CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

MEDICAL REVIEW
AND
STATISTCIAL REVIEW

Clinical and Statistical Review for New Drug Application # 21-456

Drug: Aciphex® (rabeprazole sodium)
20 mg Delayed-Release Tablets

Applicant's Proposed Indication: [redacted]

General Information:

Applicant Name:	Eisai Medical Research (formerly Eisai Inc.)
Applicant's Address:	Glenpointe Centre West 500 Frank W. Burr Blvd. Teaneck, New Jersey 07666
Applicant's Telephone:	(201) 692-9160

Submission/Review Dates:

Date of Submission:	January 9, 2002; February 12, 2002, May 9, 2002
Date of Receipt:	January 10, 2002; February 14, 2002, May 10, 2002
Date Review Begun:	March 16, 2002
Date Review Completed:	November 1, 2002

Drug Identification:

Generic Name:	Rabeprazole sodium (formerly known as E3810 or LY307640)
Pharmacologic Category:	substituted benzimidazole (proton pump inhibitor)
Proposed Trade Name:	Aciphex®
Molecular Formula:	$C_{18}H_{20}N_3O_3SNa$
Molecular Weight:	381.43 daltons
Dosage Form:	20 mg Delayed-Release Tablets
Route of Administration:	Oral

TABLE OF CONTENTS

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendations on Approvability

In this submission, the applicant demonstrates the activity of 7-days of treatment with rabeprazole, amoxicillin, and clarithromycin (RAC) in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (active or history within the past 5 years). The efficacy of RAC is compared to a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC regimen is an acceptable comparator since it consistently achieves eradication rates of approximately 70% or greater by Intention-to-Treat (ITT) analysis and 80% or greater by Per Protocol (PP) analysis.

The applicant conducted one pivotal Phase III trial in the United States (E3810-A001-604) to document the efficacy of RAC. It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of 7 days of RAC treatment versus 10 days of OAC treatment. The lower bound of the 95% confidence intervals for the difference in eradication rates for the 7-day RAC versus 10-day OAC groups are -4.4% and -5.2% for the ITT and PP analyses, respectively. Therefore, the lower bounds of the confidence intervals are greater than the allowable delta of - 15% and the *H. pylori* eradication rate for 7-day RAC treatment satisfies the efficacy criteria recommended in 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 webpage, has been shared with other sponsors developing drugs for *H. pylori* infection.

Overall eradication rates for 7-day RAC therapy in the supportive Phase III European trial (E3810-E044-603) are consistent with, although numerically higher than, the results obtained in the 7-day RAC arm in US Study 604 for the ITT (84% versus 77%) and PP (94% versus 84%) analyses, respectively. Eradication rates for 7-day OAC therapy in Study 603 (Europe) are similar to the rates with 10-day OAC therapy in Study 604 (US), for the ITT (72% versus 73%) and PP (84% versus 82%) analyses, respectively. These results are consistent with other drug therapy trials in which European rates of *H. pylori* eradication, for reasons not clearly identified, are often higher than those seen in US trials.

In the US trial (Study 604), there are no clinically meaningful differences between the 7-day RAC and 10-day OAC groups in the incidence of any adverse event (AE). For both treatments gastrointestinal AEs are the most commonly reported (e.g., dyspepsia, diarrhea, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Taste perversion is also a common AE to both treatments and has been described previously in association with clarithromycin.

Although the safety data from two European trials (Study 603 and 602) are not pooled with the US trial, the results are similar and supportive of the 7-day of RAC regimen.

Therefore, rabeprazole sodium when used in combination with amoxicillin and clarithromycin is safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

The recommendation is for approval of rabeprazole 20 mg, amoxicillin 1000 mg, plus clarithromycin 500 mg twice daily for 7 days for this indication.

B. Recommendations on Phase IV Studies and Risk Management Steps

There are no Phase IV commitments recommended at this time.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Development Program

The clinical development program for rabeprazole in combination with antimicrobials for the eradication of *H. pylori* includes three clinical pharmacology studies, two clinical pilot efficacy studies and two Phase III clinical efficacy and safety studies, one of which was conducted in the US. US Phase III Study E3810A001-604 is considered primary, while European Phase III Study E3810-E044-603 is considered supportive. The two Phase III studies will be reviewed in detail.

The US Phase III Study 604 is a randomized, multi-center, double blind, double dummy, parallel group study comparing treatment with rabeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID (RAC) for 3, 7, or 10 days to treatment with omeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID (OAC). Subjects are stratified 1:1 based on whether they had PUD (either active or history within the last 5 years) or were symptomatic with no PUD (NPUD). All treatment regimens are given for 10 days. The rabeprazole regimens supply active drug for the first 3, 7, or 10 days. Eradication of *H. pylori* is considered the primary endpoint. Secondary efficacy parameters included eradication rates in patients with susceptible organisms, resistance rates among treatment failures, and compliance. The safety population in this study consists of 788 patients as seen in Table 1 below.

European Phase III Study 603 is considered supportive. It is also a randomized, multi-center, double blind, parallel group study. In this study two rabeprazole-based regimens (rabeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID, and rabeprazole 20 mg BID + clarithromycin 500 mg BID + metronidazole 400 mg BID) are compared to two omeprazole-based regimens (omeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID, and omeprazole 20 mg BID + clarithromycin 500 mg BID + metronidazole 400 mg BID). All regimens are given for 7 days. Eradication of *H. pylori* is considered the primary endpoint. The safety population in this study consists of 345 patients as seen in Table 1 below.

TABLE 1
Extent of Exposure in Rabeprazole Clinical Trials
Number of Subjects/Patients per Treatment

Trial	Location	Duration of Treatment (days)	Number of Patients (Safety Population)		Total
			RAC	Control	
E3810-A001-604 *(Pivotal Phase III)*	US	10	198	207	405
		7	195	--	195
		3	188	--	188
E3810-E044-603 *(Supportive Phase III)*	Europe	7	87	258	345
E810-E044-602 *(Clinical Pilot)*	UK	7	19	56	75
E810-L001-601 Part I *(Clinical Pilot)*	US	14	--	26	26
E810-L001-601 Part I *(Clinical Pilot)*	US	14	--	48	48
E3810-E044-402 *(Clinical Pharmacology)*	UK	14	--	24	24
E3810-E031-118 *(Clinical Pharmacology)*	Netherlands	7	16	--	16
E3810-J081-201 *(Clinical Pharmacology)*	Japan	7	20*	--	20
TOTALS			723	619	1342

* Dose of amoxicillin in RAC regimen consisted of 750 mg instead of 1000 mg

B. Efficacy

1. Pivotal Study 604

The US multicenter Study 604 is a double blind, parallel group comparison of rabeprazole, amoxicillin, and clarithromycin (RAC) for 3, 7, or 10 days vs. omeprazole, amoxicillin and clarithromycin (OAC) for 10 days. Patients are stratified in a 1:1 ratio for those with peptic ulcer disease (active or a history of ulcer in the past five years) [PUD] and those who were symptomatic but without peptic ulcer disease [NPUD], as determined by upper gastrointestinal endoscopy. The upper limit of the 95% confidence intervals of the difference in eradication rates for (NPUD – PUD) patients combined across treatment regimens is less than 10% in both the Intention-to-Treat (ITT) and Per Protocol (PP) patient populations. Further, there is no significant treatment interaction. Therefore, it is felt that the inclusion of NPUD patients in the analysis will not artificially inflate overall eradication rates and it is considered appropriate to pool the efficacy results of these two strata. The overall *H. pylori* eradication rates, defined as negative ^{13}C-UBT for *H. pylori* ≥ 6 weeks from the end of the treatment are shown in Table 2 for 7-day and 10-day RAC and 10-day OAC treatment regimens. The eradication rates for all three regimens are found to be comparable using either the ITT or PP populations. Eradication rates in the RAC 3-day regimen are lower and not comparable to the other regimens.

TABLE 2
***H. pylori* Eradication at ≥ 6 Weeks After The End of Treatment**
Percent (%) of Patients Cured
[95% Confidence Interval]
(Number of Patients)

	Treatment Group		Difference[c] (RAC – OAC)
7-day RAC* versus 10-day OAC			
Per Protocol[a]	84.3% [78%, 89%] (N=166)	81.6% [75%, 87%] (N=179)	2.8 [- 5.2, 10.7]
Intention-to-Treat[b]	77.3% [71%, 83%] (N=194)	73.3% [67%, 79%] (N=206)	4.0 [- 4.4, 12.5]
10-day RAC* versus 10-day OAC			
Per Protocol[a]	86.0% [80%, 91%] (N=171)	81.6% [75%, 87%] (N=179)	4.4 [- 3.3, 12.1]
Intention-to-Treat[b]	78.1% [71%, 84%] (N=196)	73.3% [67%, 79%] (N=206)	4.8 [- 3.6, 13.2]

[a] Patients were included in the analysis if they had *H. pylori* infection documented at baseline, defined as a positive ^{13}C-UBT plus rapid urease test or culture and were not protocol violators. Patients who dropped out of the study due to an adverse event related to the study drug, they were included in the evaluable analysis as failures of therapy.

[b] Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and took at least one dose of study medication. All dropouts were included as failures of therapy.

[c] The 95% confidence intervals given for treatment differences in this table are not adjusted for multiple comparisons. When multiple comparisons adjustments are made, the 7-day and 10-day RAC regimens are still considered comparable to 10-day OAC.

* The 95% confidence intervals for the difference in eradication rates for 7-day RAC minus 10-day RAC are (-9.3, 6.0) in the PP population and (-9.0, 7.5) in the ITT population.

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 greater than –15% of the lower bound of the 95% confidence interval of the difference (RAC – OAC) as specified in the FDA draft Guidance for Industry – "Reduction of Gastric or Duodenal Ulcer Recurrence by Eradication of *H. pylori*".

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

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

- HAC (esomeprazole*/amoxicillin/clarithromycin)
  * formerly H199/18

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

The clinical development programs for these regimens are similar to that of RAC, except RAC used an active control and others used factorial designed studies. All programs enrolled *H. pylori*-positive patients with either an active ulcer or history of ulcer disease. Eradication is the primary endpoint in all studies. The treatment duration of the PPI varies between development programs. In the OAC studies, the use of omeprazole is continued (at a reduced dose) beyond the duration of eradication therapy for a total duration of 4 weeks, in those patients with an active ulcer at baseline. The RAC, HAC and LAC studies do not continue the PPI beyond the initial 10 days (or 7 days for RAC) of treatment, regardless of the ulcer status of the patient.

