DIVISION OF GASTROINTESTINAL AND COAGULTION DRUG PRODUCTS

MEDICAL OFFICER REVIEW

NDA: 20-973

DEC 15 1998

Sponsor: Eisai Inc.

Drug: Rabeprazole Sodium Tablets (Aciphex™)

Indications: (a) Healing of Duodenal Ulcer; (b) Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

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Medical Officer: Dr. Robert Prizont, MD

Note from the Author. Highlighted text indicates paraphrased, relevant or important information. In some sentences, Placebo is abbreviated as PBO.

Abstract. Rabeprazole (RAB) sodium is a novel Proton-Pump-H_2-Inhibitor (PPI). This review includes data from three pivotal, clinical trials to support the claim of safety and effectiveness of RABE 20 mg tablets for the treatment of active duodenal ulcers. Protocols required as primary efficacy endpoint endoscopic healing of all duodenal ulcers (DU) after 2 weeks or 4 weeks of treatment. Primary healing data was an Intent-to-Treat (ITT) comparison. Trial NRRC (100 patients) compared RAB against placebo. At Week 2, the ITT revealed no significant differences between RAB and placebo. At Week 4, there was a significantly higher proportion of DU healing in patients on RAB than in placebo. RAB was also superior to placebo in improving DU symptoms, Trial NRRL (205 patients) compared efficacy of RAB against the approved PPI omeprazole. Results showed comparable efficacy for RAB and omeprazole in healing DU at either Week 2 or Week 4. Overall, both PPIs revealed similar degree of DU symptom improvement. Trial NRRD (376 patients) was designed to show superiority of RAB over RAN. After correction for center-by-treatment interaction which occurred in 1 center (26 patients), the data revealed comparable efficacy between RAB and ranitidine in DU healing. Overall, there was acceptable safety. Included in this NDA are results from patients with ZES/hypersecretory states who showed healing of DUs by treatment with $\geq$60 mg rabeprazole.

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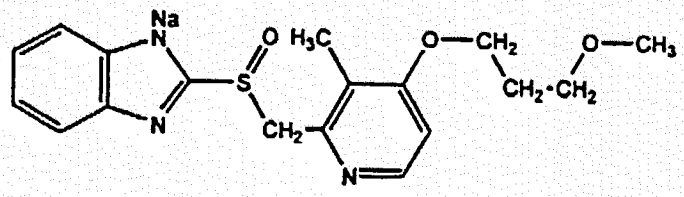
A. BACKGROUND.

1. Summary of Drug Development, Chemistry and NonClinical Pharmacology.

Rabeprazole was first studied in man 10 years ago by Ohnishi, an Eisai scientist (July 18, 1988). The sponsor states that the *"starting dose in this study, 1 mg, was selected based on the animal data and comparisons to omeprazole. This study safely escalated to 80 mg single doses"*. This study was followed by a multiple dose tolerance study, using 20 mg and 40 mg in a crossover design. *"A full Japanese NDA program was conducted based on the results of these early studies"*. In Europe and Japan Aciphex™ has the trade name of Pariet™.

Aciphex™ 10 and 20 mg enteric-coated tablets contain as active ingredient rabeprazole sodium, which is a relatively stable yellowish white solid substance soluble in water, also known in the pharmacologic and clinical literature as E3810, ER-3384, LY307640 sodium, SHKA, pariprazole and pariprazole sodium. Chemically, rabeprazole has a substituted benzimidazole ring with a structure similar to omeprazole and lanzoprazole. The following stereochemical structure was taken from Page 129, Vol. 1,



The summary section of nonclinical pharmacology submitted by the sponsor cites 32 pharmacology reports of preclinical studies, performed to evaluate the mechanism of action of sodium rabeprazole. The submitted summary states that sodium rabeprazole is a potent proton pump inhibitor (PPI). Rabeprazole was shown to be more effective than omeprazole and lanzoprazole in inhibiting H^+, K^+ - ATPase activity, and a more potent inhibitor of db-cAMP in *in vitro* stimulated gastric acid secretion than omeprazole. Rabeprazole inhibits the proton pump action by modifying a SH group of the H^+, K^+-ATPase; this effect may be slowly reverted by new ATPase synthesis. Experimental studies with *H. pylori* showed that rabeprazole may be bacteriostatic on some *H. pylori* strains. Unlike antibiotics, rabeprazole is *not* bactericidal.

