This multi-center, double blind, double dummy, randomized, stratified, parallel group study was designed to compare four *H. pylori* eradication regimens in approximately 790 planned patients (803 actually enrolled) with confirmed *H. pylori* infection. Patients were randomized into four treatment groups, with 1:1 stratification of peptic ulcer disease (PUD) patients and non-peptic ulcer disease (NPUD) patients who had undergone clinically indicated upper gastrointestinal endoscopy because of gastrointestinal symptoms and/or findings on physical examination.

Clinical Reviewer's Comment: Upon review of the pre-IND submission, the applicant was advised that the proposed study should stratify (1:1) patients with H. pylori-associated peptic ulcer disease (i.e., current ulcer or history within the past 5 years) [termed PUDs] with H. pylori-associated symptomatic patients with non-peptic ulcer disease [termed NPUDs] and that the study should be powered such that the lower-bound 95% confidence limit of the point estimate is above 60%. Previously only patients with peptic ulcer disease (current ulcer or history within the past 5 years) were considered evaluable for efficacy in pivotal studies designed to support approval of the indication: eradication of H. pylori infection to reduce the recurrence of duodenal ulcer disease. It is not known if patients with symptomatic non-ulcer disease can be used to accurately estimate eradication rates for patients with ulcer disease. If, in the proposed study, NPUD patients have higher eradication rates than PUD patients, inclusion of this sub-population in the efficacy analysis may dilute the effect of the drug therapy in the population for whom it is intended (i.e., ulcer patients).

Therefore, the applicant was advised that eradication rates for patients with PUD and NPUD should be evaluated independently. If eradication rates for PUD patients are considered clinically higher (i.e. upper bound 95% confidence limit of the difference in eradication rates [NPUD – PUD] of greater than 10% using an analysis which compares all H. pylori infected patients enrolled regardless of treatment) pooling will not be considered appropriate. In this case, demonstration of efficacy will rely only on patients with PUD and the lower-bound 95% confidence limit of the point estimate in this population should be greater than 60%. If similar or lower eradication rates are found for NPUD patients then eradication rates may be pooled. In this case, the lower-bound 95% confidence limit for the point estimate should be above 60% and the 95% confidence limit of the difference (RAC minus OAC) should be greater than –15%.

This study consisted of a screening period, a treatment period of 10 days, an end-of-treatment visit during 1-5 days post-treatment, and a post-treatment assessment at least six weeks after completion of the treatment period. The ^{13}C-urea breath test (UBT) was used to determine the presence or absence of *H. pylori* infection at the post-treatment visit ≥ 6 weeks following the end of treatment (primary efficacy variable).

Clinical Reviewer's Comment: Previously, applicants were required to perform two follow-up UBTs, one at 4 weeks and the other at 8 weeks following the end of treatment and both tests had to be negative in order for the patient to be evaluable in the Per Protocol population. If both tests were negative, no further follow-up was necessary. If at least one of the UBTs was positive, the patient was still required to undergo an endoscopy with biopsy collection for culture and susceptibility testing. However, for this submission, the Division agreed with the applicant that a single FDA-approved UBT test at ≥ 6 weeks after the end of treatment is acceptable for the determination of eradication. Patients are still

required to have follow-up endoscopic testing for antimicrobial susceptibility testing if the UBT result is positive.

During the study, the investigator assessed the presence and severity of upper gastrointestinal (GI) symptoms at the Baseline and Day 11-15 visits.

Adverse events (AEs) were recorded throughout the study. Routine laboratory safety tests were performed at Baseline and the Day 11-15 visit.

D. Inclusion Criteria

- Outpatients of either gender, aged 18 or older.
- Upper GI endoscopy clinically indicated because of gastrointestinal symptoms and/or findings on physical examination, positive *H. pylori* antibody and *H. pylori* infection documented by ^{13}C-UBT and one of the following: either Campylobacter-like Organism (CLO) test (rapid urease test) or *H. pylori* culture.
- If female, not of childbearing potential by reason of surgery, radiation, or menopause, or of childbearing potential, but using an approved method of contraception since the last menstrual period, for example, intra-uterine device (IUD), implant, double barrier method, or oral contraceptives for at least one menstrual cycle (plus, in the cycle during which antibiotics are administered, a double barrier device). Females of childbearing potential must have a negative urine pregnancy test before medication is dispensed.
- Provision of written informed consent prior to screening.

E. Exclusion Criteria

- History of definitive acid-lowering surgery or previous esophageal or gastric surgery, except for simple closure of perforated ulcer.
- History of esophageal and/or gastric varices.
- Pyloric stenosis that precluded passage of the endoscope.
- Treatment with full therapeutic doses of histamine H_2-receptor antagonists, prostaglandin analog, or sucralfate within two weeks prior to screening ^{13}C-UBT and screening endoscopy.
- Treatment with a PPI within two weeks prior to screening ^{13}C-UBT and screening endoscopy.
- Any treatment with systemic antibiotics or bismuth-containing compounds within four weeks prior to screening ^{13}C-UBT and screening endoscopy.
- Concurrent treatment with high doses of glucocorticoids (i.e., 20 mg/day of prednisone or equivalent), or extensive topical application of glucocorticoids.
- Concurrent treatment with anticoagulants or antineoplastics.
- Concurrent serious systemic disorders including renal, cardiac, or hepatic insufficiency (including compensated cirrhosis), or human immunodeficiency virus (HIV) disease.
- Treatment for cancer (e.g., chemotherapy, radiation) within the year prior to study entry, except simple excision of basal cell carcinoma.
- Endoscopic evidence of erosive or ulcerative esophagitis (defined as Grade 2 or higher on the modified Henzel Dent scale) or active, hemodynamically significant gastrointestinal bleeding.
- Pregnancy or lactation.

- Proven or suspected hypersensitivity to penicillin, amoxicillin, clarithromycin, omeprazole, or rabeprazole, or any of their inactive ingredients.
- Any condition associated with poor subject compliance (e.g., alcohol abuse, drug abuse), or inability to return for scheduled visits or comply with any other aspect of the protocol.
- Daily use of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase-2 (COX-2) inhibitors, or aspirin, except for low-dose cardiovascular prophylactic treatment (81 mg/day).
- Treatment with any investigational agent within 30 days prior to screening.
- A patient with difficulty ingesting "size "000" capsules.
- A patient who, in the opinion of the Investigator or Sponsor, was a poor medical or psychiatric candidate or for whom therapy with an investigational drug posed an unacceptable risk of injury or other adverse outcome.
- Previous receipt of any *H. pylori* eradication regimen containing amoxicillin or clarithromycin.

F. Patient Removal

Patients were able to discontinue their participation in the study at any time. Investigators were permitted to discontinue a patient from the study because of an adverse experience, an intercurrent illness that might invalidate the study or place the patient at risk, a protocol violation or unreliable behavior, or by request of the investigator or sponsor for administrative or other reasons.

G. Treatments

Eligible patients were randomized in a stratified 1:1 (PUD:NPUD) ratio to receive one of the following four regimens shown in Table 1 below. To preserve the double blind, double-dummy methods were used. Omeprazole, amoxicillin, and clarithromycin were overencapsulated, with matching placebos for each. Rabeprazole was not overencapsulated, but had a matching placebo.

Clinical Reviewer's Comment: Dissolution profiles of overencapsulated omeprazole, amoxicillin, and clarithromycin were compared to commercially available formulations and found to be similar. See Clinical Pharmacology/Biopharmaceutics review for details.

TABLE 1
Study Medication Contained in Each Treatment Regimen

Regimen	Description
RAC-3	rabeprazole 20 mg bid x 3 days amoxicillin 1000 mg bid x 3 days clarithromycin 500 mg bid x 3 days; followed by RAC (matched) placebos x 7 days omeprazole placebo x 10 days
RAC-7	rabeprazole 20 mg bid x 7 days amoxicillin 1000 mg bid x 7 days clarithromycin 500 mg bid x 7 days; followed by RAC (matched) placebos x 3 days omeprazole placebo x 10 days
RAC-10	rabeprazole 20 mg bid x 10 days amoxicillin 1000 mg bid x 10 days clarithromycin 500 mg bid x 10 days omeprazole placebo x 10 days
OAC-10	omeprazole 20 mg bid x 10 days amoxicillin 1000 mg bid x 10 days clarithromycin 500 mg bid x 10 days rabeprazole placebo x 10 days

Patients were instructed to take the medications with morning and evening meals.

H. Concomitant Therapy

Medications that patients were not allowed to take during the following phases of the study are shown in Table 2 below.

TABLE 2
Disallowed Medications by Phase of Study

Screening (Days –21 to 0)	10-Day Treatment Period	Post-Treatment (≥ 6 weeks)
Not allowed within 30 days of screening: • Any investigational agent Not allowed within four weeks of screening ^{13}C-UBT and screening endoscopy: • **Any** systemic antibiotics • Bismuth containing compounds Not allowed within two weeks of screening ^{13}C-UBT and screening endoscopy: • Full therapeutic doses of H_2 receptor antagonists • PPIs • Prostaglandin analog • Sucralfate **Not Allowed During Screening Period** Antineoplastics Anticoagulants **Daily** NSAIDs **Daily** COX-2 Inhibitors **Daily** aspirin (except low dose 81mg/day) Glucocorticoids (high doses) **Extensive** topical glucocorticoids The following antibiotics: Macrolides Tetracyclines Imidazoles Nitrofurans Aminoglycosides Quinolones Rifampin	H_2 receptor antagonists Non-study PPIs Bismuth preparations Antineoplastics Anticoagulants **Daily** NSAIDs **Daily** COX-2 Inhibitors **Daily** aspirin (except low dose 81 mg/day) Glucocorticoids (high doses) **Extensive** topical glucocorticoids The following antibiotics: Macrolides Tetracyclines Imidazoles Nitrofurans Aminoglycosides Quinolones Rifampin	PPIs Amoxicillin Clarithromycin Bismuth preparations Antineoplastics Anticoagulants **Daily** NSAIDs **Daily** COX-2 Inhibitors **Daily** aspirin (except low dose 81 mg/day) Glucocorticoids (high doses) **Extensive** topical glucocorticoids The following antibiotics: Macrolides Tetracyclines Imidazoles Nitrofurans Aminoglycosides Quinolones Rifampin No systemic antibiotics within two weeks prior to the ^{13}C-UBT at 6 weeks.

Low doses of certain disallowed medications (i.e., H_2-receptor antagonists and aspirin) were allowed during certain phases of the study and are listed below in Table 3.

TABLE 3
Allowed Medications by Phase of Study

Screening (Days –21 to 0) Within 2 weeks of ^{13}C-UBT and endoscopy	Screening (Days –21 to 0) After ^{13}C UBT and endoscopy	10-Day Treatment Period	Post-Treatment (≥ 6 weeks)
Only these acceptable doses of H_2-receptor antagonists are allowed within 2 weeks of screening ^{13}C-UBT and screening endoscopy: • Ranitidine < 300 mg/day • Cimetidine ≤ 400 mg/day • Famotidine < 40 mg/day • Nizatidine < 300 mg/day Aspirin 81 mg/day	H_2-receptor antagonists at any therapeutic dose can be used after **both** the screening ^{13}C-UBT and screening endoscopy are performed, BUT must be stopped before randomization. Please note: H_2-receptor antagonists should not be taken the day they start study medication Aspirin 81 mg/day	Rolaids®, up to 6/day Aspirin 81 mg/day	H_2-receptor antagonists allowed at any therapeutic dose Aspirin 81 mg/day

Patients were provided Rolaids® during the 10-day treatment period and instructed to take the tablets as needed per label recommendation for relief of symptoms. Patients were told not to take more than six tablets per day.

I. Efficacy and Safety Assessments

1. Screening (Days –21 to 0)

Patients who fulfilled the inclusion and exclusion criteria completed a screening assessment within 21 days prior to treatment.

Demographic data was collected along with a medical history. A physical examination was performed.

The patient's ability to ingest a size "000" capsule filled with inert material (microcrystalline cellulose) was observed with the patient swallowing one capsule with water.

Blood was collected for the following laboratory determinations:

- *H. pylori* serology: *H. pylori* antibody was tested with the FlexSure® HP serum test Patients with a positive antibody test continued to be screened for study entry.
- Hematology
- Chemistry

A urine sample was obtained for complete urinalysis, including microscopy. A urine pregnancy test was performed in women of childbearing potential, including women who were post-menopausal for less than one year or had a history of tubal ligation.

A ^{13}C-Urea Breath Test [redacted] was performed in patients with positive *H. pylori* antibody test to identify *H. pylori*-infected patients. The breath samples were sent to a central laboratory [redacted] for analysis.

An endoscopy was performed on patients with a positive *H. pylori* antibody test. Biopsies of the stomach (five from the antrum and three from the corpus) were obtained for the following analyses:

- Campylobacter-like Organism (CLO) Test (i.e., rapid urease test): two antral biopsies were taken within 5 cm of the pylorus on the greater curvature and placed into the CLO test gel and inspected for color change within 24 hours.

- Microbiology: one antral and one corpus biopsy were placed into a special transport container stored in a freezer at –20°C and shipped on dry ice to the central laboratory for microbiological analysis. Upon receipt by the central laboratory the biopsies were banked at –70°C until cultured in batches in microaerobic conditions. Gram staining, typical colony morphology, and biochemical properties identified *H. pylori*. Positive *H. pylori* strains were screened for antibiotic susceptibility to the antibiotics clarithromycin and amoxicillin using the agar dilution method of the National Committee for Clinical Laboratory Standards (NCCLS) standardized susceptibility testing procedures. The NCCLS recommended clarithromycin breakpoints for *H. pylori* isolates were used. The amoxicillin breakpoints used were those approved by the FDA and included in other labels for regimens that are used to eradicate *H. pylori*. Table 4 summarizes these testing criteria.

TABLE 4
MIC breakpoints for Amoxicillin and Clarithromycin
For Determining *H. pylori* Susceptibility Status

Susceptibility Status	Amoxicillin	Clarithromycin
Resistant	Not Defined	MIC ≥ 1 µg/mL
Intermediate	Not Defined	MIC = 0.5 µg/mL
Susceptible	MIC ≤ 0.25 µg/mL	MIC ≤ 0.25 µg/mL

- Histology: two antral and two corpus biopsies were placed into two bottles containing formalin (one bottle for the antrum biopsies and one for the corpus biopsies), labeled, and forwarded to the central laboratory for histological analysis. Biopsies were stained with hematoxylin and eosin for gastritis and a modified Giemsa stain for *H. pylori* identification. The histopathologist was blinded to the patient's clinical status, treatment, and other *H. pylori* results.

For those patients with active gastric ulcer, additional biopsies were taken to rule out malignancy. If malignancy was found, the patient was discontinued from the study.

Once sufficient information was available, the Investigator made a gastrointestinal diagnosis reflecting the patient's status at screening. There were no set criteria for making this determination but it was dependent solely on the Investigator's interpretation of the clinical findings.

2. Treatment Period (Days 1 to 10)

Upon completion of screening assessments and within 21 days of the start of the screening period and within 10 days of screening endoscopy, eligible patients were randomly assigned a unique treatment number and received one of four treatment regimens. Although gastric biopsies were processed for culture and susceptibility and examined histologically, only a positive ^{13}C-UBT plus a positive rapid urease test from the gastric biopsies were necessary for study entry.

Patients were stratified in a 1:1 ratio for patients with active PUD or a history of PUD in the past five years (the PUD group) and patients who were symptomatic but without PUD (the NPUD group).

Patients who were stratified to the PUD group included:

- patients with active ulcer ≥ 3 mm in size
- patients with a history of ulcer ≥ 3 mm in size*
- patients with a history of ulcer of unspecified size*
- patients with an active ulcer < 3 mm in size and either
  - history of ulcer ≥ 3 mm in size, or
  - history of ulcer of unspecified size

* A history of PUD within the past five years was documented by an endoscopy report or radiology report.