As seen in Table 3, the eradication rates achieved at > 4 weeks post-treatment with RAC therapy appear comparable to those observed with the other approved proton pump inhibitor (PPI)-based triple therapies:

APPEARS THIS WAY
ON ORIGINAL

TABLE 3
***H. pylori* Eradication at > 4 Weeks Post-Treatment - Comparison of Rabeprazole, Esomeprazole (H199/18), Omeprazole, and Lansoprazole Triple Therapies**

Analysis	Total Number of Patients per Group (% Eradicated) [95% CI]								
	*RAC**		*HAC***		*OAC*†				*LAC*Ψ*
	Study 604 7-day	Study 604 10-day	Study 191	Study 193	Study 126	Study 127	Study M96-446	Study 604 (vs. RAC)	M95-399
ITT	194 (77%) [71%, 83%]	196 (78%) [71%, 84%]	233 (77%) [71%, 82%]	74 (78%) [67%, 87%]	80 (69%) [57%, 79%]	73 (77%) [61%, 82%]	84 (83%) [74 %, 91%]	206 (73%) [67%, 79%]	135 (81%) [74%, 88%]
PP	166 (84%) [78%, 89%]	171 (86%) [80%, 91%]	196 (84%) [78%, 89%]	67 (85%) [74%, 93%]	64 (77%) [64%, 86%]	65 (78%) [67%, 88%]	69 (90%) [80 %, 96%]	179 (82%) [75%, 87%]	123 (84%) [76%, 90%]

* Rabeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg BID x 7 days or 10 days
** Esomeprazole 40 mg QD + amoxicillin 1000 mg BID + clarithromycin 500 mg BID x 10 days
† Omeprazole 20 mg + amoxicillin 1000 mg + clarithromycin 500 mg BID x 10 days, then omeprazole 20 mg QD for an additional 18 days in patients with an active ulcer present at the initiation of therapy for ulcer healing and symptom relief. M96-446 was an inactive DU study; therefore omeprazole was used for a duration of 10 days in all patients.
Ψ Lansoprazole 30 mg + amoxicillin 1000 mg + clarithromycin 500 mg BID x 10 days

C. Safety

A total of 703 patients (687 with *H. pylori* infection) have been exposed to rabeprazole administered concurrently with amoxicillin and clarithromycin (RAC). There was one treatment-emergent death in the two controlled (603 and 604) and one uncontrolled (602) studies that included the RAC treatment group.

1. Study 604

The safety profiles of all three rabeprazole-triple therapy (RAC) regimens are similar to omeprazole-triple therapy (OAC). The majority of the treatment-emergent adverse events (TEAEs) are considered mild or moderate and mainly affect the digestive system (i.e., dyspepsia, diarrhea, abdominal pain, nausea, and flatulence). The number of patients in each treatment group experiencing at least one serious TEAE are: 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. In only one case was the serious event judged by the investigator to be treatment-related (hyponatremia, vomiting and nausea) and it occurred in a patient randomized to OAC treatment. In nine of the 11 patients, the serious TEAE 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 who discontinued 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 gastrointestinal (i.e., diarrhea, abdominal pain, and vomiting) in nature.

There are no clinically significant changes in vital signs, physical examination and laboratory values with the exception of AST and ALT values. There are mean increases in AST (3.0 U/L) and ALT (2.1 U/L) in the 10-day RAC group that are greater when compared to the 3-day and 7-day RAC groups. There are also mean increases seen in the 10-day OAC group (4.5 U/L and 4.1 U/L, respectively) and they are higher than in the 10-day RAC group.

2. Study 603

There are no notable differences between 7-day treatment with RAC or OAC with regard to overall safety.

The safety results for 7-day RAC therapy are similar and supportive of Study 604.

One death and one serious adverse event occurred during the study. Both events are considered unrelated to study medication. An elderly (87 year old) Caucasian female with comorbid conditions including diabetes, hypertension, emphysema, nephrosclerosis, and coronary artery disease died suddenly and unexpectedly two days after competing seven days of RAC treatment. The cause of death was recorded as asystole during hemodialysis. The serious adverse event (adenocarcinoma of the colon) occurred in the OAC group.

One patient in the OAC group was permanently discontinued from study treatment due to flu-like symptoms considered to be related to study treatment.

3. Study 602

Other than one allergic reaction (in a patient who later admitted penicillin allergy), there are no significant adverse events related to RAC treatment.

D. Dosing

The proposed dose of rabeprazole (20 mg twice daily) in this regimen to treat *H. pylori* infection is greater than the dose recommended for other GI indications (20 mg once daily). The rationale for using a higher dose is as follows:

1. The dose of rabeprazole for this indication is the same as omeprazole (when used in combination with amoxicillin and clarithromycin) for treatment of *H. pylori* infection.

The applicant has conducted studies showing that rabeprazole and omeprazole are not significantly different in terms of disease healing, resolution of symptoms, and relapse of GERD pathology or symptoms. In addition, use of high doses of proton pump inhibitors (PPIs) for eradication of *H. pylori* is consistent with how the other approved PPIs are labeled.

2. Twice daily dosing should produce a consistent, elevated intragastric pH.

H. pylori grows best in a slightly acidic pH. Therefore, continuous elevation of the intragastric pH with PPIs produces a less suitable environment for growth of *H. pylori*

3. Higher PPI doses should enhance the antibacterial effects of combination therapy.

The higher pH produced by PPIs may reduce the degradation of acid-labile antimicrobials, such as amoxicillin. In addition, PPIs are thought to have antimicrobial effects of their own that are not related to the effect on pH.

In summary, approval of 20 mg rabeprazole twice daily in combination with antimicrobials for eradication of *H. pylori* is consistent with other approved PPIs for this indication and appears warranted based on what is known of the pharmacology of this infection.

E. Special Populations

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

1. Efficacy

In the pivotal US trial (Study 604) covariate analyses using logistic regression were performed by the statistical reviewer to determine whether age, gender, or race had a significant effect on the *H. pylori* eradication rates. None of these covariates had a statistically or clinically significant, based on the reviewer's assessment, effect on *H. pylori* eradication status.

2. Safety

The results of the subgroup analyses by gender in the US trial (Study 604) indicate overall that the incidence of adverse events is similar between males and females. Although the results for individual events can vary depending upon treatment, any differences that occur are slight 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 numbers of patients older than 65 years is small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly subgroups.

In the European trial (Study 603), the results are not likely to indicate clinically meaningful differences between age or gender subgroups. No analysis by race was performed since the number of patients is too small to allow any conclusions.

APPEARS THIS WAY
ON ORIGINAL

CLINICAL/STATISTICAL REVIEW

I. Introduction/Background

A. Overview of Drug, Dosage, and Indication

Drug

Generic Name:	Rabeprazole sodium
Pharmacologic Category:	substituted benzimidazole (proton pump inhibitor)
Proposed Trade Name:	Aciphex®
Dosage Form:	20 mg Delayed-Release Tablets
Route of Administration:	Oral

Applicant's Proposed Indication:

Aciphex® in combination with amoxicillin and clarithromycin [redacted] is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence.

Applicant's Proposed Dosing and Administration

TABLE 4
***H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence**

[redacted]		
Aciphex	20 mg	Twice Daily for 7 Days
Amoxicillin	1000 mg	Twice Daily for 7 Days
Clarithromycin	500 mg	Twice Daily for 7 Days

B. Important Milestones in Product Development

The applicant initially submitted a Pre-IND to DSPIDP on 10/28/98. In response to DSPIDPs comments, the applicant made suitable revisions and submitted an IND on 8/6/99.

The applicant's development plan for the indication of *H. pylori* eradication consisted of a single pivotal trial. It was designed as a multi-center, double blind, randomized, stratified, parallel group study (Protocol E3810-A001-604). The population was to consist of patients with a current, or history within the past 5 years of, peptic ulcer disease (PUD) and symptomatic non-peptic ulcer disease (NPUD). An enrollment of 790 patients at a minimum of 30 sites in the US was planned. Four treatment arms were planned: 3, 7, and 10 days of a rabeprazole-based triple therapy containing clarithromycin and amoxicillin (RAC) compared to an active control. The applicant selected the FDA-approved treatment of omeprazole, amoxicillin, and clarithromycin (OAC) for 10 days as the active-control. OAC was considered acceptable by DSPIDP as it consistently achieves eradication rates of approximately 70% or greater by Intention-to-Treat (ITT) analysis and 80% or greater by Per Protocol (PP) analysis. The Division agreed with the study design and accepted one trial as pivotal.

In addition, the applicant conducted a multi-center, randomized, double blind study in Europe (Protocol E3810-E044-603) to compare the efficacy of two rabeprazole and two omeprazole regimens for 7 days in the eradication of *H. pylori* in subjects with documented peptic ulcer disease (current or history within the past 5 years). It was agreed that this study would be considered supportive evidence of the 7-day RAC treatment.

Two other pilot studies (E3810-L001-601 and E3810-E044-602) would also be submitted as supportive evidence.

C. Other Relevant Information

Rabeprazole (NDA 20-973) was approved as monotherapy by the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) for multiple gastrointestinal indications on August 19, 1999:

- Healing of erosive or ulcerative gastroesophageal reflux disease (GERD)
- Maintenance of healing of erosive or ulcerative GERD
- Healing of duodenal ulcer
- Treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

On, February 12, 2002 the applicant also received an indication for the treatment of symptomatic GERD.

Patient exposures in the US, based on prescription data and assuming a recommended once daily dosing regimen, are in excess of 227 million patient days (as of September 2001).

Rabeprazole is approved for marketing in 77 countries outside of the US. The global rabeprazole experience exceeds — million tablets distributed (as of September 2001).

Rabeprazole has not been withdrawn from marketing in any country due to reasons of safety or efficacy.

II. Summary of Clinically Relevant Findings from Other Review Disciplines

The Division of Special Pathogen and Immunologic Drug Products (DSPIDP, HFD-590) will accept the reviews completed by chemistry, pharmacology/toxicology, and clinical pharmacology/ biopharmaceutics prepared by DGCDP for NDA 20-973.