2. Summary of Rabeprazole Pharmacokinetics and Pharmacodynamics in Humans.

The enteric coating included in the Aciphex tablet formulation allows the passage of intact rabeprazole to the upper small bowel, which is the site of drug absorption and transport into the blood stream. Four hours after a 20 mg tablet oral dose, rabeprazole reaches a plasma maximum concentration (Cmax) of 200-440 ng/ml. Subsequent to the same oral dose, rabeprazole plasma half-life ranges between 0.7-1.5 hours with a bioavailability of 52%. Circulating rabeprazole is

predominately excreted in the urine; there is no rabeprazole accumulation after once a day dosing or after multiple 20 mg doses administered over a seven day period.
During its pass thorough the liver, part of the absorbed rabeprazole is converted into thioether sulfone, desmethyl and mercapturic metabolites; this metabolic conversion is mediated by the liver P-450 3A cytochrome microsomal oxidase enzyme system.

According to the pharmacokinetic summary submitted by the sponsor, renal failure, hepatic failure and the aging process, affect rabeprazole AUC. The sponsor states that *"patients with renal failure had a mean AUC less than the mean AUC for healthy subjects, although this difference did not reach statistical significance (5% level). Patients with stable, chronic compensated cirrhosis of the liver had AUC approximately 2 fold greater than normal volunteers. The very elderly (mean age = 71 years) have a mean increase AUC relative to very young adults (mean age = 23 years); values are 1211 & 645 (ng/ml)-h, respectively"*. The pharmacokinetic changes observed in renal failure, hepatic failure and elderly, are summarized in the following Table 6B, Page 161, Vol. 1.

Table 6B: Effect of Renal Failure (A001-003), Hepatic Failure (A001-004, A001-108) and Age (A001-112) on Rabeprazole Pharmacokinetics

Effect of Renal Failure (20 mg Single-Dose)

Ten Healthy Male Subjects	Mean AUC (0 - 24h) = 613 (ng/mL)-h
Ten Patients with stable, end-stage, Renal failure requiring maintenance hemodialysis	Mean AUC (0 - 24h) = 422 (ng/mL)-h (during hemodialysis) & 370 (ng/mL)-h (post-dialysis)

Effect of Hepatic Failure (20 mg Single-Dose)

Thirteen Healthy Male Volunteers	Mean AUC (0 - 24h) = 809 (ng/mL)-h
Ten male patients with stable, chronic compensated cirrhosis of the liver	Mean AUC (0 - 24h) = 1776 (ng/mL)-h

Effect of Age (20 mg once daily for 7 days)

Twenty healthy male & females, mean age = 23.3 years	Cmax = 427 ng/mL AUC (0 - ∞) = 645 (ng/mL)-hr
Twenty healthy male & females, mean age = 71.0 years	Cmax = 669 ng/mL AUC (0 - ∞) = 1211 (ng/mL)-hr

The sponsor reports that the ***"gastric antisecretory activity begins within one hour after oral administration of 20 mg Aciphex and reaches its maximum within two to four hours. The inhibitory effect of Aciphex on acid secretion increases with repeated once daily dosing to steady-state inhibition after three days. Aciphex 20 mg inhibits basal and pentagastrin-stimulated acid secretion by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH>3 from 10% to 65%. The long pharmacodynamic action compared to the pharmacokinetics half-life (approximately one hour) presumably reflects the sustained inactivation of the H^+, K^+ATPase"***.

The difference between a placebo drug and Aciphex 20 mg enteric-coated tablets, in lowering the gastric basal acid output (BAO) and pentagastrin stimulated peak acid output (PAO), is exemplified in the table, Page 202, Vol. 1.

Parameter	Placebo	ACIPHEX™ (20 mg QD)
Basal Acid Output (mmoL/hr)[1]	2.8	0.4*
Stimulated Acid Output (mmoL/hr)[1]	13.3	0.6*
% Time Gastric pH>3[2]	10	65*

[1] Study H4M-MC-NRRB
[2] Study E3810-A001-002
*($p<0.01$ versus placebo)

The sponsor notes that the results of pharmacodynamic investigations show a *"dose-related decrease in mean intragastric acidity"* after administration of Aciphex. Concomitant to the significant decrease in gastric acidity, there is a dose-related increase in the serum gastrin levels; multiple rabeprazole oral doses may cause serum gastrin to increase by 50% to up 100%, from the baseline gastrin levels.