Patients who were stratified to the NPUD group included:

- patients with no active ulcer and no history of ulcer
- patients with an active ulcer < 3 mm in size and either:
  - no history of ulcer, or
  - history of ulcer < 3 mm in size

3. Visit Days 11 to 15

The Day 11-15 visit included a physical examination, laboratory determinations, assessment of adverse events (AEs) and concomitant medications, symptom assessment, and medication compliance assessment.

Compliance with the prescribed treatment regimen was measured by counting the returned capsules/tablets of study medication. All five pills were measured as one dose. The study monitor to assess compliance collected all unused study medication and empty wallets. Patient diary cards, which contained information on the date and time of dose administration, were collected.

4. Visit ≥ 6 Weeks Post-treatment

Post-treatment assessments were performed at least 6 weeks but not more than 10 weeks after completion of the treatment period. Patients who had taken at least one dose of medication and who had remained in the study had the post-treatment assessment performed.

All patients had a ^{13}C-UBT performed at the post-treatment assessment. If the ^{13}C-UBT was positive, the patient underwent a follow-up endoscopy and biopsies were taken for histology, CLO test (rapid urease test), and microbiology assessments (see screening evaluations, above, for details of the required biopsy samples). These biopsies were used to confirm the presence of *H. pylori* and to assess whether the organism had acquired resistance to the antibiotics used.

Patients with an ulcer at study entry had a repeat endoscopy performed at the post-treatment assessment to document ulcer status. All patients with an unresolved ulcer were to be referred to their personal physician for appropriate therapy.

During the follow-up after the 10-day treatment period, patients continued to be followed by the Investigator until study completion. Additionally, patients were referred to their personal physicians for any further care required for treatment of their conditions, if necessary. During the follow-up period, all adverse events were recorded and blood tests were taken if clinically indicated.

J. Efficacy Assessments

1. Primary Efficacy Parameter

The primary efficacy variable was eradication of *H. pylori*, measured using a ^{13}C-UBT for *H. pylori* at ≥ 42 days (i.e., ≥ 6 weeks) from the end of the treatment. Success was defined as a patient with a negative ^{13}C-UBT for *H. pylori* ≥ 42 days from the end of the treatment. A single negative ^{13}C-UBT at ≥ 42 days from the end of the treatment was considered evidence of eradication of *H. pylori*.

2. Secondary Efficacy Parameters

Secondary efficacy variables were:

- *H. pylori* eradication rates in relation to antibiotic susceptibility, determined from susceptibility testing of *H. pylori* cultured from gastric biopsies to clarithromycin and amoxicillin.
- Compliance, determined by counting the returned capsules/tablets of study medication.
- Safety variables included the incidence of adverse events; the change from screening to end of treatment in physical examination findings, vital signs assessments, and laboratory evaluations, and shifts in laboratory values from normal to abnormal, low, or high levels.

K. Statistical and Analytical Plan

1. Analysis Populations

Patients were assigned to population subsets based on the following criteria. The assignments were reviewed and approved by the applicant before the study blind was broken. Safety patients were used for all safety analyses. Efficacy analyses were performed for both Intent-to-Treat (ITT) and Per Protocol (PP) patients.

Clinical Reviewer's Comment: During protocol development, the Division shared with the applicant the draft Guidance for Industry – "Reduction of Gastric or Duodenal Ulcer

Recurrence by Eradication of H. pylori" (version 9/8/99). This document, although not posted on the FDA website, has been shared with other sponsors developing drugs for H. pylori infection. The definition of the ITT and PP populations and analyses, detailed below, are consistent with the Guidance.

All Randomized Patients
The "All Randomized" population included all patients who were randomized to a treatment regimen, regardless of whether they received any study medication or not.

Safety Patients
The Safety population included All Randomized patients who received at least one dose of study medication.

Intent-to-Treat Patients
The Intent-to-Treat (ITT) population included Safety patients and was defined as follows.

Patients were excluded from the ITT population if the following occurred:
- A negative ^{13}C-UBT for *H. pylori* at screening;
- A missing or not-determined ^{13}C-UBT for *H. pylori* at screening;
- A positive ^{13}C-UBT for *H. pylori* at screening with both a negative, missing, or not-determined culture and a negative, missing, or not-determined rapid urease test at screening.

Patients were included as failures in the ITT population if the following occurred:
- A positive ^{13}C-UBT for *H. pylori* ≥ 42 days from the end of the treatment;
- Two positive ^{13}C-UBT s for *H. pylori* ≥ 42 days from the end of the treatment;
- One positive ^{13}C-UBT for *H. pylori* and one negative ^{13}C-UBT for *H. pylori* at any time after the end of the treatment;
- ^{13}C-UBT for *H. pylori* was not determined, not assessable, or missing at Test-of-Cure Visit (≥ 42 days from the end of the treatment);
- A ^{13}C-UBT for *H. pylori* within 42 days following the end of the treatment without a ^{13}C-UBT for *H. pylori* ≥ 42 days from the end of treatment.

Patients were included as successes in the ITT population if the following occurred:
- A negative ^{13}C-UBT for *H. pylori* ≥ 42 days from the end of the treatment, and no positive ^{13}C-UBT for *H. pylori* at any time after the end of treatment;
- No failure criteria.

Per-Protocol Patients
The Per-Protocol (PP) population included ITT patients and was defined as follows. Protocol deviations were reviewed prior to breaking the blind.

Patients were excluded from the PP population if the following occurred:
- ^{13}C-UBT for *H. pylori* status was not determined, not assessable, or missing at the Test-of-Cure visit;
- Took < 75% (i.e., 15 doses) of all scheduled doses of medication and/or missed > 20% (i.e., four doses) of consecutive doses of the scheduled medication;
- Dropped from the study (without the follow-up endoscopy, when applicable) where the reason for dropout is unrelated to study medication;

- A negative ^{13}C-UBT for *H. pylori* within 42 days following the end of the treatment without a ^{13}C-UBT for *H. pylori* ≥ 42 days from the end of the treatment;
- Received a disallowed medication:
  - any PPI, within 14 days prior to screening ^{13}C-UBT for *H. pylori* and screening endoscopy up to study drug administration, or a non-study PPI any time thereafter until the end of study;
  - full therapeutic doses of H_2-receptor antagonists within 14 days prior to screening ^{13}C-UBT for *H. pylori* and screening endoscopy, or any dose during the 10-day treatment period;
  - systemic antibiotics or bismuth-containing compounds within 4 weeks prior to screening ^{13}C-UBT and screening endoscopy, or systemic antibiotics within 2 weeks prior to the ^{13}C-UBT at ≥ 42 days;
  - amoxicillin or clarithromycin following the 10 day treatment period;
  - bismuth preparations and the following antibiotics throughout the study: macrolides (other than clarithromycin), tetracyclines, imidazoles, nitrofurans, aminoglycosides, quinolones, and rifampin.

Clinical Reviewer's Comment: The low doses of H_2-receptor antagonists (see Table 3) within 14 days prior to the screening ^{13}C-UBT do not constitute exclusion of a patient from the PP analysis. During protocol development the Division and the applicant agreed upon these doses.

Patients were included as failures in the PP population if the following occurred:
- A positive ^{13}C-UBT for *H. pylori* anytime after the end of treatment;
- Dropped from the study during the treatment period where the reason for the dropout was due to an adverse event and the event was considered related to study medication;
- A ^{13}C-UBT for *H. pylori* within 42 days from the end of the treatment with a positive ^{13}C-UBT for *H. pylori* at withdrawal.

Patients were included as successes in the PP population if the following occurred:
- A negative ^{13}C-UBT for *H. pylori* ≥ 42 days from the end of the treatment, and no positive ^{13}C-UBT for *H. pylori* at any time after the end of treatment;
- No failure criteria.

1. Applicant's Proposed Efficacy Analysis

The primary efficacy endpoint was the presence or absence of *H. pylori* using ^{13}C-UBT for *H. pylori* ≥ 42 days (i.e., ≥ 6 weeks) from the end of the treatment. Secondary efficacy endpoints included the eradication rates in patients infected with antibiotic-susceptible *H. pylori*, the percentage of patients with antibiotic-resistant *H. pylori* in whom eradication failed, and the study medication compliance.

Before conducting the primary efficacy endpoint analysis, a preliminary efficacy analysis was performed comparing the eradication rates between PUD and NPUD patients for all four treatment regimens combined. Since the eradication rate for NPUD patients was not considered clinically higher than the eradication rate for PUD patients, it was considered appropriate to pool the results of these two strata. A clinical result that would be considered to be significantly higher, in this situation, was defined as an upper bound 95% confidence limit of the difference in eradication rates (NPUD - PUD) of greater than 10% using an

analysis that compared all patients enrolled into study regardless of treatment. If such a preliminary analysis result had been obtained, the demonstration of efficacy would have relied on PUD patients only and the lower bound 95% confidence limit for the eradication rate for each RAC regimen would have needed to be greater than 60%.

The primary efficacy endpoint analysis was performed as follows. Eradication rates based on the ^{13}C-UBT for *H. pylori* at least 42 days from the end of the treatment were estimated for each treatment regimen. The difference in eradication rates between each rabeprazole treatment regimen and the omeprazole treatment regimen was calculated. Therapeutic equivalence between treatments was assessed using a two-sided 95% confidence interval (CI) for the difference in the eradication rates. Two treatment regimens were declared therapeutically equivalent if this two-sided 95% CI, $[C_L, C_U]$ was within the equivalence range, [-15%, 15%], or $-15\% \leq C_L < C_U \leq 15\%$. Equally, the equivalence was established if the pair of one-sided 0.025 level tests reject the null hypotheses of non-equivalence. In addition, the lower limit of the two-sided 95% CI of the point estimate of the eradication rate should be >60% based on the ITT population within any one of the RAC and OAC treatment groups. The equivalence between the treatment regimens (comparison of each rabeprazole regimen with the control omeprazole regimen) was assessed by the Holm-Sidak stepdown closed testing procedure [Y. Hochberg and A.C. Tamhane. "Multiple Comparison Procedures" 1987, John Wiley & Sons, Inc.] that adjusts for the multiple comparisons to control the overall significance level at α=0.05.

Statistical Reviewer's Comment: Our interest in this trial is not to show equivalence, which is a two-sided comparison, but rather to show non-inferiority, which is a one-sided comparison (i.e., that the RAC regimens are no worse than the OAC regimen by the chosen delta of 15%). Since we are looking at a difference in eradication rates of (RAC – OAC) this means that we are only interested in the lower limit of the two-sided 95% confidence interval (C_L) being greater than -15%.

The comparison of eradication rates between the rabeprazole regimens (i.e., 3-day RAC vs. 7-day RAC vs. 10-day RAC) was also performed using an equivalence test with a 95% CI. As these comparisons were non-confirmatory in nature, there were no multiplicity adjustments for the p-values in these tests.

Statistical Reviewer's Comment: We attempted to determine if there was enough evidence in the trial to suggest which RAC regimen should be chosen for inclusion in the label, assuming this NDA is approved. To do this, the reviewer used a Bonferroni adjustment to account for multiple comparisons for this analysis and the primary analysis to see what conclusions may be drawn regarding the choice of a RAC regimen while protecting against inflation of the Type I error. As the primary analysis can be thought of as one test (it already controls for the multiple comparisons involved), and we have three comparisons that we would like to make in this secondary analysis (RAC-3 v. RAC-7, RAC-3 v. RAC-10, and RAC-7 v. RAC-10), the reviewer calculated 98.75% (= 100% x (1 – 0.05/4)) confidence intervals for comparing RAC regimens. The limits of these confidence intervals were then compared to –15% (for C_L) and 15% (for C_U) to determine equivalence. Note that this analysis is only exploratory, as it was not pre-specified.

A logistic analysis model was used to examine the effect of covariates on the primary efficacy outcome, eradication rates based on the ^{13}C-UBT for *H. pylori* at least 42 days from the end of the treatment, with treatment as a factor and treatment-by-covariate interactions. The covariates examined were center, age group, gender, race, smoking status, alcohol

intake, PUD strata, compliance, and primary resistance at screening. Interaction terms were tested for significance using the Wald Chi-square statistic at the 10% significance level.

2. Applicant's Proposed Safety Analysis

All safety analyses used the Safety population. All statistical tests were two-sided and the significance alpha value was ≤ 0.05.

Adverse events (AEs) are summarized in tabular form by and within body system and preferred term by treatment regimen.

The overall summary and analysis of AEs include frequencies (N and percent) for patients with at least one AE, patients with at least one drug-related AE, patients with at least one serious adverse event (SAE), patients with at least one drug-related SAE, patients with at least one AE leading to discontinuation, and patients who died.

Adverse events are summarized by relationship to the study medication and by maximum severity.

Comparisons across treatment regimens with respect to proportion of patients reporting AEs (body systems and preferred terms) were made using a Chi-square or Fisher's exact test. For body systems or preferred terms with significant differences among treatments, further comparisons were performed.

Vital signs and laboratory test values are summarized with summary statistics (N, mean, SEM, median, minimum, and maximum) for each treatment regimen at screening, at the end-of-treatment visits, and for the change from screening to the end of treatment. A one-way ANOVA model was used for the treatment regimen comparison for the change from screening to end of treatment.

Frequencies and percentages are provided for each treatment regimen for patients with and without clinically significant laboratory abnormalities at screening and end-of treatment visits and treatment-emergent abnormal values (TEAVs).

A TEAV for a laboratory parameter is defined: (1) as a value that is clinically significantly outside (above or below) the normal range post-dose, but within the normal range prior to drug administration; or (2) a value that represents a clinically significant exacerbation of an abnormality present prior to drug administration. Individual patient values identified as clinically significant abnormal laboratory values and clinically significant exacerbations of laboratory parameters are listed in Tables 5 and 6, respectively. These criteria are defined in the FDA guidelines (Leber P. U.S. Food and Drug Administration; Center for Drug Evaluation and Research; Division of Neuropharmacologic Drug Products. Form and Content of NDA Reviews: Strategic for the Efficacy Analysis. November 5, 1985). Additional criteria for variables not addressed by this FDA publication were defined by the applicant.

TABLE 5
Clinically Significant Abnormal Laboratory Values

Hemoglobin	Male: ≤ 11.5 g/dL Female: ≤ 9.5 g/dL
Hematocrit	Male: ≤ 37% Female: ≤ 32%
White Blood Cell Count (WBC)	2,800/mm or 16,000/mm
Neutrophils	15%
Eosinophils	≥ 10%
Platelet Count	75,000/mm or 700,000/mm
Alkaline Phosphatase	≥ 3 x ULN
ALT	≥ 3 x ULN
AST	≥ 3 x ULN
Creatine Kinase (CK)	≥ 2 x ULN
Total Bilirubin	≥ 2.0 mg/dL
Albumin	< 50% LLN
Glucose	< 45 mg/dL or > 160 mg/dL
Sodium	< 130 mEq/L or > 150 mEq/L
Potassium	< 3 mEq/L or > 5.5 mEq/L
Chloride	< 90 mEq/L or > 115 mEq/L
Calcium	< 8.4 mg/dL or > 11.5 mg/dL
Blood Urea Nitrogen (BUN)	≥ 30 mg/dL
Creatinine	≥ 2.0 mg/dL
Lactate Dehydrogenase (LDH)	≥ 3 x ULN

*defined by the applicant

APPEARS THIS WAY
ON ORIGINAL

TABLE 6
Clinically Significant Exacerbations of Abnormal Laboratory Values

Hemoglobin	Male: < 0.85 x Baseline value Female: < 0.85 x Baseline value
Hematocrit	Male: < 0.85 x Baseline value Female: < 0.85 x Baseline value
White Blood Cell Count (WBC)	< 0.85 x Baseline value or > 1.15 x Baseline or if Baseline value is > ULN and a post-treatment value is < LLN or if Baseline value is < LLN and a post-treatment value is > ULN
Neutrophils	< 0.85 x Baseline value
Eosinophils	> 1.5 x Baseline value
Platelet Count	< 0.85 x Baseline value
Alkaline Phosphatase	> 1.25 x Baseline value
ALT	> 1.25 x Baseline value
AST	> 1.25 x Baseline value
CK	> 1.5 x Baseline value
Total Bilirubin	> 1.25 x Baseline value
Albumin	< 0.9 x Baseline value
Glucose	< 0.8 x Baseline value or > 2 x Baseline value or if Baseline value is > ULN and a post-treatment value is < LLN or if Baseline value is < LLN and a post-treatment value is > ULN
Sodium	< 0.95 x Baseline value or > 1.05 x Baseline value or if Baseline value is > ULN and a post-treatment value is < LLN or if Baseline value is < LLN and a post-treatment value is > ULN
Potassium	< 0.9 x Baseline value or > 1.1 x Baseline value or if Baseline value is > ULN and a post-treatment value is < LLN or if Baseline value is < LLN and a post-treatment value is > ULN
Chloride	< 0.9 x Baseline value or > 1.1 x Baseline value or if Baseline value is > ULN and a post-treatment value is < LLN or if Baseline value is < LLN and a post-treatment value is > ULN
Calcium	< 0.9 x Baseline value or > 1.1 x Baseline value or if Baseline value is > ULN and a post-treatment value is < LLN or if Baseline value is < LLN and a post-treatment value is > ULN
Blood Urea Nitrogen (BUN)	> 1.2 x Baseline value
Creatinine	> 1.33 x Baseline value
LDH	> 1.5 x Baseline value

A Chi-square or Fisher's exact test was used to test for differences across treatment regimens.