In addition, the following findings pertain to rabeprazole in combination with amoxicillin and clarithromycin for up to 10 days in the treatment of *H. pylori* infection.

A. Chemistry

This application can be approved from the chemistry perspective.

Abbreviated review by Gene Holbert, Ph.D., Chemistry Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-456). For the complete information, see review by Marie Kowblansky, Ph.D., Chemistry Reviewer in HFD-180 (DGCDP) filed with NDA 20-973.

B. Pharmacology/Toxicology

This application can be approved from the pharmacology/toxicology perspective.

Additional studies have been requested as a Phase IV commitment (letter dated 5/10/02) to further evaluate the relationship between the rabeprazole/amoxicillin/clarithromycin dosing regimen and hindquarter paralysis observed in female rats in a four-week toxicity study and to conduct a four-week oral toxicity study in beagle dogs with an appropriate rabeprazole/amoxicillin/darithromycin dosing regimen.

Abbreviated review by Steven Hundley, Ph.D., Pharmacology/Toxicology Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-456). For the complete information, see review by Ke Zhang, Ph.D., Pharmacology/Toxicology Reviewer in HFD-180 (DGCDP) filed with NDA 20-973.

C. Clinical Pharmacology/Biopharmaceutics

This application can be approved from the clinical pharmacology and biopharmaceutics perspective.

Pharmacokinetic interactions among rabeprazole, amoxicillin, and clarithromycin were evaluated in a four-way crossover study (E-3810-E031-118) with 16 healthy Caucasian male volunteers. All subjects were extensive metabolizers with respect to CYP2C19. Each subject orally ingested clarithromycin 500 mg alone, amoxicillin 1000 mg alone, rabeprazole 20 mg alone, or all together twice a day for 7 days. The pharmacokinetic parameters of each drug were determined following each 7-day treatment.

In a comparison of exposure to clarithromycin between test and reference treatments, mean maximum concentration (C_{max}) and mean area under the concentration-time curve from 0 to 12 hours (AUC_{0-12}) are virtually identical. For amoxicillin exposure, the geometric mean C_{max} and AUC_{0-12} are not different between test and reference treatments because the 90% confidence intervals (90% CI) of their mean ratios are within the range of 80% - 125%. However, the geometric mean C_{max} and AUC_{0-12} of clarithromycin metabolite M5 (14-hydroxyclarithromycin) following test treatment is greater by 46% and 42%, respectively, than those following corresponding reference treatment. The geometric mean C_{max} and AUC_{0-12} of rabeprazole following test treatment are greater by 34% and 11%, respectively than corresponding reference treatment. The respective 90% CIs are 104% - 141% and 90% -137%. Although the magnitudes of these interactions are statistically significant, they are not expected to produce safety concerns.

To determine the equivalence between the over-encapsulated (for blinding purposes) active comparators of amoxicillin, clarithromycin, and omeprazole used in the pivotal clinical trial (E3810-A001-604) and corresponding regular products, their dissolution performance was compared. Omeprazole shows no difference in dissolution performance between the over-encapsulated and corresponding regular capsules. Although amoxicillin and clarithromycin demonstrate a minute difference in dissolution performance at an early time point, the dissolution performance is acceptable and meets the requirements for amoxicillin capsules and clarithromycin tablets in United States Pharmacopoeia (USP).

See complete review by Jang-Ik Lee, Ph.D., Clinical Pharmacology/Biopharmaceutics Reviewer, in HFD-590 (DSPIDP) filed with this NDA (21-456).

See also review by Carol Kronenberger, Ph.D. Clinical Pharmacology/Biopharmaceutics Reviewer in HFD-180 (DGCDP) filed with NDA 20-973.

D. Microbiology

This application can be approved from the microbiological perspective.

Rabeprazole binds to the sulfhydryl (SH) group in *Helicobacter pylori* urease active sites and inactivates the enzyme. The thioether of rabeprazole is inactive against urease.

When the activity of rabeprazole on the growth of *H. pylori* was compared to its ability to inhibit several enzyme systems, the drug's inhibition of adenine incorporation into RNA is within the same concentration range as that which inhibits growth. It has been speculated that this inhibition may play some role in the antibacterial activity of rabeprazole against *Helicobacter pylori*.

The antibacterial activity of rabeprazole and its thioether metabolite were evaluated *in vitro* against *Helicobacter pylori*. Activity was compared to other agents by the agar dilution method. Results are shown in Table 5 below.

TABLE 5
Activities of Proton Pump Inhibitors, Their Metabolites, and Antibiotics Against 15 Strains of *Helicobacter pylori*

Compound	MIC (µg/mL)		
	Range	MIC_{50}	MIC_{90}
Rabeprazole sodium		1.56	3.13
Rabeprazole thioether		1.56	1.56
Omeprazole		25	50
Omeprazole thioether		12.5	25
Lansoprazole thioether		12.5	25
Roxithromycin		0.2	50
Aminobenzyl penicillin		0.10	0.39
Ofloxacin		0.78	3.13

The above data demonstrate that rabeprazole and its thioether metabolite both have activity against *H. pylori* that is only slightly less than that of ofloxacin. Omeprazole and lansoprazole shows only slight activity against *H. pylori*.

The checkerboard titration method was employed to examine the antimicrobial effect of the combinations of rabeprazole sodium and amoxicillin, rabeprazole sodium and clarithromycin, and amoxicillin and clarithromycin with media adjusted to pH 5.5 and pH 7.1. Twenty-seven (27) strains of *H. pylori* were tested. The ΣFIC Index (Fractional Inhibitory Concentration index) was utilized to mathematically express the interaction of two antibacterial agents (i.e., synergism, additive effects, indifference, or antagonism). At pH 5.5, most strains shows an additive effect for all three combinations tested. More strains show synergism with the combination of rabeprazole and clarithromycin compared to rabeprazole and amoxicillin or amoxicillin and clarithromycin. In general, the same trend is

seen at pH 7.17, but more strains show an additive effect with rabeprazole and amoxicillin and more show synergy with rabeprazole and clarithromycin. Fewer strains show synergism with amoxicillin and clarithromycin at pH 7.17. There is no antagonism between the drugs.

In Study 604, about 9% of the *H. pylori* isolates are resistant (MIC ≥ 1 µg/mL) to clarithromycin pre-treatment. Out of the three clinical trials performed by the applicant (i.e., Studies 602, 603 and 604), only Study 604 used NCCLS methods. The distribution of pre-treatment clarithromycin MIC values is bimodal. One population has MIC values of ≤ 0.125 µg/mL and the other population has MIC values of ≥ 8 µg/mL. Only a few isolates have MIC values between these two populations. Patients with isolates that have high clarithromycin MICs do not have their *H. pylori* eradicated as readily as patients with isolates with low clarithromycin MIC values. All but two *H. pylori* isolates in this clinical trial are susceptible (MIC ≤ 0.25 µg/mL) to amoxicillin. Eradication rates do not seem to be related to amoxicillin MIC values.

Treatment with rabeprazole plus amoxicillin and clarithromycin (RAC) for 3-days results in a low *H. pylori* eradication rate of 27%. Treatment with RAC for 7-days (77% eradication rate in the ITT population) and RAC for 10-days (78% eradication rate) produce results similar to those obtained with omeprazole plus amoxicillin and clarithromycin (OAC) after 10-days of treatment (73% eradication rate).

Treatment with RAC or OAC does not appear to lead to an increase in resistance to clarithromycin. All post-treatment isolates are susceptible to amoxicillin.

In summary, this application can be approved from the microbiological prospective with minor changes suggested to the label.

See complete review by Peter A. Dionne, Microbiologist in HFD-590 (DSPIDP) filed with this NDA (21-456).

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Note: The following information is taken from the approved rabeprazole label.

Aciphex delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. After oral administration of 20 mg Aciphex, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0 to 5.0 hours (T_{max}). The rabeprazole C_{max} and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Absorption: Following oral administration of 20 mg, rabeprazole is absorbed and can be detected in plasma by 1 hour. Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. The effects of food on the absorption of rabeprazole have not been evaluated.

Distribution: Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism: Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *In vitro* studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochromes P450 3A (sulphone metabolite) and 2C19 (desmethyl rabeprazole). The thioether metabolite is formed by reduction of rabeprazole.

Elimination: Following a single 20 mg oral dose of ^{14}C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

Pharmacokinetics Special Populations
Geriatric: In 20 healthy elderly subjects administered 20 mg rabeprazole once daily for seven days, AUC values approximately doubled and the C_{max} increased by 60% compared to values in a parallel younger control group. There was no evidence of drug accumulation after once daily administration.

Pediatric: The pharmacokinetics of rabeprazole in pediatric patients under the age of 18 years have not been studied.

Gender and Race: In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies that used different formulations of rabeprazole, $AUC_{0-\infty}$ values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the United States.

Renal Disease: In 10 patients with stable end-stage renal disease requiring maintenance hemodialysis (creatinine clearance ≤5 mL/min/1.73 m^2), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared to 10 healthy volunteers.

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $AUC_{0-\infty}$ and C_{max} values increased approximately 20% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant. No information exists on rabeprazole disposition in patients with severe hepatic impairment.

Dosage Adjustment
No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased

elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

B. Pharmacodynamics

As part of their clinical development program, the applicant was interested in pursuing a treatment regimen of rabeprazole plus two antimicrobials for fewer than seven days of treatment, which is generally considered the minimum duration for effective therapy. Preliminary literature data suggests that shorter treatments can achieve > 80% eradication. The applicant conducted the following pharmacodynamic study to evaluate the onset of gastric acid inhibition in support of their development plan for a short course therapy.

Study E3810-E044-115 examines the effects of daily placebo or 20 mg doses of rabeprazole and omeprazole on 24-hour gastric acidity in healthy, *H. pylori*-negative human subjects. After eight days of dosing, rabeprazole and omeprazole reduce gastric acidity by 80% and 75%, respectively. After one day of dosing, however, the decrease in gastric acidity with rabeprazole is 86% of that observed on Day 8, whereas with omeprazole it is only 54% of that observed on Day 8. With rabeprazole, 19 of 20 subjects have a reduction in gastric acidity on Day 1 that is greater than 50% of that observed on Day 8, whereas with omeprazole, only seven of 20 subjects have a reduction in gastric acidity on Day 1 that is greater than 50% of that observed on Day 8 ($p<0.0001$). Finally, on Day 1, the intragastric pH is >4 for at least 35% of the 24-hour period in 16 of 23 (70%) rabeprazole subjects, but in only six of 23 (26%) omeprazole subjects ($p=0.0079$). Results from this pharmacodynamic study in healthy subjects, taken in conjunction with the preliminary results of shorter treatments in the literature, encouraged the applicant to pursue a shorter course of treatment with rabeprazole plus antibiotics in their Phase III trials.