3. Brief Summary of Duodenal Ulcer Disease and Zolinger-Ellison.

i. Duodenal Ulcer.

Every year, 180,000 Americans are diagnosed with duodenal ulcer disease, or DUD. Incidence of DUD, 6% to 15% in Western populations, has decreased in the last 40 years in the USA, especially in males. DUD is a chronic, recurrent condition manifested clinically by episodes of epigastric pain. The diagnosis of DUD is confirmed endoscopically by the finding of a deep mucosal discontinuation in the duodenal bulb, or ulcer, measuring an average of 0.5 cm to 2.5 cm in the larger diameter. Smoking and ingestion of NSAIDs delay healing of DU Approved drugs available for the healing of **active** duodenal ulcer include oral administration of the following medications: (a) H_2-Blockers, such as cimetidine (Tagamet®, SK&B), ranitidine (Zantac®, Glaxo), famotidine (Pepcid®, Merck), nizatidine (Axid®, Lilly), or, (b) sucralfate tablets, a complex polyaluminum hydroxide salt of sucrose sulfate that becomes highly polar at acid pH, and binds to the bed of the ulcer for up to 12 h, (Carafate®, Hoechst Marion Roussel), or, (c) H_2-Proton pump inhibitors, which act on the gastric H^+, K^+-ATPase exchanging proton hydrogens for potassium, i.e., omeprazole (Prilosec®, Astra-Merck), and lansoprazole (Prevacid®, Takeda-Abbott).

In the past, reducing the rate of DU recurrence in patients with healed DUs required continuous maintenance administration of an H_2-Blocker or an H_2-Proton pump inhibitor. Long term DU studies conducted in the last 5-10 years have clearly established that DU recurrence is closely related to the presence of *Helicobacter pylori* in the gastric and duodenal mucosa. Hence, **DU recurrence** is now prevented by a 2-4 week administration of antibiotics given at the onset of DU therapy. Antibiotics which have been shown to produce high rates of *H pylori* eradication and low rates of DU recurrence are clarithromycin, amoxicillin, and metronidazole.

ii. Zolinger-Ellison Syndrome.

This rare condition occurs in approximately 0.1 to 0.4 per million persons. It is due to endocrine gastrin-producing tumors, or gastrinomas, located either in the pancreas or duodenum

The symptomatology is characterized by the presence of abdominal pain, gastric and/or duodenal ulcers, and diarrhea. Peptic ulcer develops as a consequence of high BAO. On UGI endoscopy, gastric ulcers or DUs are usually large and multiple. They may perforate or cause serious GI bleeding. Symptoms of gastroesophageal reflux disease (GERD) are common (31% to 61% of ZE patients). The diarrhea , secretory in nature, is due to large amounts of gastric acid fluid interfering with normal small intestinal digestive and absorptive processes. About three fourths of gastrinomas occur without any associated endocrine tumor whereas one-fourth occur in the setting of multiple endocrine neoplasias (MEN I). The diagnosis is made by: a) high basal to maximum gastric acid ratio (BAO/MAO); b) high fasting serum gastrin levels; or c) by high serum gastrin levels after pancreatic stimulation with a secretin test. Treatment is based on control of the gastric hypersecretory state with large doses of H_2-Blockers or H_2-Proton pump inhibitors. If the tumor is identified and is resectable, surgery may be required.

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B. PROPOSED LABEL.

- The following sections were taken **unmodified** from the proposed label. They **refer only to indications for rabeprazole discussed** in this review, i.e., **duodenal ulcer and gastric hypersecretory states including ZE syndrome**. Similarly, proposed rabeprazole doses cited below refer solely to the DU and ZE syndrome indications

Proposed INDICATIONS.

i. Healing of Duodenal Ulcers. *ACIPHEX™ is indicated for up to 4 weeks treatment in the healing and symptomatic relief of duodenal ulcers.*

ii. Treatment of Pathological Hypersecretory Conditions, *Including Zollinger-Ellison Syndrome. ACIPHEX™ is indicated for the long term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.*

Proposed DOSAGE.

i. Healing of Duodenal Ulcers. *The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily for up to four weeks. Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.*

ii. Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome. *The dosage of ACIPHEX™ in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison Syndrome have been treated continually with ACIPHEX™ for up to one year.*

C. PIVOTAL CONTROLLED CLINICAL TRIALS IN DUODENAL ULCER.

The sponsor has reported data from **three pivotal controlled clinical studies** to support the claim for effectiveness of rabeprazole in the treatment of active duodenal ulcer. These clinical trials are:

- Study NRRC compared rabeprazole 20 mg qam and 40 mg qam to placebo (USA).
- NRRL compared, rabeprazole 20 mg qam vs. 20 mg qam omeprazole (Europe).
- Studies NRRD compared rabeprazole 20 mg qam to 150 mg bid ranitidine (USA).