L. Changes in the Conduct of the Study

The original protocol was amended four times during the study. A summary of each amendment is provided below. At the time of implementation of Amendment 1 there were no patients randomized. Under Amendment 1, there were six patients randomized; under Amendment 2, there were 641 patients randomized; under Amendment 3, 137 patients were randomized; and under Amendment 4, there were 19 patients randomized. Amendment 4 had no effect on patients already enrolled since it addressed the enrollment of additional patients.

1. Amendment 1: October 27, 1999 (Prior to Study Initiation)

This protocol amendment was implemented in response to the Division's comments:

- Criteria for stratification of patients to the PUD or NPUD group were defined.
- A history of PUD in the past five years required documentation by way of an endoscopy or radiology report.
- An inclusion criterion was amended to require a positive *H. pylori* antibody and *H. pylori* infection documented by ^{13}C-UBT and either a rapid urease test or *H. pylori* culture.
- An exclusion criteria concerning concomitant therapy was amended and disallowed patients from taking any PPIs during the screening period up to the first day of the treatment period or following the 10-day treatment period.
- The post-treatment assessment requirements were expanded to reflect the need for patients to continue to be followed by the Investigator until study completion and for patients to be referred to their personal physicians for treatment of particular conditions where necessary.
- The conditions under which a patient was considered a treatment failure in the ITT population was expanded to include patients who only had an endoscopy assessment prior to six weeks without an assessment at ≥ 6 weeks.
- The list of major protocol violations for the PP population was expanded to include H_2-receptor antagonists during the 10-day treatment period.

2. Amendment 02: December 23, 1999

This protocol amendment was implemented to maintain consistency with the inclusion criteria changes made in Amendment 01 and to bring the protocol into compliance with current procedures of the applicant.

- The schedule of assessment chart was changed to reflect the need for a positive culture or rapid urease test in compliance with changes made in Amendment 01.
- The inclusion criteria for the urine pregnancy test was amended to include testing for women who were post-menopausal for less than one year or who had a history of tubal ligation.

3. Amendment 03: July 20, 2000

This protocol amendment was implemented in response to comments from the Division:

- The treatment period was amended and required patients to be randomized within 21 days of the start of the screening period and within 10 days of the screening endoscopy.

4. Amendment 04: February 20, 2001

This protocol amendment was enacted to allow for the enrollment of additional patients.

- To ensure that there were a sufficient number of evaluable patients in the PP analysis of the study, the sample size was increased from 720 to approximately

790, with approximately 198 patients per treatment group (increased from 180 per treatment group in the original protocol).

M. Clinical Reviewer's Data Validation Methods

Validation of the efficacy data was performed by reviewing the electronic and line listing raw data for patients considered not evaluable by the applicant for either the Intention-to-Treat (ITT) or Per Protocol (PP) population. Evaluability for both populations was made according to the draft Eradication Guidance.

In addition, 10% of the evaluable population (N=68) was randomly selected (blinded to treatment) and independently reviewed. The reviewer's assessment of evaluability is the same as the applicant's for all patients in this sample.

N. Results

1. Investigators

The number of patients enrolled per site and who received at least one dose of study medication (i.e., Safety population) can be seen in Table 7 below by treatment group. The mean number of patients enrolled was 19 per site (range 1-92). Dr. Wieslaw Ignatowicz's site (Brooklyn, NY) has the highest enrollment at 12% (92/788) of the total population.

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TABLE 7
List of Investigators and Enrollment per Treatment Arm
Safety Population (N=788)

Principal Investigator	Location of Study Site	Treatment Arm				Total
		RAC 3 day	RAC 7 Day	RAC 10 Day	OAC 10 day	
Barish, C	Raleigh, NC	2	2	2	1	7
Campbell, D	Kansas City, MO	1	3	2	2	8
Cano, R	Fresno, CA	0	2	2	1	5
Caos, A	Ocoee, FL	1	2	1	2	6
Carlson, S	San Luis Obispo, CA	0	0	1	1	2
Chen, S	Kansas City, MO	4	4	3	6	17
Clements, J	Charlotte, NC	2	1	2	2	7
Duckor, S	Orange, CA	12	10	10	10	42
Eskreis, D	Greak Neck, NY	4	4	5	3	16
Fowler, F	Charlotte, NC	2	2	2	2	8
Gaddam, S	Garden Grove, CA	7	11	9	10	37
Holmes, R	Winston-Salem, NC	0	1	1	1	3
Ignatowicz, W	Brooklyn, NY	23	23	23	23	92
Jayanty, V	Houston, TX	6	7	6	6	25
Kovacs, T	Los Angeles, CA	8	9	8	10	35
Krause, R	Chattanooga, TN	8	6	8	9	31
Lanza, F	Houston, TX	2	2	3	2	9
Levine, M	Marietta, GA	4	3	3	3	13
Levine, R	Boulder, CO	0	0	1	0	1
Mangels, D	Cincinnati, OH	2	1	1	1	5
Mendolia, T	Winston-Salem, NC	2	2	1	1	6
Nett, R	San Antonio, TX	1	2	1	2	6
Orchard, D	Boise, ID	0	0	1	1	2
Pambianco, D	Charlottesville, VA	3	3	4	5	15
Pressman, J	San Diego, CA	4	4	4	4	16
Pruitt, R	Nashville, TN	5	4	6	5	20
Resnick, H	Lake Jackson, TX	2	2	2	2	8
Riff, D	Anaheim, CA	17	18	16	17	68
Saad, C	Mission Viejo, CA	2	3	2	3	10
Safdi, M	Cincinnati, OH	2	2	3	3	10
Schuman, R	West Orange, NJ	4	4	4	4	16
Schwartz, H	Miami, FL	15	16	17	18	66
Schwartz, M	Jupiter, FL	3	3	3	4	13
Shah, U	Hollywood, MD	9	11	9	11	40
Shaukat, M	Phoenix, AZ	1	3	2	2	8
Siegel, H	New York, NY	2	1	1	0	4
Sontag, S	Hines, IL	2	1	3	3	9
Stanton, D	Orange, CA	18	17	19	19	73
Vakil, N	Milwaukee, WI	1	1	0	0	2
Williams, E	Kenner, LA	1	1	1	1	4
Winston, B	Houston, TX	3	2	2	3	10
Wruble, L	Memphis, TN	3	2	4	4	13
TOTALS		**188**	**195**	**198**	**207**	**788**

2. Patient Accountability

A summary of patient disposition is presented in Table 8. There are a total of 803 All Randomized, 788 Safety, 783 Intention-to-Treat (ITT), and 683 Per Protocol (PP) patients analyzed.

A total of 112 (14%) patients discontinued. Of those patients, twenty-six (3%) discontinued due to adverse events. The percentage of patients who discontinued from the study is similar across treatment groups, ranging from 11% to 17%. The percentage of patients in the Safety, ITT, and PP populations compared with the All Randomized population is similar across treatment groups.

TABLE 8
Summary of Patient Disposition - All Randomized Patients

	RAC 3-day (N = 194)	RAC 7-day (N = 200)	RAC 10-day (N = 202)	OAC 10-day (N = 207)	Total (N = 803)
All Randomized Patients	194 (100%)	200 (100%)	202 (100%)	207 (100%)	803 (100%)
Safety Patients	188 (97%)	195 (98%)	198 (98%)	207 (100%)	788 (98%)
Intent-to-Treat Patients	187 (96%)	194 (97%)	196 (97%)	206 (99%)	783 (98%)
Per Protocol Patients	167 (86%)	166 (83%)	171 (85%)	179 (86%)	683 (85%)
Completed	161 (83%)	172 (86%)	174 (86%)	184 (89%)	691 (86%)
Discontinued Study	33 (17%)	28 (14%)	28 (14%)	23 (11%)	112 (14%)
Death	0	0	0	0	0
Adverse Event	8 (4%)	8 (4%)	4 (2%)	6 (3%)	26 (3%)
Intercurrent Illness	0	0	0	0	0
Request of Investigator/Sponsor	0	0	0	0	0
Patient Withdrew Consent	5 (3%)	1 (<1%)	4 (2%)	4 (2%)	14 (2%)
Protocol Violation	5 (3%)	4 (2%)	10 (5%)	5 (2%)	24 (3%)
Lost of Follow-Up	13 (7%)	12 (6%)	8 (4%)	7 (3%)	40 (5%)
Other	2 (1%)	3 (2%)	2 (<1%)	1 (<1%)	8 (<1%)

In the population of All Randomized patients, twenty (2%) are excluded from the ITT and 120 (15%) are excluded from the PP patient populations. The most frequent reasons for exclusion are: ^{13}C-UBT missing/not determined at ≥ 42 days after the end of treatment (8% of patients) and early withdrawal for reasons other than study drug-related AEs (9% of patients; relationship as per the Investigator). The number of excluded patients and reasons for exclusion are similar across treatment groups for both the ITT and PP patient populations can be found in Table 9.

Clinical Reviewer's Comment: Table 9 has been modified by the reviewer from the applicant's submitted table.

TABLE 9
Summary of Patient Evaluability - All Randomized Patients

Patient Population	RAC 3-day (N = 194)	RAC 7-day (N = 200)	RAC 10-day (N = 202)	OAC 10-day (N = 207)	Total (N=803)
All Randomized	**194 (100%)**	**200 (100%)**	**202 (100%)**	**207 (100%)**	**803 (100%)**
Safety	**188 (97%)**	**195 (98%)**	**198 (98%)**	**207 (100%)**	**788 (98%)**
Intent-to-Treat	**187 (96%)**	**194 (97%)**	**196 (97%)**	**206 (99%)**	**783 (98%)**
Reasons for Exclusion From Intent-to-Treat*					
Did not receive any study medication	6 (3%)	5 (3%)	4 (2%)	0	15 (2%)
Negative ^{13}C-UBT at screening	1 (<1%)	0	0	0	1 (<1%)
Missing/not determined ^{13}C-UBT at screening	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Diagnostic criteria not met	6 (3%)	6 (3%)	5 (2%)	0	17 (2%)
Per Protocol	**167 (86%)**	**166 (83%)**	**171 (85%)**	**179 (86%)**	**683 (85%)**
Reasons for Exclusion From Per-Protocol*					
Excluded from ITT	7 (4%)	6 (3%)	6 (3%)	1 (<1%)	20 (2%)
^{13}C-UBT missing/not determined at ≥ 42 days after end of treatment	15 (8%)	13 (7%)	17 (8%)	21 (10%)	66 (8%)
Compliance violation	1 (<1%)	4 (2%)	2 (<1%)	2 (<1%)	9 (1%)
Early withdrawal for reason other than study drug-related adverse event	21 (11%)	16 (8%)	17 (8%)	15 (7%)	69 (9%)
Negative ^{13}C-UBT within 42 days from end of treatment without a ^{13}C-UBT ≥ 42 days after the end of treatment	2 (1%)	3 (2%)	5 (2%)	6 (3%)	16 (2%)
Received at least one disallowed medication	10 (5%)	15 (8%)	15 (7%)	7 (3%)	47 (6%)

* Patients may have had more than one reason for exclusion, thus percents may add to more than 100% either overall or by group.

A total of 47 (6%) patients are excluded from the PP population for receiving at least one disallowed medication. These medications include: cephalexin, co-trimoxazole, amoxicillin, ampicillin, amoxicillin/clavulanate, bismuth subsalicylate, azithromycin, clarithromycin, ciprofloxacin, tetracycline, doxycycline, cimetidine, famotidine, nizatidine, ranitidine, oxaprozin, ibuprofen, naproxen, aspirin, lansoprazole, omeprazole, pantoprazole, and rabeprazole.

3. Demographic Characteristics

A summary of patient demographics for All Randomized patients is presented in Table 10.

TABLE 10
Summary of Patient Demographics - All Randomized Patients

	RAC 3-day (N = 194)	RAC 7-day (N = 200)	RAC 10-day (N = 202)	OAC 10-day (N = 207)	Total (N = 803)
Age (years)					
N	194	200	202	207	803
Mean ± SEM	45.1 ± 1.05	46.9 ± 0.95	48.2 ± 0.92	45.6 ± 0.94	46.5 ± 0.48
Range	18.0 – 86.0	22.0 – 84.0	20.0 – 82.0	19.0 – 82.0	18.0 – 86.0
Age Group					
18 – 65	174 (90%)	180 (90%)	180 (89%)	192 (93%)	726 (90%)
66 – 75	14 (7%)	15 (8%)	18 (9%)	10 (5%)	57 (7%)
>75	6 (3%)	5 (3%)	4 (2%)	5 (2%)	20 (2%)
Gender					
Female	111 (57%)	106 (53%)	106 (52%)	118 (57%)	441 (55%)
Male	83 (43%)	94 (47%)	96 (48%)	89 (43%)	362 (45%)
Race					
Hispanic	86 (44%)	93 (47%)	88 (44%)	88 (43%)	355 (44%)
White	69 (36%)	74 (37%)	83 (41%)	84 (41%)	310 (39%)
Black	33 (17%)	26 (13%)	20 (10%)	27 (13%)	106 (13%)
Asian/Pacific	4 (2%)	6 (3%)	5 (2%)	6 (3%)	21 (3%)
Other	2 (1%)	1 (<1%)	6 (3%)	2 (<1%)	11 (1%)

There are no statistically significant differences across treatment groups in any of the demographic characteristics examined: the mean age, numbers of patients within each age group, gender, and race. Most patients are in the age group 18-65 years, with mean ages ranging from 45.1 to 48.2 years. The percentage of female patients across treatment groups ranges from 52% to 57%. Most of the patients are Hispanic or White. Demographics in the Safety, ITT, and PP patient populations are similar to those in the All Randomized patient population.

In addition, nicotine and alcohol use (both incidence and duration) are not statistically significantly different across the treatment groups in the All Randomized patient population (data not shown). The incidence of nicotine use is lowest in the RAC 7-day group (39%) and highest in the RAC 10-day group (51%). Approximately half the patients (45%) are smokers with a mean duration of nicotine use ranging from 20.28 to 23.51 years. Fifty percent (50%) of the patients consume alcohol with a mean duration of alcohol consumption of 21.57 ± 0.64 (mean ± SEM) years. Similar nicotine and alcohol use occurs in the Safety, ITT, and PP patient populations.

4. Evaluation of Disease at Baseline

A summary of disease strata (i.e., PUD versus NPUD) is presented in Table 11 below. There are no statistically significant differences across treatment groups in All Randomized patients stratified to PUD or NPUD disease groups. Fifty percent (50%) of All Randomized patients are stratified to the PUD disease group. In this disease group, 318 (80%) patients have an active ulcer ≥ 3 mm and the remainder has a history of ulcer. In the NPUD group,

all but one patient in each treatment group have no active ulcer or history of ulcer. In each treatment group, there is one patient with a history of ulcer < 3 mm. Similar PUD strata are reported in the Safety, ITT, and PP patients.