Clinical Reviewer's Comment: The applicant has characterized the effect of rabeprazole monotherapy on gastric acid secretion and the results of these studies can be found in the approved package insert under the section on ***PHARMACODYNAMICS****. Since these data have little applicability to the use of rabeprazole in combination with amoxicillin and clarithromycin for H. pylori eradication, the results are not discussed here.*

IV. Description of Clinical Data and Sources

A. Overall Data

The clinical development program for rabeprazole in combination with antimicrobials for the eradication of *H. pylori* includes three clinical pharmacology studies, two clinical pilot efficacy studies and two Phase III clinical efficacy and safety studies, one of which was conducted in the US. US Phase III Study E3810A001-604 is considered primary, while European Phase III Study E3810-E044-603 is considered supportive. The two Phase III studies will be reviewed in detail.

The US Phase III Study 604 is a randomized, multi-center, double blind, double dummy, parallel group study comparing treatment with rabeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID (RAC) for 3, 7, or 10 days to treatment with omeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID (OAC). Subjects are stratified 1:1 based on whether they had PUD (either active or history within the last 5 years) or were symptomatic with no PUD (NPUD). All treatment regimens are given for 10

days. The rabeprazole regimens supply active drug for the first 3, 7, or 10 days. Eradication of *H. pylori* is considered the primary endpoint. Secondary efficacy parameters included eradication rates in patients with susceptible organisms, resistance rates among treatment failures, and compliance. The safety population in this study consists of 788 patients as seen in Table 6 below.

European Phase III Study 603 is considered supportive. It is also a randomized, multi-center, double blind, parallel group study. In this study two rabeprazole-based regimens (rabeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID, and rabeprazole 20 mg BID + clarithromycin 500 mg BID + metronidazole 400 mg BID) are compared to two omeprazole-based regimens (omeprazole 20 mg BID + amoxicillin 1 gm BID + clarithromycin 500 mg BID, and omeprazole 20 mg BID + clarithromycin 500 mg BID + metronidazole 400 mg BID). All regimens are given for 7 days. Eradication of *H. pylori* is considered the primary endpoint. The safety population in this study consists of 345 patients as seen in Table 6 below.

B. Table of Clinical Trials

As shown in Table 6 below, there were 1133 patients in the safety population of the two Phase III clinical studies. Of, those 668 (59%) received RAC treatment.

TABLE 6
Rabeprazole Phase III Clinical Trials

Trial	Location	Duration of Treatment (Days)	Number of Patients (Safety Population)		Total
			RAC	Control	
E3810-A001-604	US	10	198	207 (OAC)	405
		7	195	--	195
		3	188	--	188
E3810-E044-603	Europe	7	87	86 (OAC) 85 (RCM) 87 (OCM)	345
TOTALS			668	465	1133

V. Clinical Review Methods

A. Structure of the Review

For the purpose of obtaining the indication of *H. pylori* eradication, one US Phase III trial (Study 604) is considered pivotal. The European Phase III trial (Study 603) is considered supportive. This decision is based on the fact that there are differences in the two studies in the treatment duration of RAC (3, 7, and 10 days in Study 604 and only 7 days in Study 603) and patient population (non-US studies tend to have higher eradication rates than US studies).

B. Overview of Materials Consulted in Review

Material Submitted	Volumes 1 - 110 Electronic Data, including SAS transport files \\CDSESUB1\N21456\N_000\2002-01-09 \\CDSESUB1\N21456\N_000\2002-01-14 \CDSESUB1\N21456\N_000\2002-02-12 \\CDSESUB1\N21456\N_000\2002-03-07
Material Reviewed	Volumes 1, 11-53, 105-110 Electronic Data, including SAS transport files \\CDSESUB1\N21456\N_000\2002-01-09 \\CDSESUB1\N21456\N_000\2002-01-14 \CDSESUB1\N21456\N_000\2002-02-12 \\CDSESUB1\N21456\N_000\2002-03-07

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested for this trial.

Clinical Reviewer's Comment: A routine DSI audit was not felt to be necessary for this NDA since rabeprazole, clarithromycin, and amoxicillin are not NMEs. All three compounds have well-characterized safety profiles. In addition, other proton pump inhibitor triple therapy regimens containing clarithromycin and amoxicillin have been approved. Finally, no discrepancies were noted in the clinical data to warrant a directed (for-cause) inspection.

D. Evaluation of Financial Disclosure

There are a total of 67 investigators who enrolled patients in Studies 604 and 603.

In Study 604 three investigators

In Study 603 there were two investigators

One investigator received, but did not return, disclosure forms. Three unsuccessful attempts were made by the applicant to obtain information.

Per 21 CFR Part 54 the following steps have taken by the applicant to minimize any potential bias:

1. In the course of processing, analyzing and reporting data from the clinical trials, the Biometrics Department applied many procedures designed to ensure that errors are eliminated. Some of these procedures and their results may indicate aberrant data.
2. Standard operating procedures follow the current ICH Good Clinical Practices and the current FDA listing of disqualified/restricted/assurances list for clinical investigators.
3. Frequent monitoring of individual sites was performed by both the applicant and the CRO
4. Individual site audits were conducted
5. Enrollment was limited at individual sites to approximately 10% of the total patients in the study.

Clinical Reviewer's Comment: The reviewer feels that the applicant adequately attempted to minimize any potential bias arising in these studies.

VI. Integrated Summary of Efficacy (ISE)

Clinical Reviewer's Comment: All the following tables in the ISE are reproductions from the applicant's submission, unless otherwise noted.

A. Brief Statement of Efficacy Conclusions

The applicant conducted one pivotal Phase III trial in the United States (E3810-A001-604) which documents the efficacy of rabeprazole, amoxicillin and clarithromycin (RAC) therapy compared to an FDA-approved active control regimen of omeprazole, amoxicillin and clarithromycin (OAC).

The results of the supportive data provide further evidence of the efficacy of RAC therapy in eradication of *H. pylori*.

B. General Approach to Efficacy Review

Only the US Phase III trial (E3810-A001-604) was considered pivotal. A synopsis is provided below and the complete clinical/statistical review can be found in Appendix 3. The European trial (E3810-E044-603) is considered supportive, due to differences in the patient population compared to the US trial and lack of an approved comparator arm, but is also summarized below.

Other supportive efficacy data summarized in this section includes data from two pilot clinical trials (Studies 601 and 602).

C. Synopsis of Phase III Efficacy Results

1. Study 604

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. Those patients with active or a history of PUD in the past five years were stratified to the PUD group and patients who were symptomatic but without PUD were stratified to the NPUD group.

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. At the time, it was not known if patients with symptomatic non-ulcer disease could be used to accurately estimate eradication rates for patients with ulcer disease. If, in the proposed study, NPUD patients were found to have higher eradication rates than PUD patients, inclusion of this sub-population in the efficacy analysis would 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 initially be evaluated independently. If eradication rates for PUD patients are found to be 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 it is considered acceptable to pool eradication rates for PUDs and NPUDs.

Overall Eradication by Strata (PUD versus NPUD)

A summary of overall eradication rate by disease strata (and by treatment regimen) for patients in the ITT and PP populations are presented in Tables 7 and 8, respectively. The overall eradication rates for NPUD and PUD patients are found to be comparable in the ITT and PP patient populations based on the prespecified criteria. Thus it is felt that inclusion of NPUD patients in the analysis will not artificially inflate overall eradication rates. In addition, there is no significant treatment interaction. Therefore, it is considered appropriate to pool the efficacy results of these two strata.

Clinical Reviewer's Comment: Tables 7 and 8 have been created by the reviewer using data from tables submitted by the applicant.

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.

TABLE 7
Summary of *H. pylori* Eradication Rates and Disease Strata - Intention-to-Treat

Treatment	Eradication	NPUD n (%)	PUD n (%)	Difference in Eradication Rates (NPUD-PUD)	95% Confidence Interval [a]
Overall					
	Yes	247 (63%)	258 (66%)	-2.97%	-9.68%, 3.73%
	No	145 (37%)	133 (34%)		
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 8
Summary of *H. pylori* Eradication Rates by Disease Strata - Per Protocol

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

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 Table 9 below.

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% in the ITT patients and 86% vs. 82% in PP patients). In contrast, the 3-day RAC treatment regimen is considerable less effective than the OAC treatment in both populations (27% vs. 73% in ITT patients and 30% vs. 82% in the PP patients).

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

TABLE 9
***H. pylori* Eradication at ≥ 6 Weeks after the End of Treatment**
Per Protocol and Intention-to-Treat Analyses
Study 604

H. pylori Eradicated Follow-up Visit	RAC % (n/N)	OAC % (n/N)	Difference (RAC – OAC) %	95% CI
RAC 3 days versus OAC				
Per protocol	30 (50/167)	82 (146/179)	-51.6	- 60.6, - 42.6
Intention-to-Treat	27 (51/187)	73 (151/206)	-46.0	- 54.8, - 37.2
RAC 7 days versus OAC				
Per protocol	84 (140/166)	82 (146/179)	2.8	- 5.2, 10.7
Intention-to-Treat	77 (150/194)	73 (151/206)	4.0	- 4.4, 12.5
RAC 10 days versus OAC				
Per protocol	86 (147/171)	82 (146/179)	4.4	- 3.3, 12.1
Intention-to-Treat	78 (153/196)	73 (151/206)	4.8	- 3.6, 13.2

The applicant has followed the FDA draft Guidance for Industry – "Reduction of Gastric or Duodenal Ulcer Recurrence by Eradication of *H. pylori*" in determining efficacy of RAC. According to the document, the following recommendations are made regarding establishment of an efficacy threshold.