In the following sections, **I will briefly summarize the protocols and the sponsor's trial descriptive for each one of these three pivotal clinical studies. After each of the sponsor's descriptive section, I will comment** on the reported rabeprazole effectiveness data.

Note. Some information shown in protocols and my descriptives of efficacy reports were **scanned and copied, unmodified, from the submitted NDA package.**

STUDY NRRC. Rabeprazole vs Placebo.

The sponsor submitted the study protocol and report of this placebo controlled study in Vol. 170. Apparently, this USA study was conducted while clinical studies with rabeprazole were sponsored by Eli Lilly Co. **The experimental name given by Lilly to rabeprazole was LY307640.** Hence, the **study protocol makes reference to the experimental drug as either rabeprazole or LY307640.** In the following section, **I will summarize the relevant parts included in protocol H4M-MC-NRRC.**

i. Study Protocol H4M-MC-NRRC;

"LY407640 Versus Placebo: Dose Response Study in Patients with Active Duodenal Ulcer Disease". This protocol was completed in July 1993.

(a) Summary of Study Design. Multicenter, randomized double-blind, placebo-controlled study. According to the protocol, **100 duodenal ulcer patients were planned to be allocated to either rabeprazole 20 mg qam, rabeprazole 40 mg qam, or placebo** . The study was designed to demonstrate safety and efficacy of rabeprazole in treating patients with duodenal ulcer disease. **Treatments with study drugs were to be continued for a maximum of 4 weeks.** The primary **efficacy endpoint was the complete endoscopic healing of duodenal ulcer/s. A patient who was healed at week 2** (Visit 2) **was not required to return for week 4** (Visit 3). The presence or absence of *H. pylori* was supposed to be determined at the first and final visit. The protocol stipulates that a patient who was healed at week 2 was not required to return for week 4, but was asked to return for the follow up ^{13}C-urea breath test, between 4-5 weeks after completing week 2 and discontinuing therapy.

(b) Inclusion Criteria.

- Outpatients who have been diagnosed by upper GI endoscopy to have ***"no more than 3 active duodenal ulcers. The [largest] ulcer with the shortest dimension ≥0.3 cm and the longest dimension ≤2.5 cm as measured by open biopsy forceps".***
- Men and women, *"18 years of age and older".*
- Women not of childbearing potential by surgery, or menopause, or by contraception .

- Patients *"who are informed of the medications and procedure to be used in the study, have no language barrier, are cooperative, and sign an informed Consent Document"*.

(c) *Exclusion Criteria.*

- History of definitive acid-lowering surgery or previous esophageal or gastric surgery, except simple closure of perforation.
- Esophageal and/or gastric varices.
- Pyloric stenosis that precludes passage of the endoscope.
- Treatment with full therapeutic doses of an H_2-receptor antagonist, prostaglandin, or sucralfate for more than 5 successive days within 2 weeks prior to enrolling in the study.
- Treatment with therapeutic doses of a proton pump inhibitor for 3 consecutive days within 2 weeks prior to enrollment and any treatment with therapeutic doses of a proton pump inhibitor within 5 days prior to enrolling in the study.
- Ingestion of a bismuth-containing preparation during the week prior to enrolling in the study.
- Concurrent treatment with any of the following: macrolides, penicillins, tetracyclines, cephalosporins, quinolones, or metronidazole. Treatment with trimethoprim and sulfamethoxazole is allowed.
- Concurrent treatment with high doses of corticosteroids (ie, ≥20 mg/day of prednisone or equivalent, extensive topical application), nonsteroidal anti-inflammatory drugs (NSAIDs), or other ulcerogenic regimens.
- Concurrent treatment with anticoagulants, anticholinergics, tricyclic antidepressants, motility agents (eg, metoclopramide), or antineoplastics.
- Concurrent serious systemic disorders including either of the following:

—Renal insufficiency as documented by either of the following:
History of abnormal creatinine clearance
Abnormal urine sediment

—Hepatic insufficiency as documented by any of the following:
Alcoholic liver disease
Ascites
Chronic active hepatitis
Cirrhosis
Other known liver disease
Clinically significant abnormal AST (SGOT) or ALT (SGPT)
Clinically significant abnormal bilirubin except when due to Gilbert's syndrome (documented by fractionating the bilirubin).