TABLE 11
Summary of Disease Strata - All Randomized Patients

Diagnosis	RAC 3-day (N = 194)	RAC 7-day (N = 200)	RAC 10-day (N = 202)	OAC 10-day (N = 207)	Total (N = 803)
Patients Stratified to:					
PUD	93 (48%)	103 (52%)	100 (50%)	104 (50%)	400 (50%)
NPUD	101 (52%)	97 (49%)	102 (50%)	103 (50%)	403 (50%)
PUD Reasons					
Active ulcer ≥ 3 mm	77 (83%)[a]	85 (83%)	76 (76%)	80 (77%)	318 (80%)
History of ulcer ≥ 3 mm	15 (16%)	24 (23%)	22 (22%)	29 (28%)	90 (23%)
History of ulcer of unspecified size	11 (12%)	8 (8%)	13 (13%)	5 (5%)	37 (9%)
Active ulcer < 3 mm and either history of ulcer ≥ 3 mm or history of ulcer of unspecified size	4 (4%)	1 (1%)	5 (5%)	3 (3%)	13 (3%)
NPUD Reasons					
No active ulcer or history	100 (99%)[b]	96 (99%)	101 (99%)	102 (99%)	399 (99%)
Active ulcer < 3 mm and either no history of ulcer or history of ulcer < 3 mm in size	0	0	0	0	0
History of ulcer < 3 mm	1 (1%)	1 (1%)	1 (1%)	1 (1%)	4 (1%)

[a] Percentages are based on number of patients stratified to PUD within each treatment regimen.
[b] Percentages are based on number of patients stratified to NPUD within each treatment regimen.
Patients may have more than one condition; therefore percents may add to more than 100%.

Ulcer Histories

Ten percent (10%) of All Randomized patients have a history of gastric ulcer while 8% have a history of duodenal ulcer. Two percent (2%) of randomized patients have a history of both gastric and duodenal ulcer. There are no statistically significant differences across treatment groups. Similar ulcer histories are reported in the Safety, ITT, and PP patients.

Endoscopy Results

There are no statistically significant differences across treatment groups in endoscopic diagnosis of ulcers at screening. Gastric ulcers are present in 12%, duodenal ulcer in 30%, and both gastric and duodenal ulcer in ≤ 1% of All Randomized patients. Safety, ITT, and PP patients exhibit similar endoscopic diagnoses with no statistically significant differences across treatment groups.

5. Compliance Results

Compliance calculations based on the actual days of active treatment (i.e., 3, 7 or 10 days) show ≥ 96% of all ITT and PP patients were compliant with the treatment regimens. There are no statistically significant differences across treatment groups. Table 12 summarizes compliance based on treatment regimen for the Safety patients. The duration of dosing and

total number of doses for the 3-day and 7-day RAC treatment groups including seven and three days of placebo, respectively.

TABLE 12
Summary of Study Drug Administration – Safety Patients

	RAC 3-day (N = 188)	RAC 7-day (N = 195)	RAC 10-day (N = 198)	OAC 10-day (N = 207)
Duration of Dosing (days)				
N	188	195	198	207
Mean ± SEM	9.77 ± 0.10	9.76 ± 0.10	9.87 ± 0.07	9.79 ± 0.09
Total Number of Doses				
N	188	195	198	207
Mean ± SEM	19.37 ± 0.21	19.33 ± 0.21	19.64 ± 0.14	19.45 ± 0.18
Patient Compliance (%)				
N	188	195	198	207
Mean ± SEM	96.78 ± 1.06	96.44 ± 1.04	98.06 ± 0.72	97.08 ± 0.91

6. Eradication

Overall Eradication by Strata (PUD versus NPUD)
A summary of overall eradication rate by disease strata for patients in the ITT and PP populations are presented in Tables 13 and 14, respectively.

TABLE 13
Summary of Overall Eradication Rate by Disease Strata - Intent-to-Treat Patients

	NPUD n (%)	PUD n (%)	Difference in Eradication Rates (NPUD-PUD)	95% Confidence Interval [a]
Eradication				
Yes	247 (63%)	258 (66%)	-2.97%	-9.68%, 3.73%
No	145 (37%)	133 (34%)		

[a] Rates were to be pooled across the strata if the upper bound of the 95% confidence interval of the difference (NPUD – PUD) was < 10%.

TABLE 14
Summary of Overall Eradication Rate by Disease Strata - Per Protocol Patients

	NPUD n (%)	PUD n (%)	Difference in Eradication Rates (NPUD-PUD)	95% Confidence Interval [a]
Eradication				
Yes	238 (69%)	245 (73%)	-3.91%	-10.7%, 2.91%
No	108 (31%)	92 (27%)		

[a] Rates were to be pooled across the strata if the upper bound of the 95% confidence interval of the difference (NPUD – PUD) was < 10%.

The eradication rates combined across treatments for NPUD patients are not clinically superior to PUD patients using a margin of 10% for both the ITT and PP populations. In addition, there is no significant treatment interaction. Therefore, it is considered appropriate to pool the efficacy results of these two strata.

Eradication by Treatment Regimen In Comparison to Active Control

A summary of *H. pylori* eradication rates by treatment regimen in comparison to the active control (OAC) in the ITT and PP patient populations are presented in Tables 15 and 16, respectively.

The 7-day RAC treatment regimen is considered non-inferior to the 10-day OAC treatment regimen in eradicating *H. pylori* in both the ITT (77% vs. 73%, respectively) and PP (84% vs. 82%, respectively) patient populations. The 10-day RAC treatment regimen is also considered non-inferior to the 10-day OAC treatment regimen in both populations (78% vs. 73%, respectively, in the ITT population and 86 vs. 82%, respectively, in PP patients). In contrast, the 3-day RAC treatment regimen is significantly less effective than the OAC treatment in both populations (30% vs. 82%, respectively in the PP population).

Note: Tables 15 and 16 have been modified to show the difference in eradication rates and 95% confidence intervals for (RAC – OAC) instead of (OAC – RAC) as in the applicant's tables.

TABLE 15
Eradication Rates by Treatment Regimen In Comparison to Active Control
Intent-to-Treat Patients

Treatment	RAC n (%)	OAC n (%)	Difference in Eradication Rates (RAC - OAC)	95% Confidence Interval [a]
RAC 3-day regimen vs. OAC				
H. pylori Eradicated	51 (27%)	151 (73%)	- 46.03%	- 54.84%, - 37.22%
Not Eradicated	136 (73%)	55 (27%)		
RAC 7-day regimen vs. OAC				
H. pylori Eradicated	150 (77%)	151 (73%)	4.02%	- 4.44%, 12.5%
Not Eradicated	44 (23%)	55 (27%)		
RAC 10-day regimen vs. OAC				
H. pylori Eradicated	153 (78%)	151 (73%)	4.76%	- 3.63%, 13.2%
Not Eradicated	43 (22%)	55 (27%)		

[a]Equiv alence is defined as two-sided 95% confidence interval of difference (RAC-OAC) within the equivalence range (-15%, 15%).

TABLE 16
Eradication Rates by Treatment Regimen In Comparison to Active Control
Per Protocol Patients

Treatment	RAC n (%)	OAC n (%)	Difference in Eradication Rates (RAC - OAC)	95% Confidence Interval [a]
RAC 3-day regimen vs. OAC				
H. pylori Eradicated	50 (30%)	146 (82%)	- 51.62%	- 60.62%, - 42.62%
Not Eradicated	117 (70%)	33 (18%)		
RAC 7-day regimen vs. OAC				
H. pylori Eradicated	140 (84%)	146 (82%)	2.77%	- 5.18%, 10.7%

Not Eradicated	26 (16%)	33 (18%)		
RAC 10-day regimen vs. OAC				
H. pylori Eradicated	147 (86%)	146 (82%)	4.40%	-3.33%, 12.1%
Not Eradicated	24 (14%)	33 (18%)		

[a]Equiv alence is defined as two-sided 95% confidence interval of difference (RAC-OAC) within the equivalence range (-15%, 15%).

Statistical Reviewer's Comments (pertaining to Table 15): Recall that in the determination of equivalence between RAC and OAC treatment regimens, the sponsor used a step down, closed testing procedure that adjusts for the multiple comparisons (3 RAC to OAC comparisons) to control the overall Type I error at 5%. Adjusted p-values were calculated using the Holm-Sidak step down method; p-values less than 0.05 indicate equivalence between treatment regimens. Adjusted confidence intervals were not calculated. The adjusted p-values for the above table are 1.0, 0.016, and 0.017, for the comparisons of RAC 3-, RAC 7- and RAC 10-day to OAC 10-day, respectively. Thus, we conclude that the RAC 3-day regimen is not equivalent to the OAC 10-day regimen, but the RAC 7-day and RAC 10-day regimens are equivalent to the OAC 10-day regimen. Note that the p-values given above are actually conservative as the sponsor is testing equivalence of the regimens, i.e., that the confidence interval for the difference in rates lies entirely in the interval [-15%, 15%], while we are only interested in non-inferiority of the RAC regimens, i.e., that the lower bound of the CI is greater than -15%.

The reviewer used a Bonferroni correction to produce confidence intervals that are adjusted for the 3 multiple comparisons in the primary analysis. Using an alpha level of 0.05/3 = 0.017, the 98.3% adjusted confidence intervals for the comparisons of RAC 3-, RAC 7-, and RAC 10-day to OAC 10-day are (-57.2, -34.8), (-6.8, 14.8), and (-5.9, 15.5). For RAC 7- and RAC 10-day, the lower limits of the confidence intervals are well above -15%, indicating that these two regimens may be considered not inferior to the OAC 10-day regimen.

Sensitivity Analyses
The reviewer investigated the effect of PUD strata and missing data on the outcome for the primary efficacy variable in ITT patients.

As randomization was stratified by PUD status (PUD v. NPUD), the reviewer calculated 95% confidence intervals for the differences in eradication rates stratified by PUD status. For RAC 3-, RAC 7-, and RAC 10-day versus OAC 10-day, these stratified confidence intervals are (-54.8, -37.2), (-4.5, 12.3), and (-3.6, 13.1), respectively. Note that these confidence intervals are very similar to the unstratified confidence intervals shown in Table 15.

In the sponsor's analysis in Table 15, all subjects with missing data are assumed to be failures. About 10% of subjects had missing data (11% RAC 3-day, 9% RAC 7-day, 9% RAC-10 day, and 12% OAC 10-day). As imputing all of this missing data in the same way can sometimes bias conclusions towards equivalence in an active-controlled study, the reviewer used two other methods for imputing missing data. The first calculated eradication rates by treatment in patients with observed data, and assumed that eradication rates were the same in patients with unobserved data. The second method used a worst-case scenario and assumed all OAC subjects with missing data were eradicated while all RAC subjects with missing data were not eradicated. The second method is used only to give an

upper bound on the upper limit of the confidence interval for the difference in eradication rates, as such a scenario would be very unlikely to actually occur.

Eradication rates in subjects with observed data are 31% (51/167) for RAC 3-day, 85% (150/177) for RAC 7-day, 86% (153/178) for RAC 10-day, and 83% (151/181) for OAC 10-day. Assuming eradication rates are the same in subjects with unobserved data, the imputed eradication rates are 30% (57/187) for RAC 3-day, 85% (164/194) for RAC 7-day, 86% (168/196) for RAC 10-day, and 83% (172/206) for OAC 10-day. The 95% confidence intervals for the differences in imputed eradication rates for RAC 3-, RAC 7-, and RAC 10-day versus OAC 10-day are (-61.8, -44.2), (-6.6, 8.7), and (-5.3, 9.8), respectively. One would still conclude that the RAC 7- and 10-day regimens are not inferior to the OAC 10-day regimen, while the RAC 3-day regimen is significantly less effective than the OAC 10-day regimen.

Assuming the worst-case scenario (i.e., that all RAC subjects with missing data are failures while all OAC subjects with missing data are not), the imputed eradication rates are 27% for RAC 3-day, 77% for RAC 7-day, 78% for RAC 10-day, and 85% for OAC 10-day. The 95% confidence intervals for the differences in imputed eradication rates for RAC 3-, RAC 7-, and RAC 10-day versus OAC 10-day are (-66.7, -49.7), (-16.2, 0), and (-15.4, 0.7), respectively. As a lower limit of -15% or greater indicates non-inferiority, results are actually quite robust for RAC 7- and RAC 10-day.

Statistical Reviewer's Comments (pertaining to Table 16): The sponsor calculated p-values that were adjusted for multiple comparisons using the Holm-Sidak step down method; p-values less than 0.05 indicate equivalence between treatment regimens. The adjusted p-values for the above table are 1.0, 0.004, and 0.007, for the comparisons of RAC 3-, RAC 7- and RAC 10-day to OAC 10-day, respectively. Thus, we conclude that the RAC 3-day regimen is not equivalent to the OAC 10-day regimen, but the RAC 7-day and RAC 10-day regimens are equivalent to the OAC 10-day regimen. Again, the p-values given here are conservative when used to draw conclusions about non-inferiority of the RAC regimens as they are actually from a test for equivalence.

The reviewer used a Bonferroni correction to produce confidence intervals that are adjusted for the 3 multiple comparisons in the primary analysis. Using an alpha level of 0.05/3 = 0.017, the 98.3% adjusted confidence intervals for the comparisons of RAC 3-, RAC 7-, and RAC 10-day to OAC 10-day are (-63.1, -40.1), (-7.5, 13.0), and (-5.6, 14.4). For RAC 7- and RAC 10-day, the lower limits of the confidence intervals are well above -15%, indicating that these two regimens may be considered not inferior to the OAC 10-day regimen.

Sensitivity Analyses
The reviewer investigated the effect of PUD strata on the outcome for the primary efficacy variable in PP patients.

As randomization was stratified by PUD status (PUD v. NPUD), the reviewer calculated 95% confidence intervals for the differences in eradication rates stratified by PUD status. For RAC 3-, RAC 7-, and RAC 10-day versus OAC 10-day, these stratified confidence intervals were (-60.6, -42.6), (-5.4, 10.5), and (-3.3, 12.1), respectively. These confidence intervals are very similar to the unstratified confidence intervals shown in Table 16.

Comparison of Eradication for Rabeprazole Treatment Arms

A comparison of *H. pylori* eradication rates between rabeprazole treatment groups is presented for the ITT and PP patient populations in Tables 17 and 18.

TABLE 17
Summary of *H. pylori* Eradication Rates for Rabeprazole Treatment Arms
Intent-to-Treat Patients

Treatment	Eradication Rates n (%)	95% Confidence Interval [a]
RAC 10-day	153 (78%)	
RAC 7-day	150 (77%)	
RAC 3-day	51 (27%)	
RAC 10-day minus RAC 7-day	0.74%	-7.54%, 9.03%
RAC 10-day minus RAC 3-day	50.79%	42.15%, 59.43%
RAC 7-day minus RAC 3-day	50.05%	41.34%, 58.76%

[a] Equivalence is defined as two-sided 95% confidence interval of difference within the equivalence range (-15%, 15%).

Statistical Reviewer's Comment: Although the choice of RAC treatment regimen was not specified as part of the primary objective of the trial, and the following analysis is therefore exploratory, the reviewer used a Bonferroni adjustment to produce confidence intervals for the difference in eradication rates among RAC treatment regimens which attempt to account for multiple comparisons so that the Type I error rate remains near 5%. Assuming we have 3 RAC comparisons of interest (RAC 10- versus 7-day, RAC 10- versus 3-day, and RAC 7- versus 3-day) plus the primary comparison of interest (the RAC regimens versus OAC, which is already adjusted for the multiple comparisons within), the reviewer used an alpha level of 0.05/4 = 0.0125. The 98.75% confidence interval for RAC 10-day minus RAC 7-day is (-10.3, 11.8). The 98.75% confidence interval for RAC 10-day minus RAC 3-day is (39.3, 62.3). The 98.75% confidence interval for RAC 7-day minus RAC 3-day is (38.5, 61.6). Thus, one would conclude that both the RAC 7- and 10-day regimens are significantly more effective than the RAC 3-day regimen, while the RAC 7- and 10-day regimens are equivalent using a delta of 15% (i.e., the CI for the difference falls within the range (-15%, 15%).)