> Active controlled studies are strongly recommended and should be powered for statistical equivalence or superiority. The investigational regimen will be considered similar to the approved comparator if the lower bound of the 95% two-sided confidence

interval for the difference in eradication rates (investigational regimen minus approved active therapy) lies above –15%.

The sponsor should discuss the choice of comparator regimens well in advance of beginning the study since it is recognized that some FDA approved regimens may be less ideal for comparative trials.

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 greater 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 had a significant effect on the *H. pylori* eradication rates. None of these covariates had a statistically or clinically significant, based on the reviewer's assessment, effect on *H. pylori* eradication status.

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 10 and 11. 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.

TABLE 10
Summary of *H. pylori* Eradication Rates for Rabeprazole Treatment Arms
Intent-to-Treat Patients
Study 604

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 a comparison of the duration of RAC treatment 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 11
Summary of *H. pylori* Eradication Rates for Rabeprazole Treatment Arms
Per Protocol Patients
Study 604

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%.

Susceptibility in Relation to Eradication

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.

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 was small, particularly in the 7-day RAC, 10-day RAC and OAC regimens, and therefore, no meaningful conclusions can be drawn from these data.

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

2. Study 603

This is a Phase III, multi-center, double blind, randomized, parallel group trial in 345 *H. pylori* positive patients with documented peptic ulcer disease conducted in 25 centers in Germany, Poland, Iceland, Ireland, the Netherlands, and the United Kingdom. Patients must have a documented diagnosis of peptic ulcer disease in the last five years and a positive UBT as well as positive urease test (CLO test) for *H. pylori* following a screening upper gastrointestinal endoscopy.

Eligible patients were randomized to receive one of the following 7-day *H. pylori* eradication regimens:

RAC: Rabeprazole 20 mg + Amoxicillin 1000 mg + Clarithromycin 500 mg
RCM: Rabeprazole 20 mg + Clarithromycin 500 mg + Metronidazole 400 mg
OAC: Omeprazole 20 mg + Amoxicillin 1000 mg + Clarithromycin 500 mg
OCM: Omeprazole 20 mg + Clarithromycin 500 mg + Metronidazole 400 mg

The all three medications within each regimen were taken twice daily, after breakfast and after an evening meal.

To maintain the double blind, a double-dummy technique was used for all study medication (with the exception of clarithromycin).

Patients returned for a follow-up visit 4 weeks after the end of treatment for a UBT. If negative, they returned for another UBT 4 weeks later (i.e., 12 weeks after the end of treatment). If either UBT was positive, patients underwent an endoscopy with biopsies obtained for susceptibility testing.

The primary efficacy endpoint is the presence or absence of *H. pylori* post-treatment as defined as two negative UBTs (4 and 12 weeks following the end of treatment).

Clinical Reviewer's Comment: The UBT used pre- and post-treatment in this study was not a FDA-approved diagnostic. Therefore, results from this study are supportive, but should be interpreted with caution.

The ITT population is defined as all randomized patients with a positive screening UBT who received at least one dose of study medication. The PP population is defined as all randomized patients who received at least one dose of study medication, with the exception of those subjects having protocol violations. The main reasons for exclusion from the PP analysis are: administration of a prohibited medication, a negative UBT 4 weeks following the end of treatment without a repeat test at 12 weeks following the end of treatment, and failure to return for the follow-up visit.

Two primary comparisons were performed on the PP population, one to determine whether rabeprazole and omeprazole were therapeutically equivalent and one to determine whether amoxicillin and metronidazole were therapeutically equivalent. Equivalence was assessed using a two-sided 95% confidence interval for the difference in eradication rates between the two treatments.

The primary analysis indicates that rabeprazole and omeprazole have very similar eradication rates (87% and 85%, respectively) in the PP population as shown in Table 12. Overall, the two PPIs are therapeutically equivalent, the 95% confidence interval for the difference in percentage eradicated (-7.2%, +9.7%) being entirely within the interval (-15%, +15%) when averaging the effect across antibiotics. Adjusting the estimates by pooled center and antibiotics confirms these results (95% confidence intervals -7.5%, +9.4%).

Table 12
Analysis of *H. Pylori* Eradication Pooled Across Antibiotics – PP Population

	Eradication Rates N	(%)	% difference	95% CI
Stratified by Pooled Center				
Rabeprazole	109	87	+1.2	-7.2, +9.7
Omeprazole	110	85		
Stratified by Pooled Center and Antibiotics				
Rabeprazole	109	87	+1.0	-7.5, +9.4
Omeprazole	110	85		

Rabeprazole and omeprazole also have very similar eradication rates (77% and 75%, respectively) in the ITT population as shown in Table 13. Overall, the two PPIs are therapeutically equivalent, the 95% confidence interval for the difference in percentage eradicated (-7.4%, +10.4%) being entirely within the interval (-15%, +15%) when averaging the effect across antibiotics. Adjusting the estimates by pooled center and antibiotics confirms these results (95% confidence intervals -6.9%, +10.6%).

TABLE 13
Analysis of *H. Pylori* Eradication Pooled Across Antibiotics – ITT Population

	Eradication Rates N	(%)	% difference	95% CI
Stratified by Pooled Center				
Rabeprazole	126	77	+1.5	-7.4, +10.4
Omeprazole	128	75		
Stratified by Pooled Center and Antibiotics				
Rabeprazole	126	77	+1.8	-6.9, +10.6
Omeprazole	128	75		

The test for interaction between the PPI and antibiotic treatment factors was assessed and found to be statistically significant in both the PP and ITT populations (p=0.039 and p=0.017, respectively). Further data analyses were performed to explore this interaction. Separate analyses of the rabeprazole versus omeprazole treatment groups within each antibiotic were performed. The 95% confidence intervals for the differences in eradication rates were determined to see whether equivalence could be claimed in one or both of the following subsets of patients:

a) subjects given amoxicillin, and
b) subjects given metronidazole

The results of the additional analyses are presented in Tables 14 and 15 for the PP and ITT populations, respectively.

From Table 14 it can be seen that in the amoxicillin subset, rabeprazole has a higher eradication rate than omeprazole (94% compared with 84%, respectively) in the PP population, with a 95% confidence interval for the difference of -0.7%, +20.4%.

TABLE 14
Analysis of *H. Pylori* Eradication for Subsets – PP Population

	Rabeprazole No. (%) of Subjects eradicated		Omeprazole No. (%) of Subjects eradicated		% difference	95% CI
Amoxicillin	61 (94)		53 (84)		+9.8	-0.7, +20.4
Metronidazole		48 (79)		57 (86)	-8.1	-21.4, +5.1
% difference	+14.9		-2.3			
95% CI	+2.8, +27.0		-14.4, +9.9			

From Table 15 it can be seen that in the amoxicillin subset, rabeprazole has a higher eradication rate than omeprazole (84% compared with 72%, respectively) in the ITT population, with a 95% confidence interval for the difference of +0.5%, +24.5%.

TABLE 15
Analysis of *H. Pylori* Eradication for Subsets – ITT Population

	Rabeprazole No. (%) of Subjects eradicated		Omeprazole No. (%) of Subjects eradicated		% difference	95% CI
Amoxicillin	70 (84)		61 (72)		+12.5	+0.5, +24.5
Metronidazole		56 (69)		67 (79)	-9.1	-21.9, +3.7
% difference	+14.8		-7.4			
95% CI	+2.3, +27.2		-19.8, +5.1			

Clinical and Statistical Reviewer's Comment: In the ITT analysis, RAC is superior to OAC. In the PP analysis, RAC narrowly misses the criteria for superiority since the 95% confidence interval of the difference includes zero, but is only slightly below zero (-0.7). It is important to keep in mind that the comparator in this study is a 7-day treatment regimen of OAC, which is shorter than the FDA-approved 10-day regimen. Nonetheless, this data lends further support to results obtained in the pivotal study, in which 7-days of RAC is equivalent to 10-days of OAC.

D. Other Supportive Efficacy Data

Clinical Reviewer's Comment: Tables 16-18 were modified by the reviewer from the applicant's submitted tables.

1. Study 601

This pilot study was divided into two parts. Part one is a randomized, double-blind, parallel-group, placebo-controlled trial in 26 *H. pylori* positive subjects (by ^{13}C-UBT) comparing the efficacy of once daily or twice daily rabeprazole 20 mg with placebo in bacterial eradication. Eradication rates, defined as the proportion of subjects in each group with a negative ^{13}C-UBT 4 weeks post-therapy, are shown in Table 16. No differences are observed in either the rates of eradication when patients are given rabeprazole 20 mg either once or twice daily in comparison to placebo.

TABLE 16
***H. pylori* Eradication by Treatment Regimen**
Study 601 (Part I)

Treatment	n/N (%)
Placebo	0/8 (0)
Rabeprazole once daily	8/9 (88.9)
Rabeprazole twice daily	9/9 (100)

The second part of the study evaluates the efficacy of the combination of rabeprazole 20 mg twice daily plus amoxicillin 500 mg four times daily with amoxicillin 500 mg four times daily as monotherapy in 48 subjects with *H. pylori* infection. Eradication rates, defined as the proportion of subjects in each group with a negative ^{13}C-UBT 4 weeks post-therapy, are

shown in Table 17. Administration of rabeprazole with amoxicillin results in a higher rate of *H. pylori* eradication than amoxicillin alone.

TABLE 17
***H. pylori* Eradication by Treatment Regimen**
Study 601 (Part II)

Treatment	n/N (%)
Amoxicillin	3/24 (12.5)
Rabeprazole + Amoxicillin	15/24 (62.5)

2. Study 602

This is a Phase II, single center, double-blind, randomized, parallel-group comparison of four treatment regimens used for eradication of *H. pylori* in 75 patients with chronic antral gastritis with or without peptic ulcer disease conducted in the United Kingdom. Each of the following four treatment regimens was administered for 7 days:

RAC: Rabeprazole 20 mg + Amoxicillin 1000 mg + Clarithromycin 500 mg twice daily
RAM: Rabeprazole 20 mg + Amoxicillin 1000 mg + Metronidazole 400 mg twice daily
RCM: Rabeprazole 20 mg + Clarithromycin 500 mg + Metronidazole 400 mg twice daily
RC: Rabeprazole 20 mg + Clarithromycin 500 mg twice daily

Patients underwent an endoscopy performed prior to treatment with eight mucosal biopsies (2 antral biopsies for rapid urease test, 2 antral and 2 corpus biopsies for histopathology, and 1 antral and 1 corpus biopsy for culture) taken for determination of *H. pylori* infection and antimicrobial susceptibility testing. To be considered evaluable a patient had to have both a positive ^{13}C-UBT and histology or culture. Eradication of *H. pylori* is defined as two negative ^{13}C-UBTs performed 4 and 8 weeks post-treatment. The results are shown in Table 18 below. The 7-day RAC regimen is highly effective (94.7% and 100% eradication in the ITT and PP analyses, respectively), and despite the small sample size, results in a statistically significantly superior eradication rate compared to dual therapy with RC.