- Patients undergoing treatment for cancer (eg. chemotherapy, radiation) within the previous year.
- Esophageal erosions or ulceration. An ulceration is defined as a break in the mucosa with penetration through the muscularis mucosa.
- Presence of gastric ulcer disease or prepyloric ulcer disease.
- Presence of more than three duodenal ulcerations.
- Endoscopic evidence of active gastrointestinal bleeding.
- Patients with Zollinger-Ellison syndrome.
- Women who are pregnant or lactating.
- Any condition associated with poor patient compliance (eg. alcohol abuse, drug abuse).
- Any clinically significant abnormality as indicated by laboratory tests at the admission visit of leukocyte count, hemoglobin, or urea nitrogen.
- Use of aspirin except for cardiovascular prophylactic treatment of not more than 165 mg/day (see Section 3.8).

(d) Concomitant Therapy. Patients were allowed to use acetominophen for relief of pain. The protocol established that ***although Mylanta® was provided, patients would not be discontinued if they take other antacids during the study.*** While on study, patients were not allowed to take high doses of corticosteroids, NSAIDs, H_2-Blockers, proton pump inhibitors, sucralfate, prostaglandins, anticholinergics, oral bismuth preparations, motility agents, any systemic antibiotics except trimethoprim and sufamethoxazole.

(e) Relief of Gastrointestinal Symptoms. The protocol states that ***other measures of efficacy were the relief of daytime and nighttime ulcer pain.*** According to the protocol, severity of pain would be rated in a 5 nominal scale from 0=none, 1=mild, 2=moderate, 4=severe, 5=terrible. In addition, the design establishes a patient well-being rating from 0=very good, to 4=very poor.

(g) Schedule of Events. In ATTACHMENT NRRC.1, the protocol included the following schedule of events. Note. The following chart was scanned from Page 122, Vol. 170. The chart includes an error, i.e., the title reads *LY307640 Versus Placebo: Dose Response in Patients with Active **Gastric** Disease* (instead of *Active **Duodenal** Disease*).

Schedule of Events
LY307640 Versus Placebo: Dose-Response Study in Patients with Active Gastric Ulcer Disease

Activity	Week 0/ Visit 1	Week 2/ Visit 2	Week 4/ Visit 3
Informed consent	X		
Patient number assignment	X		
Kit number assignment	X		
Initial history	X		
Physical examination	X		X[a]
Vital signs and weight	X	X	X
Clinical evaluation	X	X	X
Endoscopy	X	X	X
Helicobacter pylori ^{13}C breath test	X		X[d]
Helicobacter pylori serology	X		
Medication - blinded	X[b]	X	
Chemistry panel (contract laboratory)	X	X[c]	X[a]
Urinalysis (contract laboratory)	X	X[c]	X[a]
Serum pregnancy test (if applicable) (contract laboratory)	X		
Hematology (contract laboratory)	X	X[c]	X[a]
Electrocardiogram	X		X[a]
Admission clinical report form	X		
Follow-up clinical report form		X	X
Discharge summary clinical report form			X[a]

[a]To be completed when patient discontinues treatment with study drug.
[b]Patient randomized and medication dispensed only if patient meets inclusion/exclusion criteria.
[c]Only if clinically indicated.
[d]To be completed when patient discontinues treatment with study drug and repeated between 4 and 5 weeks later if the patients' ulcer was healed (as defined in Section 3.9.1.1.) at the completion of therapy.

ii. Descriptive for Study H4M-MC-NRRC.

Brief summary from the sponsor's report. All Tables were scanned from Volume 170.

(a) Patient Disposition. Patient enrollment started in November 1993 and was completed in May 1994. **Twenty one USA investigators enrolled a total of 100 DU patients.** Eleven investigators enrolled 6-9 patients each while the remaining 10 enrolled 1-4 patients each.