TABLE 18
Summary of *H. pylori* Eradication Rates for Rabeprazole Treatment Arms
Per Protocol Patients

Treatment	Eradication Rates n (%)	95% Confidence Interval [a]
RAC 10-day	147 (86%)	
RAC 7-day	140 (84%)	
RAC 3-day	50 (30%)	
RAC 10-day minus RAC 7-day	1.63%	-5.99%, 9.24%
RAC 10-day minus RAC 3-day	56.02%	47.32%, 64.73%
RAC 7-day minus RAC 3-day	54.40%	45.49%, 63.30%

[a] Equivalence is defined as two-sided 95% confidence interval of difference within the equivalence range (-15%, 15%).

Statistical Reviewer's Comment: As with the ITT analysis above, the following analysis is exploratory, as it was not pre-specified in the protocol. The reviewer used a Bonferroni adjustment to account for the 3 RAC comparisons of interest plus the primary comparison of interest (the RAC regimens versus OAC) to control the Type I error near 5%. The alpha

level used was 0.05/4 = 0.0125. The 98.75% confidence interval for RAC 10-day minus RAC 7-day is (-8.6, 11.9). The 98.75% confidence interval for RAC 10-day minus RAC 3-day is (44.4, 67.7). The 98.75% confidence interval for RAC 7-day minus RAC 3-day is (42.5, 66.3). Thus, one would conclude that both the RAC 7- and 10-day regimens are significantly more effective than the RAC 3-day regimen, while the RAC 7- and 10-day regimens are equivalent using a delta of 15%.

In the ITT and PP patient populations, the 7-day RAC treatment regimen produces statistically equivalent *H. pylori* eradication rates (77% and 84%, respectively) to the 10-day RAC treatment regimen (78% and 86%, respectively). The 3-day RAC treatment regimen is not equivalent to either the 7-day or 10-day RAC treatment regimens and produces a *H. pylori* eradication rate significantly less than the eradication rates produced by the 7-day and 10-day RAC treatment regimens.

Comparison of Eradication by Treatment Regimen and Disease Strata

A summary of eradication rates by treatment and disease strata (i.e., PUD versus NPUD) in patients in the ITT and PP populations are presented in Table 19 and 20, respectively. In general, analysis by regimen and disease strata shows no significant differences in eradication rates favoring NPUD patients compared to PUD patients. In the 10-day RAC regimen the difference in eradication rates is small in the ITT population (79% for NPUD vs. 77% for PUD) and the upper bound of the 95% CI was > 10%. In the PP population, the eradication rate is 86% for both NPUD and PUD patients.

Analysis of disease strata with the logistic model demonstrated no relationship between disease strata and eradication rates (see next subsection).

Clinical Reviewer's Comment: The eradication rates in the 7-day RAC arm appear numerically lower for the NPUD compared to PUD strata in both the ITT (73% versus 81%) and PP (80% versus 89%) populations. However, these differences are not clinically significant (i.e., the upper bound of the 95% confidence interval of the difference (NPUD – PUD) is less than 10%. In addition, there was no significant treatment interaction.

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TABLE 19
***H. pylori* Eradication Rates by Treatment Regimen and Disease Strata**
Intention-to-Treat Patients

Treatment	Eradication	NPUD n (%)	PUD n (%)	Difference in Eradication Rates (NPUD-PUD)	95% Confidence Interval [a]
RAC 3-day					
	Yes	27 (28%)	24 (27%)	1.17%	-11.7%, 14.01%
	No	70 (72%)	66 (73%)		
RAC 7-day					
	Yes	68 (73%)	82 (81%)	-8.07%	-19.9%, 3.79%
	No	25 (27%)	19 (19%)		
RAC 10-day					
	Yes	78 (79%)	75 (77%)	1.47%	-10.2%, 13.12%
	No	21 (21%)	22 (23%)		
OAC 10-day					
	Yes	74 (72%)	77 (75%)	-2.91%	-15.0%, 9.22%
	No	29 (28%)	26 (25%)		

[a] Rates for NPUD were considered not clinically higher if the upper bound of the 95% confidence interval of the difference (NPUD – PUD) was < 10%.

TABLE 20
***H. pylori* Eradication Rates by Treatment Regimen and Disease Strata**
Per Protocol Patients

Treatment	Eradication	NPUD n (%)	PUD n (%)	Difference in Eradication Rates (NPUD-PUD)	95% Confidence Interval [a]
RAC 3-day					
	Yes	27 (30%)	23 (29%)	0.85%	-13.1%, 14.85%
	No	62 (70%)	55 (71%)		
RAC 7-day					
	Yes	63 (80%)	77 (89%)	-8.76%	-19.9%, 2.42%
	No	16 (20%)	10 (11%)		
RAC 10-day					
	Yes	74 (86%)	73 (86%)	0.16%	-10.3%, 10.64%
	No	12 (14%)	12 (14%)		
OAC 10-day					
	Yes	74 (80%)	72 (83%)	-2.32%	-13.7%, 9.09%
	No	18 (20%)	15 (17%)		

[a] Rates for NPUD were considered not clinically higher if the upper bound of the 95% confidence interval of the difference (NPUD – PUD) was < 10%.

Subgroup Analyses of *H. pylori* Eradication

Statistical Reviewer's Comments: Results for the primary efficacy variable for various subgroups including age, gender, race, smoking status, alcohol intake, PUD strata, and compliance with treatment regimen were performed by the reviewer.

Tables 21 and 22 below summarize results for the primary efficacy variable by treatment regimen and subgroup for intent-to-treat and per protocol patients, respectively. In both patient populations, eradication rates in the various subgroups are found to be generally consistent with respect to overall treatment eradication rates. Two exceptions are that (1) eradication rates are somewhat lower in black patients compared to whites and Hispanics for the treatment regimens that showed efficacy (i.e., RAC 7-day, RAC 10-day, and OAC 10-day), although the number of black patients studied is small, and (2) among patients who are non-compliant with their treatment regimen, almost none had their H. pylori eradicated. Eradication rates by subgroup are generally similar among the RAC 7-day, RAC 10-day, and OAC 10-day treatment regimens. The only substantial difference in eradication rates between the RAC 7- and 10-day regimens occurs in elderly patients (>65 years old), where the RAC 7-day eradication rate is about 20 percentage points lower than the RAC 10-day eradication rate in ITT patients, and 30 percentage points lower in PP patients. As the number of elderly patients studied is small, however, one cannot drawn any substantive conclusions from this result.

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TABLE 21
Summary of *H. pylori* Eradication Rates ≥ 6 Weeks from the End of Treatment by Subgroup Intent-to-Treat Patients

Subgroup	RAC 3-Day % (n/N)	RAC 7-Day % (n/N)	RAC 10-Day % (n/N)	OAC 10-Day % (n/N)
Age				
≤65 years old	26 (43/168)	79 (137/174)	77 (134/174)	74 (141/191)
>65 years old	42 (8/19)	65 (13/20)	86 (19/22)	67 (10/15)
Gender				
Male	27 (21/79)	80 (73/91)	82 (77/94)	76 (68/89)
Female	28 (30/108)	75 (77/103)	75 (76/102)	71 (83/117)
Race				
White	29 (20/68)	78 (58/74)	77 (63/82)	71 (60/84)
Hispanic	25 (20/80)	79 (69/87)	82 (70/85)	78 (68/87)
Black	27 (9/33)	73 (19/26)	67 (12/18)	63 (17/27)
Other	33 (2/6)	57 (4/7)	73 (8/11)	75 (6/8)
Smoking Status				
Yes	30 (25/83)	77 (58/75)	73 (73/100)	72 (71/99)
No	25 (26/104)	77 (92/119)	83 (80/96)	75 (80/107)
Alcohol Intake				
Yes	28 (25/90)	81 (79/97)	76 (76/100)	72 (76/105)
No	27 (26/97)	73 (71/97)	80 (77/96)	74 (75/101)
PUD Strata				
PUD	27 (24/90)	81 (82/101)	77 (75/97)	75 (77/103)
NPUD	28 (27/97)	73 (68/93)	79 (78/99)	72 (74/103)
Compliance				
Yes	28 (51/181)	80 (148/185)	79 (153/193)	76 (151/199)
No	0 (0/6)	22 (2/9)	0 (0/3)	0 (0/7)

TABLE 22
Summary of *H. pylori* Eradication Rates ≥ 6 Weeks from the End of Treatment by Subgroup Per Protocol Patients

Subgroup	RAC 3-Day % (n/N)	RAC 7-Day % (n/N)	RAC 10-Day % (n/N)	OAC 10-Day % (n/N)
Age				
≤65 years old	28 (42/149)	87 (130/150)	85 (131/154)	82 (136/166)
>65 years old	44 (8/18)	63 (10/16)	94 (16/17)	77 (10/13)
Gender				
Male	29 (21/73)	88 (71/81)	86 (74/86)	87 (66/76)
Female	31 (29/94)	81 (69/85)	86 (73/85)	78 (80/103)
Race				
White	31 (20/65)	85 (56/66)	85 (60/71)	82 (58/71)
Hispanic	29 (20/69)	87 (65/75)	91 (69/76)	83 (65/78)
Black	30 (8/27)	75 (15/20)	71 (10/14)	74 (17/23)
Other	33 (2/6)	80 (4/5)	80 (8/10)	86 (6/7)
Smoking Status				
Yes	33 (25/75)	83 (53/64)	82 (69/84)	81 (67/83)
No	27 (25/92)	85 (87/102)	90 (78/87)	82 (79/96)
Alcohol Intake				
Yes	30 (24/81)	88 (75/85)	81 (74/91)	82 (74/90)
No	30 (26/86)	80 (65/81)	91 (73/80)	81 (72/89)
PUD Strata				
PUD	29 (23/78)	89 (77/87)	86 (73/85)	83 (72/87)
NPUD	30 (27/89)	80 (63/79)	86 (74/86)	80 (74/92)
Compliance				
Yes	31 (50/161)	87 (140/161)	87 (147/169)	84 (146/174)
No	0 (0/6)	0 (0/5)	0 (0/2)	0 (0/5)

Covariate Analyses of *H. pylori* Eradication

A logistic analysis model was used to examine the effect of covariates, with treatment as a factor, and treatment by covariate interactions.

Statistical Reviewer's Comments: The reviewer also performed logistic regression analyses to determine the effect of covariates on eradication rates, while accounting for treatment assignment. The results of the reviewer's analyses, and not those of the applicant, are shown below.

For each covariate investigated, the logistic regression model included the covariate and treatment as factors and a treatment-by-covariate interaction term. While the applicant used three difference models for each covariate, examining treatment pairs separately (i.e., RAC 3-day v. OAC 10-day, RAC 7-day v. OAC 10-day, and RAC 10-day v. OAC 10-day), the reviewer used one model incorporating all of the data and all four treatment regimens. Results were similar using both approaches. Covariates investigated were center, age, gender, race, smoking status, alcohol intake, PUD strata, and compliance. Both age and compliance were modeled twice, first as continuous variables (number years old and percentage drug taken, respectively), and second as categorical variables (younger v. older patients, using 65 years of age as the cutoff point, and compliant v. not compliant, where compliance was defined as a subject who took at least 75% of their medication and did not miss more than 4 consecutive doses). A 5% significance level was used for main factors

(i.e., treatment and covariates), while a 10% significance level was used for interaction terms.

In the ITT population, the only covariate with a significant effect on eradication rates is the percent of drug taken (i.e., compliance treated as a continuous variable). The p-value is < 0.001. Not surprisingly, the more drug a subject took the more likely they are to be successfully eradicated of H. pylori. Interestingly, compliance is not significant when treated as a categorical variable. There are no significant treatment-by-covariate interactions.

In the PP population, again the only covariate with a significant effect on eradication rates is compliance treated as a continuous variable (p < 0.001). There is one significant treatment-by-covariate interaction in the PP population: the treatment-by-age group interaction is significant (p = 0.03). This result appears to be driven by the fact that in younger patients, 7-day RAC 7-day performs better than 10-day OAC, but in older patients 10-day OAC performs better than 7-day RAC. The treatment-by-age interaction is not significant when age was treated as a continuous variable, however.

7. Evaluability Status

Baseline *H. pylori* infection status based on results of the three pre-treatment diagnostic tests (UBT, culture, and rapid urease test) in the population of All Randomized patients is presented in Table 23. The results of the post-treatment endoscopic tests (culture, histology, and rapid urease test) are shown in Table 24.

Clinical Reviewer's Comment: Although biopsies were obtained for histological diagnosis pre-treatment, they were not used to determine patient evaluability, therefore, the results are not reported in Table 23.

TABLE 23
Classification of *H. pylori* Infection Based on Diagnostic Tests for *H. pylori* at Baseline
All Randomized Patients

UBT	Culture	Rapid Urease Test	Patient Status	RAC 3 day (N=194)	RAC 7 day (N=200)	RAC 10 day (N=202)	OAC 10 day (N=207)
Three Tests Available							
+	+	+	Infected	150 (77%)	160 (80%)	153 (76%)	148 (71%)
+	+	-	Infected	0	0	0	1 (<1%)
+	-	+	Infected	43 (225)	33 (17%)	42 (21%)	52 (25%)
+	-	-	Not Infected	0	0	1 (<1%)	0
-	+	+	Infected	0	0	0	0
-	+	-	Infected	0	0	0	0
-	-	+	Not Infected	0	0	0	0
-	-	-	Not Infected	0	0	0	0
Two Tests Available							
+	+	NA	Infected	0	0	0	0
+	-	NA	Not Infected	0	0	0	0
+	NA	+	Infected	0	7 (4%)	5 (2%)	5 (2%)
+	NA	-	Not Infected	0	0	0	0
-	+	NA	Infected	0	0	0	0
-	-	NA	Not Infected	0	0	0	0
-	NA	+	Not Infected	1 (<1%)	0	0	0
-	NA	-	Not Infected	0	0	0	0
NA	+	+	Infected	0	0	0	1 (<1%)
NA	+	-	Infected	0	0	0	0
NA	-	+	Not Infected	0	0	0	0
NA	-	-	Not Infected	0	0	0	0
Zero or One Test Available							
+	NA	NA	Not Infected	0	0	0	0
-	NA	NA	Not Infected	0	0	0	0
NA	+	NA	Infected	0	0	0	0
NA	-	NA	Not Infected	0	0	0	0
NA	NA	+	Not Infected	0	0	0	0
NA	NA	-	Not Infected	0	0	0	0
NA	NA	NA	Not Infected	0	0	0	0

Clinical Reviewer's Comment: All patients in Table 24 have a positive UBT therefore all are considered infected, regardless of the results of the endoscopic tests.