TABLE 18
***H. pylori* Eradication by Treatment Group**
Intention-to-Treat and Per Protocol Patients
Study 602

Treatment Group	ITT		PP	
	n/N (%)	Significant p-values	n/N (%)	Significant p-values
RAC	18/19 (94.7)	p = 0.042 RAC vs. RC	18/18 (100)	p =0.019 RAC vs. RC
RAM	17/19 (89.5)	--	15/17 (88.2)	--
RCM	18/18 (100)	p = 0.008 RCM vs. RC	17/17 (100)	p = 0.019 RCM vs. RC
RC	12/19 (63.2)	p = 0.008 RC vs. RCM	12/18 (66.7)	p = 0.019 RC vs. RCM

Susceptibility to amoxicillin, metronidazole, and clarithromycin was determined by E-test.

Breakpoints used were as follows:

Amoxicillin
susceptible, MIC ≤ 0.25 μg/mL, resistant MIC > 0.25 μg/mL

Clarithromycin
susceptible, MIC ≤ 0.1 μg/mL, resistant MIC > 0.1 μg/mL

Metronidazole
susceptible, MIC ≤ 8 μg/mL, resistant > 8 μg/mL

Clinical Reviewer's Comment: The E-test is not an approved NCCLS susceptibility test method for H. pylori. The breakpoints used for clarithromycin are also not the approved NCCLS breakpoints of susceptible ≤ 0.25 μg/mL, intermediate 0.5 μg/mL, and resistant ≥ 1.0 μg/mL. Therefore, results from this study are supportive, but should be interpreted with caution.

All amoxicillin MICs are ≤ 0.064 μg/mL. The metronidazole MICs vary from 0.032 μg/mL to ≥ 32 μg/mL. Most isolates with metronidazole MICs of ≥ 32 μg/mL are eradicated. Almost all pre-treatment clarithromycin MICs are ≤ 0.38 μg/mL. After treatment failure, especially with rabeprazole and clarithromycin alone, MIC values increase to ≥ 0.5 μg/mL.

E. Summary of Efficacy

The applicant conducted one pivotal trial in the US (E3810-A001-604) to document the efficacy of a varying duration of RAC therapy (3-, 7-, and 10-days) versus 10-days of OAC therapy. Study 604 is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of 7-day and 10-day RAC treatment regimens compared to 10 days of OAC. The lower bound of the 95% confidence interval of the difference (RAC - OAC) for both the ITT and PP analyses achieve the pre-specified criteria of greater than -15%. Therefore, the efficacy criteria recommended in the FDA draft Guidance are satisfied.

Other findings include:

- Covariate analyses using logistic regression as well as examination of eradication rates within age, gender, and race subcategories indicate that none of these covariates have a statistically or clinically significant effect on eradication status.

- No conclusions can be drawn regarding the rates of emerging resistance to either RAC or OAC due to the few number of patients with culture results available post-treatment.

The results of the supportive data provide further evidence of the efficacy of RAC therapy:

- In the supportive Phase III European Study E3810-E044-603, seven (7) days of treatment with RAC is highly effective and produces a higher eradication rate than 7 days of treatment with OAC. In a subset analysis, the RAC eradication rate is 94% compared to 84% with OAC in the PP population and 84% versus 72% in the ITT population. The treatment difference is statistically significant in the ITT analysis (i.e., the 95% confidence interval of the difference lies entirely above zero), suggesting that

RAC is superior to OAC in this analysis, and narrowly misses the criteria for superiority in the PP analysis.

- In the two-part pilot study (E3810-L001-601), no differences are observed in either the rates of eradication when patients are given rabeprazole 20 mg either once or twice daily in comparison to placebo. In Part II of this study, administration of rabeprazole with amoxicillin results in a higher rate of *H. pylori* eradication than amoxicillin alone. The eradication rate for rabeprazole plus amoxicillin dual therapy for 14 days is 63%.

- Study E3810-E044-602 shows that 7-days of RAC is highly effective (94.7% and 100% eradication in the ITT and PP analyses, respectively), and despite the small sample size, results in a statistically significantly superior eradication rate compared to dual therapy with RC.

VII. Integrated Summary of Safety (ISS)

Clinical Reviewer's Comment: All the following tables in the ISS are reproductions from the applicant's submission, unless otherwise noted.

A. Brief Statement of Safety Conclusions

There are no clinical meaningful differences between RAC and OAC therapy in the incidence of adverse events (AEs) in the pivotal US trial (Study 604). Although the safety data from the European trial (Study 603) are not pooled with the US trial, the results are supportive of each other with regards to 7-day RAC therapy.

B. Description of Drug Exposure

The safety database for this NDA contains data from three clinical pharmacology studies, two clinical pilot trials, one pivotal Phase III trial, and one supportive Phase III trial. The number of patients exposed and the duration of exposure is shown in Table 19 below.

Clinical Reviewer's Comment: Table 19 was created by the reviewer.

TABLE 19
Extent of Exposure in Rabeprazole Clinical Trials
Number of Subjects/Patients per Treatment

Trial	Location	Duration of Treatment (days)	Number of Patients (Safety Population)		Total
			RAC	Control	
E3810-A001-604 *(Pivotal Phase III)*	US	10	198	207 (OAC)	405
		7	195	--	195
		3	188	--	188
E3810-E044-603 *(Supportive Phase III)*	Europe	7	87	258 (86 OAC)	345
E810-E044-602 *(Clinical Pilot)*	UK	7	19	56	75
E810-L001-601 Part I *(Clinical Pilot)*	US	14	--	26	26
E810-L001-601 Part I *(Clinical Pilot)*	US	14	--	48	48
E3810-E044-402 *(Clinical Pharmacology)*	UK	14	--	24	24
E3810-E031-118 *(Clinical Pharmacology)*	Netherlands	7	16	--	16
E3810-J081-201 *(Clinical Pharmacology)*	Japan	7	20*	--	20
TOTALS			723	619	1342

* Dose of amoxicillin in RAC regimen consisted of 750 mg instead of 1000 mg

C. Methods and Specific Findings of Safety Review

The safety information reviewed in this section only includes data from the three clinical trials with one or more arms consisting of RAC or OAC treatment. These data have been taken from the final clinical study reports for each trial and are not pooled. The emphasis of this safety review is on RAC and OAC. Therefore, data from other drug regimens included in Studies 603 and 602 will not be discussed. In addition, data from Study 601, as well as the clinical pharmacology studies, will not be discussed because RAC or OAC treatment was not used.

1. Overview of Adverse Events

This section discusses the treatment-emergent adverse events (TEAEs). A TEAE is defined as an adverse event that either began after the first dose of study medication, or one that was present at screening, but increased in intensity during the treatment or follow-up periods.

Study 604

A summary of the most common TEAEs (≥ 5% in any group) for the Safety population in Study 604 is presented in Table 20 below.

TABLE 20
Summary of Treatment-Emergent Adverse Events (≥ 5%) - Safety Patients
Study 604

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 body system with the most reported TEAEs in each group is the digestive system and common events include dyspepsia, diarrhea, and abdominal pain.

Study 603
Table 21 below shows the most frequently occurring TEAEs (reported in more than 10 subjects combined across all four treatment arms) by COSTART preferred term. The most frequent occurring events are diarrhea and taste perversion. The treatment groups are not found to differ significantly in the proportions of subjects with and without adverse events.

TABLE 21
Most Frequently Occurring Adverse Events After Randomization
by Preferred Term and Treatment Group
Study 603

No. of Subjects	RAC (N=87)	OAC (N=86)
Diarrhea	11	18
Taste perversion	12	11
Dyspepsia	5	3
Abdominal Pain	6	5
Headache	2	4
Influenza-like symptoms	1	6
Nausea	0	2

Study 602
Of the 19 patients in the RAC treatment arm, 17 (89.5%) experienced at least one or more TEAEs. The most commonly reported events are: diarrhea (9 patients), taste perversion (8 patients), and dyspepsia, dizziness, rash, and headache (all in 2 patients each).

2. Adverse Events by Relationship to Treatment

Study 604

TEAEs are reported by ≥ 1% of patients with at least one event in any treatment group and that are judged to be either possibly or probably related to the study medication (relationship as per the Investigator) are summarized in Table 22. 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 22
Summary of Patients with Treatment-Emergent Adverse Events Considered Possibly or Probably Related[a] to Study Medication (≥ 1%) – Safety Patients
Study 604

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.

Study 603

The applicant did not tabulate the incidence of TEAEs by relationship to treatment.

Study 602

The most commonly reported TEAEs in patients who received RAC treatment that are regarded as possibly or probably related to study medication include: taste perversion (8 patients), diarrhea (7 patients), and headache (2 patients).

3. Adverse Events by Subgroup (Age, Gender and Ethnicity)

A summary of demographic characteristics for patients in the safety populations of the US and European Phase III trials are shown in Table 24 below.

Clinical Reviewer's Comment: Table 24 was created by the reviewer. In the European trial (603) only the demographic characteristics for the RAC and OAC treatment arms are shown. Due to the small number of patients in Study 602 who received RAC, subgroup analyses were not done for this study.

TABLE 24
Demographic Characteristics – Percentage (%) of Patients
Studies 604 and 603

Characteristic		US Trial [N=788] (E3810-A001-604)				European Trial* [N=345] (E3810-E044-603)	
		RAC 3 day [N=188]	RAC 7 day [N=195]	RAC 10 day [N=198]	OAC 10 day [N=207]	RAC 7 day [N=87]	OAC 7 day [N=86]
Age	< 65 years	169	172	172	190	73	61
	≥ 65 years	19	23	26	17	14	25
Gender	Male	79	91	94	89	57	50
	Female	109	104	104	118	30	36
Race	White	68	74	83	84	81	83
	Black	33	26	18	27	1	1
	Hispanic	81	88	86	88	3	2
	Other	6	7	11	8		

* the race subgroups in the European trial (603) were identified as White, Black, Oriental and Other. The summary of AEs in the Oriental subgroup was not produced, as the incidence of AEs was not >1% in either treatment group for this subgroup. In addition, the Hispanic population is represented in the category of "Other".