Of the 100 patients enrolled, 7 patients (7%) were discontinued from the study (4 in the placebo group, 2 in the rabeprazole 20 mg group, and 1 in the rabeprazole 40 mg group). There were no significant differences between the groups in final patient disposition, as shown in the following Table NRRC.5.2.

Table NRRC.5.2
Summary of Disposition of Patients

		Rabeprazole		p-value[a]		
				Placebo vs Rabeprazole		Rabeprazole
Disposition	Placebo (N=33)	20 mg (N=34)	40 mg (N=33)	20 mg	40 mg	20 mg vs 40 mg
Completed Study	29 (88%)	32 (94%)	32 (97%)	.363	.139	.586
Dropped out of Study	4 (12%)	2 (6%)	1 (3%)			
Lack of efficacy	3 (9%)	1 (3%)	1 (3%)			
Protocol violation	1 (3%)	0 (0%)	0 (0%)			
Patient decision	0 (0%)	1 (3%)	0 (0%)			

[a] Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square Statistic.

(b) Patient Demographics. The **sponsor states** *that **the three treatment groups were comparable in demographic** and baseline characteristics. **Seventy percent of patients (70/100) were male**, and the mean age of all patients was 50 years. **Overall, 49% of patients were smokers**, and 33% and 78% of patients, respectively, consumed alcohol and caffeine. Slightly more than half of the enrolled patients (56/100, 56%) were using antacids before study entry, and the mean number of doses used per day was 1.6. At study entry, **the mean number of ulcers per patient was 1.100 and the mean width and length of the largest ulcer was 0.499 cm and 0.583 cm**, respectively.* About one third of all patients had few or several episodes of duodenal ulcer pain, one third had many painful episodes, and one third had continuous abdominal pain.

The following Table NRRC.6.1. illustrates demography.

Table NRRC.6.1
Summary of Demographic and Baseline Characteristics

		Rabeprazole		
Characteristic	Placebo (N=33)	20 mg (N=34)	40 mg (N=33)	Total (N=100)
Sex				
Male	26 (79%)	22 (65%)	22 (67%)	70 (70%)
Female	7 (21%)	12 (35%)	11 (33%)	30 (30%)
Age (yr)				
Mean	49.8	50.5	49.8	50.0
S.D.	14.3	12.0	14.5	13.5
Minimum	24	31	21	21
Maximum	82	75	77	82

(continued)

Table NRRC.6.1
Summary of Demographic and Baseline Characteristics

Characteristic	Placebo (N=33)	Rabeprazole 20 mg (N=34)	Rabeprazole 40 mg (N=33)	Total (N=100)
Tobacco Consumption				
No	15 (45%)	15 (44%)	22 (67%)	52 (52%)
Yes	18 (55%)	19 (56%)	11 (33%)	48 (48%)
Alcohol Consumption				
No	20 (61%)	25 (74%)	22 (67%)	67 (67%)
Yes	13 (39%)	9 (26%)	11 (33%)	33 (33%)
Caffeine Consumption				
No	8 (24%)	6 (18%)	8 (24%)	22 (22%)
Yes	25 (76%)	28 (82%)	25 (76%)	78 (78%)
Antacid Use				
No	15 (45%)	14 (41%)	15 (45%)	44 (44%)
Yes	18 (55%)	20 (59%)	18 (55%)	56 (56%)
Number of Doses of Antacid Used per Day (based on average of last three days)				
N	33	34	32	99
Mean	1.9	1.3	1.6	1.6
S.D.	2.5	1.4	1.7	1.9
Minimum	0	0	0	0
Maximum	10	5	5	10
Number of Duodenal Ulcers				
Mean	1.121	1.088	1.091	1.100
S.D.	0.331	0.288	0.292	0.302
Minimum	1.00	1.00	1.00	1.00
Maximum	2.00	2.00	2.00	2.00
Width of Largest Ulcer (cm)				
Mean	0.456	0.511	0.531	0.499
S.D.	0.261	0.366	0.393	0.343
Minimum	0.01	0.01	0.01	0.01
Maximum	1.20	1.50	1.50	1.50
Length of Largest Ulcer (cm)				
Mean	0.588	0.544	0.619	0.583
S.D.	0.360	0.434	0.459	0.417
Minimum	0.01	0.01	0.01	0.01
Maximum	1.20	1.50	1.50	1.50

(continued)