TABLE 24
Endoscopic Test Results for *H. pylori* at Follow-up
Only Patients with Positive UBT at Follow-up

Culture	Histology	Rapid Urease Test	RAC 3 day (N=116)	RAC 7 day (N=27)	RAC 10 day (N=25)	OAC 10 day (N=30)
Three Tests Available						
+	+	+	59 (51%)	13 (48%)	14 (56%)	11 (37%)
+	+	-	2 (2%)	0	0	1 (3%)
-	+	+	33 (28%)	8 (30%)	6 (24%)	6 (20%)
-	+	-	1 (<1%)	0	0	2 (7%)
+	-	+	2 (2%)	0	0	0
+	-	-	0	0	0	1 (3%)
-	-	+	2 (2%)	1 (4%)	0	2 (7%)
-	-	-	1 (<1%)	0	2 (8%)	3 (10%)
Two Tests Available						
+	+	NA	0	0	0	0
+	-	NA	1 (<1%)	0	1 (4%)	0
+	NA	+	0	1 (4%)	0	1 (3%)
+	NA	-	0	0	0	0
-	+	NA	0	0	0	0
-	-	NA	0	0	0	0
-	NA	+	0	0	0	0
-	NA	-	0	0	0	0
NA	+	+	4 (3%)	0	0	1 (3%)
NA	+	-	1 (<1%)	0	0	0
NA	-	+	0	0	0	0
NA	-	-	0	0	0	0
Zero or One Test Available						
+	NA	NA	0	0	0	0
-	NA	NA	0	0	0	0
NA	+	NA	0	0	0	0
NA	-	NA	0	0	0	0
NA	NA	+	0	0	0	0
NA	NA	-	0	0	0	0
NA	NA	NA	10 (9%)	4 (15%)	2 (8%)	2 (7%)

8. Susceptibility

Screening (Pre-Treatment) Susceptibility in Relation to Eradication

A summary of *H. pylori* eradication by susceptibility to amoxicillin, clarithromycin, and both antimicrobials at screening (i.e., pre-treatment) in the ITT and PP populations are presented in Tables 25 and 26, respectively.

Amoxicillin

For amoxicillin-susceptible *H. pylori*, the eradication rates in the ITT population are 25% in the 3-day RAC, 75% in the 7-day RAC, 79% in the 10-day RAC, and 73% in the 10-day OAC treatment groups. In the PP population, the eradication rates for amoxicillin-

susceptible *H. pylori* are 26% in the 3-day RAC, 85% in the 7-day RAC, 86% in the 10-day RAC, and 81% in the 10-day OAC treatment.

There are only two patients (0588001716 and 0609001553) in the study with *H. pylori* isolates resistant to amoxicillin at screening, both of which are also resistant to clarithromycin at screening. Both patients are in the 7-day RAC arm. In one patient, the bacterium was eradicated and in the other patient it was not. For both patients, the *H. pylori* isolate MIC is 0.5 µg/mL.

Clarithromycin
For clarithromycin-susceptible *H. pylori*, the eradication rates in the ITT population are 27% (33/124) in the 3-day RAC, 80% (103/129) in the 7-day RAC, 83% (111/133) in the 10-day RAC, and 79% (96/121) in the 10-day OAC treatment groups. In the PP population, the eradication rates for clarithromycin-susceptible *H. pylori* are 28% (32/113) in the 3-day RAC, 90% (95/105) in the 7-day RAC, 91% (106/116) in the 10-day RAC, and 89% (95/107) in the 10-day OAC groups.

For clarithromycin non-susceptible *H. pylori* (i.e., intermediate and resistant), the eradication rates in the ITT population are 0% (0/10) in the 3-day RAC, 31% (5/16) in the 7-day RAC, 11% (1/9) in the 10-day RAC, and 28% (5/18) in the 10-day OAC treatment groups. In the PP population, the eradication rates for clarithromycin non-susceptible *H. pylori* are 0% (0/8) in the 3-day RAC, 36% (5/9) in the 7-day RAC, 11% (1/9) in the 10-day RAC, and 27% (4/15) in the 10-day OAC groups.

Amoxicillin and Clarithromycin
In *H. pylori* organisms susceptible to both antibiotics, the eradication rates are 27% in the 3-day RAC, 80% in the 7-day RAC, 83% in the 10-day RAC, and 79% in the 10-day OAC groups. In the PP population, the eradication rates for organisms susceptible to both antibiotics are 28% in the 3-day RAC, 90% in the 7-day RAC, 91% in the 10-day RAC, and 89% in the 10-day OAC groups.

TABLE 25

***H. pylori* Eradication Rates by Antimicrobial Susceptibility at Screening Intention-to-Treat Patients**

Treatment	Amoxicillin		Clarithromycin		Both Antibiotics [a]	
	Helicobacter Outcome					
	Eradicated [b]	Not Eradicated	Eradicated	Not Eradicated	Eradicated	Not Eradicated
RAC 3-day (N = 134)						
Susceptible	33 (25%)	101 (75%)	33 (27%)	91 (73%)	33 (27%)	91 (73%)
Intermediate	0	0	0	1 (100%)	0	1 (100%)
Resistant	0	0	0	9 (100%)	0	9 (100%)
RAC 7-day (N = 145)						
Susceptible	107 (75%)	36 (25%)	103 (80%)	26 (20%)	103 (80%)	26 (20%)
Intermediate	0	0	0	0	0	0
Resistant	1 (50%)	1 (50%)	5 (31%)	11 (69%)	5 (31%)	11 (69%)
RAC 10-day (N = 142)						
Susceptible	112 (79%)	30 (21%)	111 (83%)	22 (17%)	111 (83%)	22 (17%)
Intermediate	0	0	0	0	0	0
Resistant	0	0	1 (11%)	8 (89%)	1 (11%)	8 (89%)
OAC 10-day (N = 139)						
Susceptible	101 (73%)	38 (27%)	96 (79%)	25 (21%)	96 (79%)	25 (21%)
Intermediate	0	0	1 (100%)	0	1 (100%)	0
Resistant	0	0	4 (24%)	13 (76%)	4 (24%)	13 (76%)

[a] Both antibiotics: Resistance was defined as susceptible if the organism was susceptible to both amoxicillin and clarithromycin, intermediate if the organism was susceptible to amoxicillin and intermediate to clarithromycin, and resistant if the organism was resistant to either antibiotic.

[b] To test the hypothesis that the eradication rates among organisms susceptible to the antibiotics was ≥ 80%. Eradication was defined by a negative ^{13}C-UBT at end of study.

TABLE 26
***H. pylori* Eradication Rates by Antimicrobial Susceptibility at Screening**
Per Protocol Patients

Treatment	Amoxicillin		Clarithromycin		Both Antibiotics [a]	
	Helicobacter Outcome					
	Eradicated [b]	Not Eradicated	Eradicated	Not Eradicated	Eradicated	Not Eradicated
RAC 3-day (N = 121)						
Susceptible	32 (26%)	89 (74%)	32 (28%)	81 (72%)	32 (28%)	81 (72%)
Intermediate	0	0	0	0	0	0
Resistant	0	0	0	8 (100%)	0	8 (100%)
RAC 7-day (N = 119)						
Susceptible	99 (85%)	18 (15%)	95 (90%)	10 (10%)	95 (90%)	10 (10%)
Intermediate	0	0	0	0	0	0
Resistant	1 (50%)	1 (50%)	5 (36%)	9 (64%)	5 (36%)	9 (64%)
RAC 10-day (N = 125)						
Susceptible	107 (86%)	18 (14%)	106 (91%)	10 (9%)	106 (91%)	10 (9%)
Intermediate	0	0	0	0	0	0
Resistant	0	0	1 (11%)	8 (89%)	1 (11%)	8 (89%)
OAC 10-day (N = 122)						
Susceptible	99 (81%)	23 (19%)	95 (89%)	12 (11%)	95 (89%)	12 (11%)
Intermediate	0	0	1 (100%)	0	1 (100%)	0
Resistant	0	0	3 (21%)	11 (79%)	3 (21%)	11 (79%)

[a] Both antibiotics: Resistance was defined as susceptible if the organism was susceptible to both amoxicillin and clarithromycin, intermediate if the organism was susceptible to amoxicillin and intermediate to clarithromycin, and resistant if the organism was resistant to either antibiotic.
[b] To test the hypothesis that the eradication rates among organisms susceptible to the antibiotics was ≥ 80%. Eradication was defined by a negative ^{13}C-UBT at end of study.

Emerging Resistance

A summary of shift in clarithromycin susceptibility from screening to test of cure (i.e., emerging resistance) is presented for the ITT and PP populations in Tables 27 and 28, respectively. Only patients with a positive ^{13}C-UBT at the test of cure visit (i.e., ≥ 42 days following the end of treatment) had a follow-up endoscopy performed and biopsy samples obtained for susceptibility testing. The number of these patients was small, particularly in the 7-day RAC, 10-day RAC and OAC regimens.

Clinical and Statistical Reviewers' Comment: Tables 27 and 28 should be interpreted with caution as the small number of patients for which data are available, particularly in the 7-day RAC, 10-day RAC and OAC regimens, are small and most likely do not represent the entire original ITT or PP population.

TABLE 27
Summary of Shift in Clarithromycin Susceptibility – Intent-to-Treat Patients

Treatment	Clarithromycin Susceptibility at Screening		
	Susceptible	Intermediate	Resistant
RAC 3-day – Test of Cure (N = 43)			
Susceptible	38 (88%)	0	0
Intermediate	1 (2%)	0	0
Resistant	2 (5%)	0	2 (5%)
RAC 7-day – Test of Cure (N = 10)			
Susceptible	2 (20%)	0	2 (20%)
Intermediate	0	0	1 (10%)
Resistant	1 (10%)	0	4 (40%)
RAC 10-day – Test of Cure (N = 10)			
Susceptible	3 (30%)	0	0
Intermediate	1 (10%)	0	0
Resistant	2 (20%)	0	4 (40%)
OAC 10-day – Test of Cure (N = 9)			
Susceptible	0	0	1 (11%)
Intermediate	0	0	0
Resistant	2 (22%)	0	6 (67%)
Total – Test of Cure (N = 72)			
Susceptible	43 (60%)	0	3 (4%)
Intermediate	2 (3%)	0	1 (1%)
Resistant	7 (10%)	0	16 (22%)

Includes only patients with a positive ^{13}C-UBT at post-treatment and pre- and post-antibiotic susceptibility results.

TABLE 26
Summary of Shift in Clarithromycin Susceptibility – Per Protocol Patients

Treatment	Clarithromycin Susceptibility at Screening		
	Susceptible	Intermediate	Resistant
RAC 3-day – Test of Cure (N = 43)			
Susceptible	38 (88%)	0	0
Intermediate	1 (2%)	0	0
Resistant	2 (5%)	0	2 (5%)
RAC 7-day – Test of Cure (N = 7)			
Susceptible	2 (29%)	0	2 (29%)
Intermediate	0	0	1 (14%)
Resistant	0	0	2 (29%)
RAC 10-day – Test of Cure (N = 9)			
Susceptible	3 (33%)	0	0
Intermediate	1 (11%)	0	0
Resistant	1 (11%)	0	4 (44%)
OAC 10-day – Test of Cure (N = 9)			
Susceptible	0	0	1 (11%)
Intermediate	0	0	0
Resistant	2 (22%)	0	6 (67%)
Total – Test of Cure (N = 68)			
Susceptible	43 (63%)	0	3 (4%)
Intermediate	2 (3%)	0	1 (1%)
Resistant	5 (7%)	0	14 (21%)

Only includes patients with a positive ^{13}C-UBT at post-treatment and pre- and post-antibiotic susceptibility results.

Emerging Resistance by Eradication Status

A summary of shift in clarithromycin susceptibility by eradication status from screening to test of cure is presented for the ITT and PP populations in Tables 29 and 30, respectively.

TABLE 29
Summary of Shift in Clarithromycin Susceptibility by Eradication Status
Intent-to-Treat Patients

Clarithromycin Pretreatment Results		*H. pylori* Negative (Eradicated)	*H. pylori* Positive (Not Eradicated) Post-treatment Susceptibility Results			
			Susceptible	Intermediate	Resistant	No MIC
RAC 3-day						
Susceptible	124	33	41	1	2	47
Intermediate	1	0	0	0	0	1
Resistant	9	0	0	0	2	7
No MIC	53	18	9	0	2	24
RAC 7-day						
Susceptible	129	103	2	0	1	23
Intermediate	0	0	0	0	0	0
Resistant	16	5	2	1	4	4
No MIC	49	42	1	0	2	4
RAC 10-day						
Susceptible	133	111	3	1	2	16
Intermediate	0	0	0	0	0	0
Resistant	9	1	0	0	5	3
No MIC	54	41	1	0	2	10
OAC 10-day						
Susceptible	121	96	0	0	2	23
Intermediate	1	1	0	0	0	0
Resistant	17	4	1	0	8	4
No MIC	67	50	0	0	3	14

TABLE 30
Summary of Shift in Clarithromycin Susceptibility by Eradication Status
Per Protocol Patients

Clarithromycin Pretreatment Results		*H. pylori* Negative (Eradicated)	*H. pylori* Positive (Not Eradicated) Post-treatment Susceptibility Results			
			Susceptible	Intermediate	Resistant	No MIC
RAC 3-day						
Susceptible	113	32	41	1	2	37
Intermediate	0	0	0	0	0	0
Resistant	8	0	0	0	2	6
No MIC	46	18	9	0	2	17
RAC 7-day						
Susceptible	105	95	2	0	0	8
Intermediate	0	0	0	0	0	0
Resistant	14	5	2	1	2	4
No MIC	47	40	1	0	2	4
RAC 10-day						
Susceptible	116	106	3	1	1	5
Intermediate	0	0	0	0	0	0
Resistant	9	1	0	0	5	3
No MIC	46	40	1	0	2	3
OAC 10-day						
Susceptible	107	95	0	0	2	10
Intermediate	1	1	0	0	0	0
Resistant	14	3	1	0	8	2
No MIC	57	47	0	0	3	7

9. Safety Analyses

A summary of overall treatment-emergent adverse events (TEAEs) in the Safety population is presented in Table 31. There are no statistically significant differences across treatment groups in the occurrence of TEAEs.

TABLE 31
Overall Summary of Treatment-Emergent Adverse Events – Safety Patients

	RAC 3-day (N = 188)	RAC 7-day (N = 195)	RAC 10-day (N = 198)	OAC 10-day (N = 207)
Number of Patients With at Least One:				
Event	107 (57%)	109 (56%)	104 (53%)	122 (59%)
Possibly or Probably Drug-Related [a] Event	49 (26%)	58 (30%)	57 (29%)	73 (35%)
Serious Event	2 (1%)	3 (2%)	4 (2%)	2 (<1%)
Drug-Related[a] Serious Event	0	0	0	1 (<1%)
Event Leading to Discontinuation from the Study	7 (4%)	7 (4%)	4 (2%)	5 (2%)

[a] Relationship as per the Investigator.

Clinical Reviewer's Comment: The total number of discontinuations in Table 31 (23 patients) differs from Table 8 (26 patients), because three of the 26 AEs are not treatment-emergent (Patients 587001327 in 3-day RAC, 598001071 in 7-day RAC, and 607001776 in 10-day OAC).

Note: Patient identifiers => first 4 digits are the site number, next two digits are "00", and the last 4 digits are the patient number.

A summary of the most common TEAEs (≥5% in any group) for the Safety population is presented in Table 32 below.

TABLE 32
Summary of Treatment-Emergent Adverse Events (≥ 5%) - Safety Patients

Preferred Term	RAC 3-day (N = 188)	RAC 7-day (N = 195)	RAC 10-day (N = 198)	OAC 10-day (N = 207)
Dyspepsia	17 (9%)	22 (11%)	11 (6%)	22 (11%)
Diarrhea	15 (8%)	19 (10%)	16 (8%)	22 (11%)
Taste Perversion	9 (5%)* **	11 (6%)**	20 (10%)	23 (11%)
Abdominal Pain	15 (8%)	11 (6%)	15 (8%)	17 (8%)
Headache	8 (4%)	9 (5%)	16 (8%)	6 (3%)
Nausea	12 (6%)	14 (7%)	8 (4%)	15 (7%)
Flatulence	10 (5%)	14 (7%)	9 (5%)	5 (2%)
Infection	10 (5%)	4 (2%)	7 (4%)	5 (2%)
Anorexia	9 (5%)	5 (3%)	6 (3%)	7 (3%)

Patients are counted only once per event.
* $p \leq 0.05$ vs. 10-day RAC group, from Chi-square test.
** $p \leq 0.05$ vs. 10-day OAC group, from Chi-square test.

There are no statistically significant treatment group differences in the percentage of patients reporting TEAEs (57% 3-day RAC, 56% 7-day RAC, 53% 10-day RAC, and 59% 10-day OAC; p=0.624, from Chi-square or Fisher's exact test, as appropriate). No more than 11% of patients in any treatment group experienced an individual TEAE. The gastrointestinal TEAEs reported by the largest number of patients in each group include dyspepsia, diarrhea, abdominal pain, nausea, flatulence, and anorexia.

