

[a] H 199/18 was administered as 40 mg qd in SH-QBE-0034 and as 20 mg bid in SH-QBE-0040.

2. Discontinuations Due to Adverse Events

None of the subjects in SH-QBE-0040 discontinued due to one or more AEs. In SH-QBE-0034, two subjects discontinued due to an AE. Subject 10, a 21-year-old male with no relevant medical history, was treated with amoxicillin, 1000 mg bid for 7 days. Two days after the last intake of amoxicillin, the subject experienced an erythematous rash and discontinued from the study. The rash resolved 19 days later.

Subject 16, a 25 year old male, with no relevant medical history, was treated with the triple therapy combination for 7 days. Two days after the last intake of the triple therapy combination, the subject experienced exanthema and discontinued from the study. The subject completely recovered 7 days later.

3. Serious Adverse Events

No subject died during the course of either clinical pharmacology study. In addition, only one subject (Subject 12 in Study SH-QBE-0034) experienced a non-fatal SAE. This 39-year-old female with a medical history of anal abscess (surgery 5 months earlier showed granuloma) complained of anal discomfort on the first day of H 40 qd. The subject experienced increased pain and palpable abscess the following day. She was admitted to the surgical department for incision and drainage after a further 2 days. The subject was given morphine, dixyrazine, and ketobemidone hydrochloride. Treatment with study drug continued unchanged. At the time of the last contact, the subject felt well and was awaiting surgery. The investigator assessed the causality between study drug and event as unlikely.

4. Clinical Laboratory Results

In both clinical pharmacology studies, isolated changes both within and outside the reference ranges were found for most of the laboratory parameters (hematology and blood chemistry). In addition, some subjects had laboratory abnormalities reported as AEs; however, the laboratory findings did not raise any safety concerns in either study.

R. Conclusions

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

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

- Although the safety data from the non-US studies was not pooled with the US studies, the results were supportive of each other.

- In the non-US studies, there were no clinically meaningful differences between the HAC group and the OAC group in the incidence of any AE.

- In both the US and non-US studies, the overall percentages of patients who discontinued due to an AE or experienced a non-fatal SAE were low. There were no

clinically meaningful differences among treatment groups in the rate of discontinuations due to AEs or non-fatal SAEs. Not unexpectedly, for patients who received HAC or HC, discontinuations due to AEs most frequently involved the GI system.

- Only two deaths occurred in the clinical program for H 199/18. Both deaths were unlikely to be related to study drug.

- Results of the subgroup analyses of AEs by demographic and baseline characteristics showed that:

  - elderly patients who receive HAC may be more likely to report GI side effects compared to younger patients.
  - female patients who receive HAC may be more likely to report GI side effects and special senses/other disorders than males, and males may be more likely to have liver and biliary system disorders than females, although the overall incidence was relatively low.
  - Caucasian patients who receive HAC may be more likely to report GI side effects compared to Black patients.

  Pediatric patients (< 18 years) and patients with renal or hepatic impairment were specifically excluded from these studies, therefore it is not possible to comment on the AE profile in these populations.

- In the US Phase III studies, there were no clinically meaningful changes from Baseline to the Day 11 visit within or between treatment groups in any of the laboratory parameters analyzed, with the possible exception of ALAT/SGPT and ASAT/SGOT. For both of these parameters, a slightly greater percentage of patients in the HAC group experienced elevations in these liver enzymes when compared to the HC group. A moderate increase in ASAT/SGOT has been observed with amoxicillin. The clinical relevance of these changes is not known.

- In the US Phase III studies, there were no clinically meaningful changes within or between treatment groups in any vital sign parameters analyzed.

XI. Dosing and Administration Issues

Esomeprazole was studied at a dose of 40 mg once daily for the eradication of *H. pylori*. In studies for other GI indications (healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic GERD), a dose of 20 mg was found to be equivalent to 40 mg in terms of the degree of acid suppression.

Clinical Reviewer's Comment: Based on MO's review for NDA 21-153.

Use of higher dose for eradication of *H. pylori* is consistent with how the other approved PPIs are labeled. The *H. pylori* indicated doses of omeprazole and lansoprazole are higher than the traditional GI indications, excluding [redacted] for purposes of this discussion. Omeprazole is dosed 20 mg twice daily in combination with amoxicillin and clarithromycin and 40 mg once daily in combination with clarithromycin for eradication of *H. pylori*. The dose of omeprazole is 20-40 mg once daily for other GI indications (see table below). Lansoprazole is dosed 30 mg three times daily in combination with amoxicillin and 30 mg twice daily in combination with amoxicillin and clarithromycin for eradication of *H. pylori*. The dose of lansoprazole is 15-30 mg once daily for other GI indications (see table below).

Approved Doses of Omeprazole and Lansoprazole for Various GI Indications*

Omeprazole		Lansoprazole	
20 mg QD	**40 mg QD**	**15 mg QD**	**30 mg QD**
Treatment of active duodenal ulcer	Treatment of active gastric ulcer	Treatment of active duodenal ulcer and maintenance of healing	Treatment of active gastric ulcer
Treatment of symptomatic GERD and erosive esophagitis		Treatment of symptomatic GERD	Treatment of erosive esophagitis
Maintenance of healing of erosive esophagitis		Maintenance of healing of erosive esophagitis	

*excluding [redacted]

The mechanism of action of PPIs in the treatment of *H. pylori* is believed to be more complex than just inhibition of acid suppression.

- Co-administration of a PPI with antimicrobials appears to enhance the action of the antimicrobials by several possible mechanisms. PPIs have direct antimicrobial activity against *H. pylori in vitro* by inhibiting bacterial urease. Inhibition of this enzyme can decrease the bacteria's ability to colonize the gastric mucosa.

- The decrease in gastric acidity produced by PPIs may reduce the degradation of acid-labile antimicrobials, such as amoxicillin, and also enhance eradication of the organism. In addition, an increased pH is a less suitable environment for growth of *H. pylori*.

- Finally, *H. pylori* affects the magnitude of acid inhibition produced by PPIs. Omeprazole has been shown to produce greater acid suppression in infected subjects than in uninfected controls and duodenal ulcer patients.

In summary, approval of the 40 mg dose of esomeprazole in combination with antimicrobials for eradication of *H. pylori* is consistent with other approved PPIs for this indication and appears warranted based on what is known of the pharmacology of this infection.