Study 604

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.

Clinical Reviewer's Comment: For safety tables by subgroup see the review of Study 604 in Appendix 1.

Study 603

The most frequently reported adverse events by age (< 65 and ≥ 65) and gender are shown below in Table 25A and 25B. Although there may be small differences between the groups for various TEAEs, the results are not likely to indicate clinically meaningful differences.

No analysis by race was performed since the number of patients in the Black and Other race categories is too small to allow any conclusions.

TABLE 25A
Patients (%) with Most Frequently Occurring Adverse Events
by Treatment and Age
Safety Population
Study 603

Preferred Term	RAC (N=87)		OAC (N=86)	
	< 65 yrs (N=73)	≥ 65 yrs (N=14)	< 65 yrs (N=61)	≥ 65 yrs (N=25)
Diarrhea	8 (11)	3 (21)	13 (21)	5 (20)
Taste perversion	9 (12)	3 (21)	7 (11)	4 (16)
Dyspepsia	5 (7)	0	2 (3)	1 (4)
Abdominal Pain	5 (7)	1 (7)	4 (7)	1 (4)
Headache	2 (3)	0	3 (5)	1 (4)
Influenza-like symptoms	1 (1)	0	6 (10)	0
Nausea	0	0	2 (3)	0

Patients are only counted once per event

TABLE 25B
Patients (%) with Most Frequently Occurring Adverse Events
by Treatment and Gender
Safety Population
Study 603

Preferred Term	RAC (N=87)		OAC (N=86)	
	Males (N=57)	Females (N=30)	Males (N=50)	Females (N=36)
Diarrhea	7 (12)	4 (13)	12 (24)	6 (17)
Taste perversion	6 (11)	6 (20)	4 (8)	7 (19)
Dyspepsia	4 (7)	1 (3)	1 (2)	2 (6)
Abdominal Pain	5 (9)	1 (3)	3 (6)	2 (6)
Headache	0	2 (7)	2 (4)	2 (6)
Influenza-like symptoms	0	1 (3)	2 (4)	4 (11)
Nausea	0	0	2 (4)	0

Patients are only counted once per event

4. Discontinuations from Study Due to Adverse Events

Study 604

Table 26 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 to a non-treatment-emergent event (i.e., adenocarcinoma).

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 were 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 were 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).

Clinical Reviewer's Comment: Table 26 was modified by the reviewer from the applicant's submitted table.

APPEARS THIS WAY
ON ORIGINAL

TABLE 26
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.

TABLE 26 (continued)
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]
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.

Study 603
One patient in the OAC arm discontinued due to an adverse event. No patients discontinued in the RAC arm. The OAC patient discontinued from study medication due to a flu-like syndrome but completed the follow-up assessments.

Patient 248 was a 48-year-old Caucasian female who received OAC. At screening, she had a current history of menopausal syndrome and suspected osteoarthritis. She received no significant prior or concomitant medications. On the third day of administration, She was diagnosed with flu-like syndrome. Study treatment was discontinued permanently. The event lasted six days and was regarded by the investigator as moderate intensity and remotely related to the study treatment.

Study 602
One patient in the RAC treatment arm discontinued due to an adverse event. Patient 155 was a 49 year-old Caucasian male with a history of penicillin allergy (unknown to the investigator at the time of enrollment). He was withdrawn from the study after one dose of RAC because of a mild allergic reaction described as itching of the skin around the neck area and hot and burning ears. The itching resolved within 24 hours, and the patient recovered completely. The investigator regarded the event to be probably related to the

study medication. The patient's concomitant medications included paracetamol/ dextropropoxyphene

5. Deaths

There were two deaths reported in the clinical development program of RAC *for H. pylori* infection (all six trials). In Study 603, Patient 561 died suddenly and unexpectedly three days after completing seven days of treatment with RAC. In Study 602, Patient 11 died 65 days after completing treatment with RAC.

Patient 561 was an 87-year-old Caucasian female who randomized to RAC treatment. At screening, she had a current history of epigastric pain, a gastric ulcer (with bleeding), nephrosclerosis, renal failure necessitating hemodialysis, diabetes mellitus type II, arterial hypertension, arteriosclerosis, coronary heart disease, emphysema, pleural exudation, diabetic retinopathy and anemia. Concomitant treatments during the study included enalapril, erythropoietin, heparin, isosorbide dinitrate, molsidomine, ranitidine and Renavit. She completed 7 days of treatment with RAC and died suddenly and unexpectedly two days later. The cause of death is unknown (no known autopsy), but the suspected cause of death was recorded as asystole during hemodialysis. The event is regarded by the investigator as unrelated to the study treatment.

Clinical Reviewer's Comment: Renal failure is an exclusion criterion for the study, so the patient should not have been enrolled into the study. Nonetheless, it is unlikely that the study medications she received (i.e., RAC) contributed to her death.

Rabeprazole is extensively metabolized by the liver. Renal failure has not been shown to alter the pharmacokinetics of the drug. In addition, studies in healthy subjects have not shown rabeprazole to have any significant drug interactions with medications metabolized by the CYP 450 enzyme system, although no patient studies have been conducted. Due to the effect of rabeprazole on gastric acid section, drug interactions are possible with medications that are dependent on a low gastric pH for absorption. Clarithromycin does have the potential for interacting with drugs metabolized by the CYP 450 enzymes. However, none of the patient's concomitant medications are known to be metabolized by this pathway. Clarithromycin and amoxicillin are both partially renally eliminated, but only amoxicillin should be dose adjusted in patients with severe renal impairment.

In the reviewer's opinion, altered pharmacokinetics of rabeprazole, clarithromycin, and amoxicillin due to renal failure and/or drug interactions are not believed to play a role in the cause of death of this patient.

Patient 11 was a 64 years old Caucasian male who received RAC treatment. At screening, there was no reported medical history or pre-existing conditions, and the patient's laboratory data indicated that he had a mild iron-deficiency anemia that did not worsen between screening and the end of study evaluation. The patient received only one concomitant medication, ferrous sulfate, during the study. Approximately three weeks after his last dose, the patient experienced diarrhea of moderate intensity, which was later found to be associated with carcinoma of the colon. Approximately, two months after completing study medication, the patient underwent colon surgery and died 2 days following surgery of a small bowel infarction. In the investigator's opinion, neither the occurrence of the cancer or the small bowel infarction is related to the study medication.

Clinical Reviewer's Comment: Agree with the investigators' assessment in both cases. It is unlikely that these patients' deaths were related to study treatment.

6. Non-Fatal Serious Adverse Events

Study 604

A total of 23 non-fatal serious adverse events (SAEs) occurred in 15 patients during this study. Table 27 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). The SAE in the OAC patient is considered by the investigator not to be related to study medication.

TABLE 27
Listing of Patients with Non-Fatal Serious Adverse Events – All Randomized Patients
Study 604

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.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Study 603
There was one non-fatal serious adverse event that occurred in the OAC treatment arm. None occurred in the RAC arm.

Patient 579 was a 55-year-old Caucasian male who was diagnosed with adenocarcinoma of the colon during the study. At screening, he had a current history of diarrhea, duodenal ulcer, hypothyroidism, psychosis and varicosis. He received no significant prior or concomitant medications other than thyroxine. Four days after initiating OAC treatment, the patient was diagnosed by histopathology as having adenocarcinoma of the colon. The subject continued on the study treatment and received no additional medication while on study. The event was regarded by the investigator as unrelated to the study treatment. The event remained unresolved at the end of the study.

Study 602
There was one serious non-fatal adverse event. A patient (Screening #90), who received RAC and successfully completed the study, admitted that he had not taken one of the rabeprazole tablets and the adjacent antibiotic capsule himself, and that it was possible that these had been taken, without noticeable effect, by his 12 year old daughter.

Clinical Reviewer's Comment: The applicant, and not the investigator, reported this event as a SAE.

7. Pregnancy

No female of childbearing age had a positive pregnancy test at screening. Four patients discontinued from Study 604 due to pregnancy: three of the patients delivered normal healthy babies (one patient in each of the following treatment arms: 7-day RAC, 10-day RAC, and 10-day OAC) and one 10-day RAC patient was lost to follow-up.

8. Clinical Laboratory Evaluations

Study 604
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 28 and 29 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 28
Summary of Change from Screening to End of Treatment for ALT (SGPT)
Safety Patients
Study 604

	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 29
Summary of Change from Screening to End of Treatment for AST (SGOT)
Safety Patients
Study 604

	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%

Study 603

There are no statistically or clinically significant differences in values at screening or in change from screening to follow-up across treatment groups in hematology or clinical chemistry values. One patient in the RAC and OAC treatment groups each report hematology-related adverse events (eosinophilia and anemia, respectively). Both events are regarded as unrelated to treatment by the study investigator and eventually resolved (eosinophilia without treatment and anemia with the addition of ferrous sulphate).

Clinical Reviewer's Comment: Unlike Study 604, there are no notable changes recorded in the RAC or OAC treatment groups for ALT and AST values. However, increases in mean

and median ALT and AST values at Day 8/9 compared with Day 0 were recorded in the RCM and OCM treatment groups.

Study 602
There are no statistically or clinically significant differences in values at screening or in change from screening to follow-up for the RAC treatment group in hematology or clinical chemistry values.

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

For all three studies (604, 603, and 602), there are no statistically or clinically significant changes across treatment groups from screening to follow-up in sitting systolic and diastolic blood pressure, sitting pulse, respiration rate, temperature, and weight.

D. Summary of Safety

1. Study 604

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

- The percentage of patients with adverse events 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 treatment emergent adverse events (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.

- There does not appear to be a relationship between discontinuation of study medication and duration of treatment. Eight patients discontinuing were 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 were gastrointestinal in nature.

- No deaths occurred in this study.