Overall Analysis of Adverse Events

Statistical analyses were performed to determine if there were statistically significant differences across treatment groups in specific TEAEs. Examining events occurring at a frequency of ≥ 5%, taste perversion is the only event that exhibited statistically significant differences across treatment groups. There are fewer patients experiencing taste perversion with the 3-day and 7-day RAC treatment regimens compared to the OAC treatment regimen ($p<0.05$). There are also fewer patients experiencing taste perversion with the 3-day RAC treatment regimen compared to 10-day RAC ($p<0.05$). There are no statistically significant differences between any of the other treatment groups.

Clinical and Statistical Reviewers' Comment: Although the applicant emphasizes the difference in taste perversion in the RAC groups compared to OAC, the study is not powered to demonstrate differences in the incidence of individual AEs between the treatment regimens.

Analysis of Adverse Events by Subgroup (Age, Gender and Ethnicity)

The most frequently reported adverse events (> 5% incidence overall) by age (< 65 and ≥ 65), gender, and race (Caucasian, Black, Asian, Other) are shown below in Tables 33-35.

As seen in Table 33, overall patients < 65 years old have a slightly lower incidence of diarrhea than patients ≥ 65 years. This is also true for all RAC treatment arms, but not for

OAC treatment where more younger patients have diarrhea. Taste perversion is also slightly lower overall in the younger patients and in the RAC 3-day, RAC 7-day, and OAC 10-day treatment arms, whereas the incidence is similar in the 10-day RAC arm. Younger patients have a higher incidence of abdominal pain and flatulence, both overall and for each treatment arm. It should be noted that the number of older patients in each treatment arm represents only about 10% of the population in that arm, so interpretation of these conclusions should be done with caution.

As seen in Table 34, overall the incidence of TEAEs is similar for males and females. Diarrhea occurs more frequently in males, while abdominal pain in more common in females in the 3-day RAC arm. Headache occurs more frequently in females in all treatment arms, except the 3-day RAC arm where it is more common in males. Nausea is more common in females in the 7-day RAC, 10-day RAC, and 10-day OAC arms. Taste perversion is more common in males compared to females in the 7-day RAC arm. Overall, these differences are small and unlikely to result in clinically meaningful differences.

As seen in Table 35 for the race analyses overall and by treatment arm Blacks appear to have a higher incidence of dyspepsia, diarrhea, and nausea than other races. Taste perversion occurs in both Whites and Blacks more frequently than in other races, except in the 10-day RAC group. The numbers of patients in the "Other" races category are small and therefore no reliable conclusions can be drawn from this group.

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TABLE 33
Patients (%) with Treatment-Emergent Adverse Events (≥ 5%) by Age
Safety Population

Preferred Term	Overall (N=788)		RAC 3-day (N = 188)		RAC 7-day (N = 195)		RAC 10-day (N = 198)		OAC 10-day (N = 207)	
	< 65 yrs (N=703)	≥ 65 yrs (N=85)	< 65 yrs (N=169)	≥ 65 yrs (N=19)	< 65 yrs (N=172)	≥ 65 yrs (N=23)	< 65 yrs (N=172)	≥ 65 yrs (N=26)	< 65 yrs (N=190)	≥ 65 yrs (N=17)
Dyspepsia	66 (9)	6 (7)	16 (9)	1 (5)	19 (11)	3 (13)	10 (6)	1 (4)	21 (11)	1 (6)
Diarrhea	62 (9)	10 (12)	13 (8)	2 (11)	16 (9)	3 (13)	12 (7)	4 (15)	21 (11)	1 (6)
Taste Perversion	54 (8)	9 (11)	7 (4)	2 (11)	9 (5)	2 (9)	18 (10)	2 (8)	20 (11)	3 (18)
Abdominal Pain	55 (8)	3 (4)	14 (8)	1 (5)	10 (6)	1 (4)	17 (9)	1 (4)	55 (8)	0
Headache	35 (5)	4 (5)	7 (4)	1 (5)	8 (5)	1 (4)	14 (8)	2(8)	6 (3)	0
Nausea	44 (6)	5 (6)	11 (7)	1 (5)	12 (7)	2 (9)	6 (3)	2 (8)	15 (8)	0
Flatulence	38 (5)	0	10 (6)	0	14 (8)	0	9 (5)	0	5 (3)	0
Infection	23 (3)	3 (4)	10 (6)	0	3 (2)	1 (4)	7 (4)	0	3 (2)	2 (12)
Anorexia	26 (4)	1 (1)	9 (5)	0	5 (3)	0	6 (3)	0	6 (3)	1 (6)

Patients are counted only once per event.

TABLE 34
Patients (%) with Treatment-Emergent Adverse Events (≥ 5%) by Gender
Safety Population

Preferred Term	Overall (N=788)		RAC 3-day (N = 188)		RAC 7-day (N = 195)		RAC 10-day (N = 198)		OAC 10-day (N = 207)	
	Male (N=353)	Female (N=435)	Male (N=79)	Female (N=109)	Male (N=91)	Female (N=104)	Male (N=94)	Female (N=104)	Male (N=89)	Female (N=118)
Dyspepsia	33 (9)	39 (9)	9 (11)	10 (9)	9 (10)	10 (10)	7 (7)	8 (8)	11 (12)	11 (9)
Diarrhea	36 (10)	36 (8)	9 (11)	6 (6)	9 (10)	10 (10)	7 (7)	9 (9)	11 (12)	11 (9)
Taste Perversion	31 (9)	32 (7)	5 (6)	4 (4)	7 (8)	4 (4)	9 (10)	11 (11)	10 (11)	13 (11)
Abdominal Pain	24 (7)	34 (8)	4 (5)	11 (10)	5 (5)	6 (6)	7 97)	8 98)	8 (9)	9 (8)
Headache	14 (4)	25 (6)	5 (6)	3 (3)	2 (2)	7 (7)	6 (6)	10 (10)	1 (1)	5 (4)
Nausea	13 (4)	36 (8)	5 (6)	7 (6)	2 (2)	12 (12)	1 (1)	7 (7)	5 (6)	10 (8)
Flatulence	20 (6)	18 (4)	5 (6)	5 (5)	7 (8)	7 (7)	5 (5)	4 (4)	3 (3)	2 (2)
Infection	15 (4)	11 (3)	6 (8)	4 (4)	3 (3)	1 (<1)	3 (3)	4 (4)	3 (3)	2 (2)
Anorexia	13 (4)	14 (3)	4 (5)	5 (5)	3 (3)	2(2)	2 (2)	4 (4)	4 (4)	3 (3)

Patients are counted only once per event.

TABLE 35A
Patients (%) with Treatment-Emergent Adverse Events (≥ 5%) by Race Overall Safety Population

Preferred Term	Overall (N=788)			
	White (N=309)	Black (N=104)	Hispanic (N=343)	Other (N=32)
Dyspepsia	25 (8)	17 (16)	24 (7)	6 (19)
Diarrhea	27 (9)	15 (14)	30 (9)	0
Taste Perversion	31 (10)	8 (9)	20 (6)	4 (13)
Abdominal Pain	23 (7)	8 (8)	24 (7)	3 (9)
Headache	12 (4)	6 (6)	19 (6)	2 (6)
Nausea	9 (3)	13 (13)	25 (7)	2 (6)
Flatulence	14 (5)	6 (6)	16 (5)	2 (6)
Infection	9 (3)	2 (2)	13 (4)	2 (6)
Anorexia	8 (3)	5 (5)	12 (3)	2 (6)

Patients are counted only once per event.

TABLE 35B
Patients (%) with Treatment-Emergent Adverse Events (≥ 5%) by Race and Treatment Safety Population

Preferred Term	RAC 3-day (N = 188)				RAC 7-day (N = 195)				RAC 10-day (N = 198)				OAC 10-day (N = 207)			
	White (N=68)	Black (N=33)	Hispanic (N=81)	Other (N=6)	White (N=74)	Black (N=26)	Hispanic (N=88)	Other (N=7)	White (N=83)	Black (N=18)	Hispanic (N=86)	Other (N=11)	White (N=84)	Black (N=27)	Hispanic (N=88)	Other (N=8)
Dyspepsia	5 (7)	6 (18)	5 (6)	1 (17)	9 (12)	3 (12)	8 (9)	2 (29)	4 (5)	2 (11)	3 (3)	2 (18)	7 (8)	6 (22)	8 (9)	1 (13)
Diarrhea	3 (4)	7 (21)	5 (6)	0	9 (12)	1 (4)	9 (10)	0	7 (8)	3 (17)	6 (7)	0	8 (10)	4 (15)	10 (11)	0
Taste Perversion	5 (7)	0	4 (5)	0	8 (11)	1 (4)	1 (1)	1 (14)	9 (11)	2 (11)	8 (9)	1 (9)	9 (11)	5 (19)	7 (8)	2 (25)
Abdominal Pain	7 (10)	4 (12)	4 (5)	0	4 (5)	0	7 (8)	0	8 (10)	1 (6)	4 (5)	2 (18)	4 (5)	3 (11)	9 (10)	1 (13)
Headache	2 (3)	3 (9)	3 (4)	0	1 (1)	2 (8)	5 (6)	1 (14)	6 (7)	1 (6)	8 (9)	1 (9)	3 (4)	0	3 (3)	0
Nausea	4 (6)	3 (9)	4 (5)	1 (17)	2 (3)	4 (15)	8 (9)	0	3 (4)	2 (11)	3 (3)	0	0	4 (15)	10 (11)	1 (13)
Flatulence	1 (1)	1 (3)	7 (9)	1 (17)	4 (5)	3 (12)	6 (7)	1 (14)	6 (7)	1 (6)	2 (2)	0	3 (4)	1 (4)	1 (1)	0
Infection	3 (4)	2 (6)	5 (6)	0	1 (1)	0	2 (2)	1 (14)	3 (4)	0	4 (5)	0	2 (2)	0	2 (2)	1 (13)
Anorexia	1 91)	3 (9)	5 (6)	0	2 (3)	1 (4)	1 (1)	1 (14)	3 (4)	0	3 (3)	0	2 (2)	1 (4)	3 (3)	1 (13)

Patients are counted only once per event.

Analysis of Adverse Events by Relationship to Study Medication

Adverse events by relationship to study medication and severity are shown in Table 36 below. The percentage of patients with TEAEs judged to be treatment-related is slightly higher in the 10-day OAC group (35%) compared to patients in the 3-day RAC (26%), 7-day RAC (29%), and 10-day RAC (29%) groups. The majority of the TEAEs are considered mild or moderate. Severe events occur in 4%, 8%, and 11% of the 3-day, 7-day, and 10-day RAC groups versus 12% in the OAC group.

TABLE 36
Summary of Patients with Treatment-Emergent Adverse Events by Relationship to Study Medication and Maximum Severity – Safety Patients

	RAC 3-day (N = 188)	RAC 7-day (N = 195)	RAC 10-day (N =198)	OAC 10-day (N = 207)	Total (N = 788)
Relationship [a,b]					
Not related	58 (31%)	51 (26%)	47 (24%)	49 (24%)	205 (26%)
Possibly related	32 (17%)	38 (19%)	39 (20%)	48 (23%)	157 (20%)
Probably related	17 (9%)	20 (10%)	18 (9%)	25 (12%)	80 (10%)
Severity [a]					
Mild	57 (30%)	53 (27%)	50 (25%)	63 (30%)	223 (28%)
Moderate	43 (23%)	41 (21%)	43 (22%)	47 (23%)	174 (22%)
Severe	7 (4%)	15 (8%)	11 (6%)	12 (6%)	45 (6%)

[a] Patients were counted only once per event. If a patient had more than one instance of an event, only the most severe instance was included in the summary.
[b] Relationship as per the Investigator.

TEAEs that are reported by ≥1% of patients with at least one event in any treatment group and that were judged to be either possibly or probably related to the study medication (relationship as per the Investigator) are summarized in Table 37.

TABLE 37
Summary of Patients with Treatment-Emergent Adverse Events Considered Possibly or Probably Related[a] to Study Medication (≥ 1%) – Safety Patients

Preferred Term	RAC 3-day (N = 188)	RAC 7-day (N = 195)	RAC 10-day (N = 198)	OAC 10-day (N = 207)
Taste Perversion	6 (3%)	11 (6%)	19 (10%)	23 (11%)
Diarrhea	11 (6%)	15 (8%)	14 (7%)	21 (10%)
Nausea	9 (5%)	5 (3%)	5 (3%)	12 (6%)
Headache	2 (1%)	4 (2%)	10 (5%)	2 (<1%)
Abdominal Pain	7 (4%)	3 (2%)	7 (4%)	5 (2%)
Dyspepsia	6 (3%)	7 (4%)	2 (1%)	9 (4%)
Flatulence	6 (3%)	5 (3%)	5 (3%)	2 (<1%)
Vaginal moniliasis	2 (1%)	4 (2%)	2 (1%)	7 (3%)
Anorexia	4 (2%)	2 (1%)	2 (1%)	4 (2%)
Dry mouth	0	1 (<1%)	3 (2%)	4 (2%)
Vomiting	2 (1%)	2 (1%)	2 (1%)	4 (2%)
Dizziness	3 (2%)	2 (1%)	2 (1%)	1 (<1%)
Rash	4 (2%)	2 (1%)	1(<1%)	1 (<1%)
Constipation	1 (<1%)	4 (2%)	2 (1%)	1 (<1%)
Gastrointestinal disorder	3 (2%)	0	0	1 (<1%)
Chest pain substernal	3 (2%)	1 (<1%)	0	0
Asthenia	2 (1%)	1 (<1%)	0	3 (1%)
Eructation	2 (1%)	1 (<1%)	1 (<1%)	2 (<1%)
Pruritus	0	1 (<1%)	2 (1%)	1 (<1%)
Tongue disorder	0	2 (1%)	0	0
Pain	0	0	0	3 (1%)

[a] Relationship of AE to study medication as per the Investigator.
Patients are counted only once per event.
If a patient had more than one instance of an event, only the most severe instance was included in the summary.

Deaths
There were no deaths reported in this study.

Non-Fatal Serious Adverse Events
A total of 23 SAEs occurred in 15 patients during this study. Table 38 below lists the 15 patients who experienced SAEs. The SAEs were treatment-emergent in 11 of these patients. In four of the 15 patients, the SAEs were not considered treatment-emergent because they occurred before the study medication was started (3-day RAC patients 0587001327 and 0616001429, 7-day RAC patient 0598001071, and 10-day OAC patient 0607001776).

In the 11 patients with treatment-emergent SAEs, there is a similar percentage of patients from each treatment group: two (1%) 3-day RAC patients, three (2%) 7-day RAC patients, four (2%) 10-day RAC patients, and two (<1%) 10-day OAC patients (p=0.821). Only one patient (OAC patient 0617001360) experienced SAEs (hyponatremia, vomiting and nausea) that were considered possibly related to study drug (relationship as per the Investigator). In nine of the 11 patients, the SAE occurred during the follow-up period of the study (six to 79 days after the final dose of study medication). Two SAEs occurred during the treatment period, and both led to the discontinuation from the study (abdominal pain in 10-day RAC patient 0593002478 and hyponatremia in 10-day OAC patient 0617001360).