Table NRRC.6.1 (concluded)
Summary of Demographic and Baseline Characteristics

Characteristic	Placebo (N=33)	Rabeprazole 20 mg (N=34)	Rabeprazole 40 mg (N=33)	Total (N=100)
Duodenal Ulcer Pain Frequency Grade				
0=None	1 (3%)	3 (9%)	2 (6%)	6 (6%)
1=Few	4 (12%)	5 (15%)	3 (9%)	12 (12%)
2=Several	6 (18%)	4 (12%)	10 (30%)	20 (20%)
3=Many	11 (33%)	11 (32%)	7 (21%)	29 (29%)
4=Continual	11 (33%)	11 (32%)	11 (33%)	33 (33%)
H Pylori Infection (delta per thousand)				
Positive (≥2.40)	22 (67%)	22 (65%)	18 (55%)	62 (62%)
Negative (<2.40)	8 (24%)	12 (35%)	13 (39%)	33 (33%)
Positive (≥6.00)	20 (61%)	20 (59%)	16 (48%)	56 (56%)
Negative (<6.00)	10 (30%)	14 (41%)	15 (45%)	39 (39%)
Missing	3 (9%)	0 (0%)	2 (6%)	5 (5%)

Protocol Violations. The sponsor states that ***there were no protocol violations that were considered to affect study results***. Endoscopy window violations were only observed in 3 placebo patients (2 on week 2; 1 on week 4), 4 rabeprazole 20 mg patients (2 on week 2, and 2 on week 4), and 2 rabeprazole 40 mg patients (1 on week 2, and 1 on week 4).

(d) Efficacy Results.

1. Ulcer Healing, The **sponsor notes** that the **primary efficacy endpoint**, DU healing by UGI endoscopy, was assessed by two different approaches. The **first approach** examined the Intention-To-Treat **(ITT) which**, by using the last-observation-carried-forward (LOCF), **incorporated** ***all randomized patients*** *who had at least one post dose measurement of any of the efficacy variables".* The **second approach** evaluated **healing response** rates based *on completed visits, or endoscopies performed (referred to as the ENDO methods in this document).*

In the following Table NRRC.6.2, the **sponsor presented the number and percentage of patients who were healed at weeks 2 and 4 for the ITT and ENDO analyses.** The sponsor summarized the results by stating that *for the ITT population, DU healing rates at Week 2 were twice as high in the 20 mg (44%) and 40 mg (42%) as compared to placebo groups and the difference approached significance (p≤0.075). At Week 4, the healing rates were 79% and 91% in the 20 mg and 40 mg groups respectively, compared to 39% in the placebo group.* ***At Week 4, the healing rates were significantly higher in both rabeprazole groups than in the placebo group (p≤0.001).***

There was no difference in healing rates between the two rabeprazole doses (**no dose response**).

Table NRRC.6.2

Summary of Duodenal Ulcer Healing Rates

				p-value[a]		
						Rabeprazole
		Rabeprazole		Placebo vs Rabeprazole		20 mg vs
Week	Placebo	20 mg	40 mg	20 mg	40 mg	40 mg
Intent-to-Treat Analysis						
2	7/33 (21%)	15/34 (44%)	14/33 (42%)	.058	.075	.868
4	13/33 (39%)	27/34 (79%)	30/33 (91%)	.001	<.001	.210
ENDO Analysis						
2	7/31 (23%)	15/34 (44%)	14/33 (42%)	.095	.106	.868
4	13/29 (45%)	27/31 (87%)	30/32 (94%)	<.001	<.001	.361

[a] Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square Statistic.

Healed: Complete regeneration of the mucosa (re-epithelialization) with no visible ulcer craters.

2. Duodenal Ulcer Pain. The sponsor notes that improvement rates in **DU pain frequency** rates at week 2 were 77% for both rabeprazole groups, vs 47 % in the placebo group. At week 4, improvement of pain frequency rates was 84 % for both rabeprazole groups and 59% for placebo. Differences between each rabeprazole dose and PBO reached significance at week 2 and week 4. **Complete resolution rates in DU pain** at week 2 were 39% and 29% in the 20 mg and 40 mg group, respectively, compared to 13% in the placebo. At week 4, the corresponding complete resolution rates were 55%, 48%, and 16%, for the 20 mg group, 40 mg group, and PBO. The differences for rabeprazole groups and PBO were statistically significant. The rates of DU **pain improvement and resolution are** displayed in the next Table NRRC.6.3.