- A similar percentage of patients in each treatment group experienced at least one treatment-emergent serious adverse event (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). No SAE was judged to be treatment related in any of the RAC arms. There was one case were the SAE was judged by the investigator to be treatment-related (hyponatremia, vomiting and nausea). It occurred in a patient who received treatment with OAC. In nine of the 11 patients, the SAE occurred during the follow-up period of the study.

- 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.

2. Study 603

- There are no notable differences between 7-day treatment with RAC or OAC with regard to overall safety.
- The safety results for 7-day RAC therapy are similar and supportive of Study 604.
- One death and one serious adverse event occurred during the study. Both events were considered unrelated to study medication. The death (sudden, unexpected death) occurred in the RAC treatment group, and the serious adverse event (adenocarcinoma of the colon) occurred in the OAC group.
- One patient in the OAC group was permanently discontinued from study treatment due to flu-like symptoms considered to be related to study treatment.

3. Study 602

- Other than one allergic reaction (in a patient who later admitted penicillin allergy), there are no significant adverse events related to RAC treatment. Of the events considered to be possibly or possibly related to study medication, the most frequently reported are taste perversion, diarrhea, and headache.

VIII. Dosing, Regimen, and Administration Issues

The proposed dose of rabeprazole (20 mg twice daily) is greater than the dose recommended for other GI indications (20 mg once daily). The rationale for using a higher dose is as follows:

1. The dose of rabeprazole for this indication is the same as omeprazole (when used in combination with amoxicillin and clarithromycin) for treatment of *H. pylori* infection.

The applicant has conducted studies showing that rabeprazole and omeprazole are not significantly different in terms of disease healing, resolution of symptoms, and relapse of GERD pathology or symptoms.

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

combination with amoxicillin and clarithromycin for eradication of *H. pylori* and 20-40 mg once daily for other GI indications.

TABLE 30
Approved Doses of Other PPIs for Various GI Indications*

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

*excluding eradication of *H. pylori* and treatment of Zollinger-Ellison syndrome

2. Twice daily dosing should produce a consistent, elevated intragastric pH.

Proton pump inhibitors effect the growth of *H. pylori* by raising the intragastric pH. *H. pylori* grows best in a slightly acidic pH. Therefore, in order to achieve inhibition of bacterial growth, the pH should remain consistently elevated. However, it has been shown that a single daily 20 mg dose of rabeprazole or omeprazole increases the 24-hour gastric acidity above a pH of 4 for the first 14 hours after dosing, but the pH decreases below 4 for the subsequent 10 hours. Adding a second daily dose of rabeprazole ensures that maximal acid suppression is maintained throughout the day and night.

Also, it has been shown that in *H. pylori*-positive subjects the acid inhibition produced by PPIs is magnified (i.e., it is easier to maintain an elevated pH). However, use of an eradication regimen results in clearance of the organism and possibly loss of this effect. The second daily dose of rabeprazole may be necessary to maintain the inhibitory effect on gastric acid and to increase pH.

Therefore, addition of a second 20 mg rabeprazole dose should produce maximum acid suppression and consistently elevate the intragastric pH such that eradication of *H. pylori* infection is achieved.

3. Higher PPI doses should enhance the antibacterial effects of combination therapy.

The higher pHs produced by PPIs may reduce the degradation of acid-labile antimicrobials, such as amoxicillin.

In addition, the mechanism of action of PPIs in the treatment of *H. pylori* is believed to be more complex than just inhibition of acid suppression. Co-administration of a PPI with antimicrobials appears to enhance the action of the antimicrobials by several possible mechanisms.

PPIs have direct antimicrobial activity against *H. pylori in vitro* by inhibiting bacterial urease. Inhibition of this enzyme can decrease the bacteria's ability to colonize the gastric mucosa. In addition, PPIs also possess anti-*H. pylori* activity independent of urease by affecting the components of the bacterial cell membrane.

In summary, approval of 20 mg rabeprazole twice daily in combination with antimicrobials for eradication of *H. pylori* is consistent with other approved PPIs for this indication and appears warranted based on what is known of the pharmacology and pathophysiology of this infection.

IX. Use in Special Populations

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

A. Efficacy

In the US trial (Study 604) covariate analyses using logistic regression were performed by the statistical reviewer to determine whether age, gender, or race had a significant effect on the *H. pylori* eradication rates. None of these covariates had a statistically or clinically significant, based on the reviewer's assessment, effect on *H. pylori* eradication status.

B. Safety

The results of the subgroup analyses by gender in the US trial (Study 604) indicate overall that the incidence of adverse events is similar between males and females. Although the results for individual events can vary depending upon treatment, any differences that occur are slight 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 numbers of patients ≥ 65 years of age is small and therefore no reliable conclusions can be drawn regarding the incidence of adverse events been young and elderly subgroups.

In the European trial (Study 603), the results are not likely to indicate clinically meaningful differences between age or gender subgroups. No analysis by race was performed since the number of patients is too small to allow any conclusions.

X. Conclusions and Recommendations

A. Conclusions

In this submission, the applicant demonstrates the activity of 7-days of treatment with rabeprazole, amoxicillin, and clarithromycin (RAC) in the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease (active or history within the past 5 years). The efficacy of RAC is compared to a FDA-approved regimen consisting of omeprazole, amoxicillin, and clarithromycin (OAC). The OAC regimen is an acceptable comparator since it consistently achieves eradication rates of approximately 70% or greater by Intention-to-Treat (ITT) analysis and 80% or greater by Per Protocol (PP) analysis.

The applicant conducted one pivotal Phase III trial in the United States (E3810-A001-604) to document the efficacy of RAC. It is a well-conducted randomized, active-controlled clinical trial that demonstrates the non-inferiority of 7 days of RAC treatment versus 10 days of OAC treatment. The lower bound of the 95% confidence intervals for the difference in eradication rates for the 7-day RAC versus 10-day OAC groups are -4.4% and -5.2% for the ITT and PP analyses, respectively. Therefore, the lower bounds of the confidence intervals are greater than the allowable delta of - 15% and the *H. pylori* eradication rate for 7-day RAC treatment satisfies the efficacy criteria recommended in 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.

Overall eradication rates for 7-day RAC therapy in the supportive Phase III European trial (E3810-E044-603) are consistent with, although numerically higher than, the results obtained in the 7-day RAC arm in US Study 604 for the ITT (84% versus 77%) and PP (94% versus 84%) analyses, respectively. Eradication rates for 7-day OAC therapy in Study 603 (Europe) are similar to the rates with 10-day OAC therapy in Study 604 (US), for the ITT (72% versus 73%) and PP (84% versus 82%) analyses, respectively. These results are consistent with other drug therapy trials in which European rates of *H. pylori* eradication, for reasons not clearly identified, are often higher than those seen in US trials.

In the US trial (Study 604), there are no clinically meaningful differences between the 7-day RAC and 10-day OAC groups in the incidence of any adverse event (AE). For both treatments gastrointestinal AEs are the most commonly reported (e.g., dyspepsia, diarrhea, abdominal pain, and nausea) and may be attributed to use of antimicrobial agents. In addition, headache is frequently reported in both groups, which is a common AE associated with proton pump inhibitors. Taste perversion is also a common AE to both treatments and has been described previously in association with clarithromycin.

Although the safety data from two European trials (Study 603 and 602) are not pooled with the US trial, the results are similar and supportive of the 7-day of RAC regimen.

B. Recommendations

Rabeprazole sodium when used in combination with amoxicillin and clarithromycin is safe and effective for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. The recommendation is for approval of rabeprazole 20 mg, amoxicillin 1000 mg, plus clarithromycin 500 mg twice daily for 7 days for this indication.

In general, the labeling proposed by the sponsor is acceptable. However, with regard to the Clinical Studies section, the eradication data for the RAC 3-day and 10-day regimens will be added. This additional data is meant to highlight that the eradication rates achieved with the 7-day regimen are similar to 10-days of therapy, which is currently the shortest duration for an approved *H. pylori* treatment regimen. In addition, the inferior data from the 3-day regimen highlights the importance of adherence to 7-days of therapy. The Dosage and Administration section will also be modified to alert the prescriber to the importance of compliance with the full 7-days of treatment.

/S/

Joette M. Meyer, Pharm.D.
Clinical Reviewer, DSPIDP,ODE IV, CDER

/S/

Nancy P. Silliman, Ph.D.
Statistical Reviewer, DB III, CDER

Concurrence:
HFD-590/TLMO/RocaR
HFD-590/TLStat/HigginsK
HFD-590/DivDir/AlbrechtR
HFD-590/OfficeDir/GoldbergerM

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 1 – INDIVIDUAL STUDY REVIEW FOR STUDY 604

I. Clinical and Statistical Review of Study 604

Clinical Reviewer's Comment: All the following tables in this review are reproductions from the applicant's submission, unless otherwise noted.

Title
Comparison of the Efficacy and Safety of Three Rabeprazole-based Triple Therapy Regimens to Omeprazole-based Triple Therapy for Eradication of *Helicobacter pylori*

Protocol Number
E3810-A001-604

Study Initiation December 6, 1999

Study Completion June 4, 2001

A. Investigators and Study Administrative Structure

Forty-seven (47) sites were initiated for enrollment into the trial, but only 42 enrolled patients.

Qualified personnel from Eisai, Inc. or its designee and monitored the study. One central laboratory was utilized for the study. Microbiological culture evaluations, 13 C-Urea Breath Tests (13 C-UBT), and clinical laboratory tests were performed by formerly known as performed data management and final statistical analyses.

B. Study Objectives

Primary Objective
The primary objective of this study was to test the hypothesis that treatment with rabeprazole, amoxicillin, and clarithromycin (RAC) for 3 days, 7 days, or 10 days is equivalent in effectiveness in eradicating *H. pylori* infection to 10 days of treatment with omeprazole, amoxicillin, and clarithromycin (OAC).

Secondary Objectives
- To test the hypothesis that in patients infected with organisms susceptible to the antibiotics tested, eradication rates will be ≥ 80%.
- To test the hypothesis that with each regimen, ≥ 85% of patients in whom eradication failed would be infected with *H. pylori* resistant to one or both of the antibiotics.
- To test the hypothesis that compliance with the rabeprazole-based combinations is equivalent to that of omeprazole-based therapy.
- To compare the safety profile of the rabeprazole-based combinations with that of omeprazole-based therapy.

C. Investigational Plan