TABLE 38
Listing of Patients with Non-Fatal Serious Adverse Events – All Randomized Patients

Patient ID/Gender/ Age	Serious Adverse Event(s)	Duration (Days)	Serious Adverse Event Criteria	Relationship [a]	D/C
3-day RAC					
0587001327/M/59	Gastrointestinal carcinoma	Unresolved	hospitalization	not related	yes
0598001472/M/53	Cholecystitis	8	hospitalization	not related	no
	Pain	2	hospitalization	not related	no
	Urinary retention	2	hospitalization	not related	no
0610001051/M/74	Vestibular disorder	1.5	hospitalization	not related	no
0616001429/M/63	Nausea	6	hospitalization	not related	no
	Vomiting	6	hospitalization	not related	no
7-day RAC					
0591001199/F/42	Uterine disorder	≤ 1	hospitalization	not related	no
0598001071/M/61	Gastrointestinal carcinoma	unresolved	hospitalization	not related	yes
0614002021/M/54	Chest pain substernal	1	hospitalization	not related	no
0620001121/M/59	Chest pain	3	hospitalization	not related	no
10-day RAC					
0593002478/F/60	Abdominal pain	11	hospitalization	not related	yes
0604001781/M/54	Carcinoma of lung	unresolved	medically significant	not related	no
0608002011/F/42	Vaginal hemorrhage	2	hospitalization	not related	no
0610001052/F/73	Dizziness	5	hospitalization	not related	no
	Pneumonia	5	hospitalization	not related	no
10-day OAC					
0607001776/F/38	Gastrointestinal carcinoma	unresolved	medically significant	not related	yes
0611001163/M/37	Abdominal pain	7	hospitalization	not related	no
	Gastroenteritis	7	hospitalization	not related	no
	Colitis	7	hospitalization	not related	no
0617001360/F/51	Hyponatremia	unresolved	hospitalization	possibly	yes
	Vomiting	1	hospitalization	possibly	yes
	Nausea	2	hospitalization	possibly	yes

D/C=Patient discontinued study M=male; F=female
[a] Relationship as per the Investigator.

Discontinuations Due to Adverse Events

Table 39 below lists the 26 patients with AEs resulting in discontinuation from study. A total of 26 patients discontinued from the study due to AEs, but only 23 patients discontinued due to TEAEs. Three patients discontinued due adenocarcinoma, which is considered to be a non-treatment-emergent event (patients 0587001327, 0598001071, 0607001776).

In the 23 patients with TEAEs, there does not appear to be a relationship between discontinuation of study medication and duration of treatment. Eight patients are in the 3-day RAC group, eight in the 7-day RAC group, four in the 10-day RAC group, and six in the 10-day OAC group. The most common TEAEs leading to discontinuations are diarrhea, vomiting and abdominal pain (5 patients each); dizziness (5 patients); nausea (three patients); and anxiety, asthenia, dyspnea, rash, and taste perversion (2 patients each).

Four patients completed dosing with study medication, but discontinued from the follow-up period of the study (patients 0587001327, 0597001223, 0598001071, 0598001187).

One patient (0617001360) discontinued medication prior to the SAE that led to discontinuation from the study.

Five patients discontinued study medication due to AEs, but remained in the study (3-day RAC patient 0604001783, 7-day RAC patients 0591001420 and 0611001609; 10-day RAC patients 0585001529 and 0617002071). All five of these AEs are considered possibly or probably related to study drug. The AEs are rash (in two patients) and gastrointestinal (nausea, constipation and diarrhea) in one patient each.

Five patients discontinued due to SAEs: three due to gastrointestinal carcinoma; one due to abdominal pain; and one due to hyponatremia, vomiting, nausea, and asthenia.

Clinical Reviewer's Comment: Table 39 was modified by the reviewer from the applicant's submitted table.

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TABLE 39
Listing of Patients Discontinued from the Study Due to Adverse Events
All Randomized Patients

Patient ID/Gender/ Age	Adverse Event(s) Leading to D/C	Duration (Days)	Serious Adverse Event Criteria	D/C [a]	Relationship [b]
3-day RAC					
0580001703/F/84	Dizziness	2		S, P	possibly
	Rhinitis	1	none	S, P	possibly
	Dyspnea	≤1		P	not related
0587001327/M/59	Gastrointestinal carcinoma	unresolved	hospitalization	P	not related
0597001223/M/35	Pneumonia	6	none	P	not related
0597001271/F/36	Diarrhea	unresolved	none	S, P	possibly
	Dizziness	unresolved	none	S, P	possibly
	Asthenia	unresolved	none	S, P	possibly
0597001578/M/34	Abdominal pain	3	none	S, P	possibly
	Chest pain substernal	3	none	S, P	possibly
0597002493/F/75	Abdominal pain	unresolved	none	S, P	possibly
	Palpitation	1	none	S, P	possibly
0616001777/M/64	Taste perversion	1	none	S, P	possibly
	Gastrointestinal disorder	1	none	S, P	possibly
	Diarrhea	1	none	S, P	possibly
0638001793/F/24	Rash	unresolved	none	S, P	possibly
7-day RAC					
0580001702/M/26	Flatulence	unresolved	none	S	not related
	Dyspepsia	unresolved	none	S	not related
	Abdominal Pain	unresolved	none	S	not related
	Dyspepsia	unresolved	none	S	not related
	Vomiting	1	none	S, P	probably
0587001730/M/53	Allergic reaction	4	none	S, P	probably
0591001600/F/33	Headache	2	none	S, P	possibly
	Diarrhea	1	none	S, P	possibly
0598001071/M/61	Gastrointestinal carcinoma	unresolved	hospitalization	P	not related
0608001517/M/64	Dyspnea	3	none	S, P	not related
0608001660/F/84*	Diarrhea	2	none	S, P	possibly
	Nausea	2	none	S, P	possibly
0617001147/F/39	Anxiety	unresolved	none	S, P	not related
0617002417/F/24	Amblyopia	≤1	none	S, P	possibly
	Dizziness	≤1	none	S, P	possibly

D/C=discontinuation; M=male; F=female
[a] S=Study drug discontinued; P=Patient discontinued;
[b] Relationship as per the Investigator.

* Though patient 0608001660 discontinued study medication due to AEs and was listed as a premature discontinuation, she returned for the final ^{13}C-UBT assessment. Therefore, she should have been listed as not having discontinued the study.

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TABLE 39 (continued)
Listing of Patients Discontinued from the StudyDue to Adverse Events
All Randomized Patients

Patient ID/Gender/ Age	Adverse Event(s) Leading to D/C	Duration (Days)	Serious Adverse Event Criteria	D/C[a]	Relationship[b]
10-day RAC					
0590001409/F/61	Abdominal pain	2.5	none	S, P	possibly
0593002478/F/60	Abdominal pain	11	hospitalization	S, P	not related
	Vomiting	11	none	P	not related
0598001187/F/64	Hepatitis C virus	unresolved	none	P	not related
0617001625/F/48	Reaction unevaluable	4	none	S, P	possibly
10-day OAC					
0591001688/F/54	Pruritus	unresolved	none	S, P	possibly
	Rash	unresolved	none	S, P	possibly
	Rash	unresolved	none	S, P	possibly
0607001776/F/38	Gastrointestinal carcinoma	unresolved	medically significant	S, P	not related
0611002466/F/57	Taste perversion	7	none	S, P	probably
	Anxiety	6	none	S, P	probably
0617001226/F/19	Dizziness	3.5	none	S, P	possibly
	Diarrhea	unresolved	none	S, P	possibly
	Vomiting	≤1	none	S, P	possibly
0617001360/F/51	Hyponatremia	unresolved	hospitalization	P	possibly
	Vomiting	1	hospitalization	P	possibly
	Nausea	2	hospitalization	P	possibly
	Asthenia	5	none	P	possibly
0622000033/M/42	Nausea	1	none	S	possibly
	Vomiting	1	none	S, P	possibly

D/C=discontinuation; M=male; F=female
[a] S=Study drug discontinued; P=Patient discontinued;
[b] Relationship as per the Investigator.

Pregnancy
No female of childbearing age had a positive pregnancy test at screening. Four patients discontinued due to pregnancy: three of the patients delivered normal healthy babies (7-day RAC patient 059101686; 10-day RAC patient 0617001359; 10-day OAC patient 0638001335) and one was lost to follow-up (10-day RAC patient 0608002011).

Clinical Laboratory Evaluation
There are no statistically significant differences in values at screening or in change from screening to endpoint across treatment groups in hematology or clinical chemistry values, with the exception of ALT, AST, total serum protein and uric acid.

Clinical Reviewer's Comment: Only the changes in ALT and AST were felt to be clinically significant and are discussed further below.

Tables 40 and 41 present summaries of changes from screening to end of treatment for ALT (SGPT) and AST (SGOT), respectively.

For ALT (SGPT), the change from screening is higher in the OAC (4.5 ± 1.52 U/L) and RAC 10-day (3.0 ± 0.93 U/L) treatment groups compared to the RAC 3-day (0.8 ± 0.74 U/L) and RAC 7-day (-0.1 ± 1.26 U/L) groups.

For AST (SGOT), the change from screening is highest in the OAC (4.1 ± 1.61 U/L), followed by the RAC 10-day (2.1 ± 0.51 U/L), RAC 3-day (1.0 ± 0.42 U/L), and RAC 7-day (0.1 ± 0.85 U/L) treatment groups.

However for both ALT and AST, mean and median values remain within the normal range at the end of treatment for all four regimens and the percentage of patients with shifts from normal to high is low (0 to three percent) and similar across regimens.

TABLE 40
Summary of Change from Screening to End of Treatment for ALT (SGPT)
Safety Patients

	3-day RAC (N = 188)	7-day RAC (N = 195)	10-day RAC (N = 198)	10-day OAC (N = 207)
Screening				
mean ± SEM (U/L)	22.2 ± 1.15	26.4 ± 1.87	22.2 ± 1.10	21.1 ± 1.11
median	18.0	18.0	18.0	17.0
End of Treatment				
mean ± SEM	23.0 ± 0.99	26.2 ± 1.47	25.2 ± 1.29	25.6 ± 1.73
median	19.0	19.0	21.0	19.0
Change from Screening				
mean ± SEM	0.8 ± 0.74	-0.1 ± 1.26	3.0 ± 0.93	4.5 ± 1.52
median	1.0	1.0	1.0	2.0
Shift				
Normal → High	2%	3%	2%	4%

TABLE 41
Summary of Change from Screening to End of Treatment for AST (SGOT)
Safety Patients

	3-day RAC (N = 188)	7-day RAC (N = 195)	10-day RAC (N = 198)	10-day OAC (N = 207)
Screening				
mean ± SEM (U/L)	20.3 ± 0.52	22.7 ± 1.06	20.5 ± 0.48	19.5 ± 0.49
median	19.0	19.0	19.0	18.0
End of Treatment				
mean ± SEM	21.3 ± 0.53	22.7 ± 0.74	22.6 ± 0.68	23.6 ± 1.71
median	20.0	20.0	20.0	20.0
Change from Screening				
mean ± SEM	1.0 ± 0.42	0.1 ± 0.85	2.1 ± 0.51	4.1 ± 1.61
median	1.0	0.0	1.0	2.0
Shift				
Normal → High	3%	0	2%	2%

Vital Signs, Physical Findings and other Observations Related to Safety

There are no statistically significant changes across treatment groups from screening to end of treatment in sitting systolic and diastolic blood pressure, sitting pulse, respiration rate, temperature, and weight.

O. Reviewers' Conclusions of Study 604

1. Efficacy Conclusions

- When compared to 10 days of treatment with OAC, both the 7-day and 10-day RAC treatment regimens achieve the pre-specified criteria of less than 15% of the lower bound of the 95% confidence interval of the difference (RAC - OAC) for both the ITT and PP analyses. Therefore, the efficacy criteria recommended in the FDA draft Guidance are satisfied.

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

- For clarithromycin-susceptible *H. pylori*, the eradication rates in the ITT population are 27% (33/124) in the 3-day RAC, 80% (103/129) in the 7-day RAC, 83% (111/133) in the 10-day RAC, and 79% (96/121) in the 10-day OAC treatment groups. In the PP population, the eradication rates for clarithromycin-susceptible *H. pylori* are 28% (32/113) in the 3-day RAC, 90% (95/105) in the 7-day RAC, 91% (106/116) in the 10-day RAC, and 89% (95/107) in the 10-day OAC groups.

- For clarithromycin non-susceptible *H. pylori* (i.e., intermediate and resistant), the eradication rates in the ITT population are 0% (0/10) in the 3-day RAC, 31% (5/16) in the 7-day RAC, 11% (1/9) in the 10-day RAC, and 28% (5/18) in the 10-day OAC treatment groups. In the PP population, the eradication rates for clarithromycin non-susceptible *H. pylori* are 0% (0/8) in the 3-day RAC, 36% (5/9) in the 7-day RAC, 11% (1/9) in the 10-day RAC, and 27% (4/15) in the 10-day OAC groups.

- There are only two patients in the study with *H. pylori* resistant to amoxicillin at screening. Both patients are in the 7-day RAC arm and in both cases the *H. pylori* is also resistant to clarithromycin. In one patient, the bacterium was eradicated and in the other patient it was not.

- A follow-up endoscopy was performed and biopsy samples were obtained only in patients with a positive ^{13}C-UBT at the post-treatment assessment to assess whether the organism had acquired resistance to the antibiotics used. The number of these patients is small, particularly in the 7-day RAC, 10-day RAC and OAC regimens and therefore no meaningful conclusions can be drawn from these data.

- Study medication compliance was ≥ 95% in each regimen and there are no statistically significant differences across treatment groups.

- Overall, the 7-day RAC treatment regimen is comparable in efficacy to as the 10-day RAC and OAC treatment regimens in all efficacy parameters measured. The 3-day RAC treatment regimen is not comparable in efficacy to the other regimens for the eradication of *H. pylori*.

2. Safety Conclusions

- The safety profiles of all three rabeprazole-triple therapy (RAC) regimens are similar to omeprazole-triple therapy (OAC).

- The percentage of patients with TEAEs judged to be treatment-related is slightly higher in the 10-day OAC group (35%) compared to patients in the 3-day RAC (26%), 7-day RAC (29%), and 10-day RAC (29%) groups. The majority of the TEAEs are considered mild or moderate and most commonly affected the digestive system. Severe events occur in 4%, 8%, and 11% of the 3-day, 7-day, and 10-day RAC groups versus 12% in the OAC group.

- Overall the incidence of TEAEs is similar for males and females. Diarrhea occurs more frequently in males, while abdominal pain in more common in females in the 3-day RAC arm. Headache occurs more frequently in females in all treatment arms, except the 3-day RAC arm where it is more common in males. Nausea is more common in females in the 7-day RAC, 10-day RAC, and 10-day OAC arms. Taste perversion is more common in males compared to females in the 7-day RAC arm. Overall, these differences are small and unlikely to result in clinically meaningful differences.

- For the race analysis, overall and by treatment arm, Blacks appear to have a higher incidence of dyspepsia, diarrhea, and nausea than other races. Taste perversion occurs in both Whites and Blacks more frequently than in other races, except in the 10-day RAC group.

- The number of patients in the categories of age > 65 years and Other races is small; and therefore, no reliable conclusions can be drawn regarding the incidence of adverse events in these subgroups.

- No deaths occurred in this study.

- A similar percentage of patients in each treatment group experienced at least one treatment-emergent SAE: two (1%) 3-day RAC patients, three (2%) 7-day RAC patients, four (2%) 10-day RAC patients, and two (<1%) 10-day OAC patients (p=0.821). There was one case were the SAE was judged by the Investigator to be treatment-related (hyponatremia, vomiting and nausea) and it occurred in an OAC patient. In nine of the 11 patients, the SAE occurred during the follow-up period of the study.

- There does not appear to be a relationship between discontinuation of study medication and duration of treatment. Eight patients discontinued in the 3-day RAC group, eight in the 7-day RAC group, four in the 10-day RAC group, and six in the 10-day OAC group. The most common TEAEs leading to discontinuations are gastrointestinal in nature.

- There are no statistically significant changes in vital signs, physical examination and laboratory values with the exception of AST (SGOT) and ALT (SGPT) levels. At the end of treatment, there is a statistically significant change from screening in mean AST and ALT levels which were elevated in the 10-day RAC and OAC groups by 3.0 and 4.5 U/L and 2.1 and 4.1 U/L, respectively, compared to almost no change in the 3-day and 7-day RAC groups (0.8 and -0.1 U/L and 1.0 and 0.1 U/L, respectively). However, the

number of patients with shifts from normal to high was small and similar across regimens.

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