patients with prior gastric surgery. **Secondary efficacy** endpoints included endoscopically documented healing and maintenance of healing of ***any upper GI lesion***, and, relief of symptoms related to gastric hypersecretion.

(e) Disease diagnostic Criteria, The protocol established the following disease diagnostic criteria.

- Patients with idiopathic gastric acid hypersecretion whose basal rate of gastric acid secretion is ≥15 mEq/hour, without prior gastric surgery and who have a normal fasting serum gastrin level, and negative secretin test.
- Patients with gastric acid hypersecretion who have ZES as determined by the following criteria :-

  1. Basal gastric acid hypersecretion defined as ≥ 15 mEq/hour in patients without acid lowering gastric surgery or > 5 mEq/hour in patients with prior gastric surgery.
  2. Fasting hypergastrinemia - and -
  3. A positive secretin test - or -
  4. A histologic diagnosis of gastrinoma.

(f) Inclusion Criteria. They are as follows:

- Patients with idiopathic gastric acid hypersecretion whose basal rate of gastric acid secretion is > 15 mEq/hour who do not have ZES.
- Patients with gastric acid hypersecretion who have ZES defined by fasting hypergastrinemia with gastric acid hypersecretion with a positive secretin test or a histologic diagnosis of gastrinoma
- Male patients 18 years of age or older or female patients 18 years of age or older, not of childbearing potential by reason of surgery or radiation; menopause or females of childbearing potential using an approved method of contraception, eg. IUD, birth control pill, implant or barrier device.

(g) Exclusion Criteria. They are the following:

- Women who are pregnant or are lactating.
- Any condition associated with poor patient compliance, eg. alcohol abuse, drug abuse.
- Patients who have received any investigational agent within the previous 30 days.
- Inability of patient to return for scheduled visits.
- Patients who, in the opinion of the investigator, are poor medical or psychiatric risks for therapy with an investigational drug.

(h) Duration of the Study and Schedule of Events. The protocol planned for a 2 year follow-up study. The following chart (Appendix 3 of the protocol, illustrates Visit dates and schedule of methodologies.

Schedule of Events
Open Label Use of Rabeprazole (LY307640, E3810) in the Study of Patients with Idiopathic Gastric Acid Hypersecretion and Patients with Zollinger-Ellison Syndrome

Activity	Wk. Prior to Day 1 Visit 1	Day 1 Visit 2	Day 2[a] Visit 3	Month 3 Visit 4	Month 6 Visit 5	Month 12 Visit 6	Month 24 Visit 7
Informed Consent	x						
Patient # Assignment	x						
Initial History	x						
Physical Examination	x						
Vital Signs & Weight	x			x	x	x	x[b]
Clinical Evaluation	x			x	x	x	x[b]
Secretory Studies - Dosage Adjustment	x	x	x[a]	x	x	x	x[b]
Endoscopy	x			x[c]	x[c]	x[c]	x[b,c]
Argyrophil enterochromaffinlike cell growth biopsy	x[d]				x	x	x[b]
Antral Biopsies	x				x	x	x[b]
CLO Test or Breath Test	x						x[b]
Medication Dispensed	x						x[b]
Chemistry Panel	x	x	x	x	x	x	x[b]
Urinalysis	x	x	x	x	x	x	x[b]
Urine Pregnancy Test (if applicable)	x						
Hematology	x	x	x	x	x	x	x[b]

a. May be repeated as per Section 3.9.2.2
b. To be repeated at 12 month intervals and/or if patient leaves study
c. If required as per protocol 3.9.2.2 and/or 3.9.2.3
d. If endoscopic lesions present at baseline

iii. Descriptive of Study A001-501 *(Submitted in Vols.1, 222, and 227).*

- The sponsor states this study is currently ongoing and is being conducted in the USA and Europe, and, as of October 31, 1997, 10 patients were enrolled into the study, nine were active and one was dropped out. No other report or analyses on efficacy was submitted; the sponsor states as follows:

Analysis on the primary and secondary parameters was not conducted for the interim report.

The following is the information provided by the sponsor:

1. In the Integrated Summary of Effectiveness (ISE), the sponsor included the **CRFs from 7 of the enrolled patients (Vol. 248)**. Most of the patients fulfill the diagnosis of gastric acid hypersecretory states and a few the diagnosis of ZES. **Rabeprazole doses ranged from 60 mg to 120 mg.**

2. In the same ISE volume, the sponsor included a letter from Dr. Jerry D. Gardner, MD, stating that he had ***reviewed the data from patients with Zollinger-Ellison syndrome or gastric acid hypersecretion treated with rabeprazole***, and that the **starting dose** should be 60 mg rabeprazole once daily

3. **The sponsor also submitted narratives for 3 patients who were discontinued due to serious ADEs.** This safety information of 2 of the 3 patients will be included in the safety section of this review. The report of **Patient 003** will be included in this section. Medical past history and dose of rabeprazole given to these 3 patients is as follows:

Patient 001. 75 year old male with past medical history of duodenal ulcer diagnosed in 1982, and excision of two colonic adenomas in 1994, obesity, dyspnea due to obesity, and idiopathic gastric acid hypersecretion. Enrolled in the study with a diagnosis of ZES/idiopathic gastric acid hypersecretion and **treated for 3 months with 60 mg rabeprazole.**

Patient 003. 41 year old male with past history of hyperthyroidism resolved by partial thyroidectomy (1994-1995), hypercholesterolemia, mild esophagitis, severe duodenitis, and gastrinoma (onset not available) for which he had been treated with omeprazole 30 mg/day. Enrolled in the study with a diagnosis of ZES. After stopping omeprazole therapy and before starting rabeprazole treatment, this patient was treated with ranitidine 300 mg bid for 4 days. On October 9, 1996, prior to receiving the first rabeprazole dose, the patient started with epigastric pain and diarrhea, which persisted despite the initiation of rabeprazole treatment. One day after initiation of rabeprazole therapy, patient's BAO was 59.88 mmol H^+/hour. UGI endoscopy revealed ulcerative esophagitis, diffuse erosive duodenitis, and large amounts of intragastric fluid. Intravenous omeprazole 40 mg/day was started and discontinued one day later. The six day therapy course with rabeprazole is shown in the following sponsor table. The sponsor states that ***further details of the patient's hospital course are not available.*** A follow up investigation **on October 21, 1996, (study day 13) revealed a BAO reduced to 0.14 mm H^+/hour.**

Date	Rabeprazole	Omeprazole
Oct. 9, 1996	40 mg PO BID	N/A
Oct. 10, 1996	40 mg PO BID	40 mg IV/day
Oct. 11, 1996	40 mg PO BID	20 mg PO BID
Oct. 12, 1996	40 mg PO BID	20 mg PO BID
Oct. 13, 1996	40 mg PO BID	20 mg PO/day
Oct. 14, 1996	60 mg PO BID	N/A

Patient 004. 57 year old male with a past history of vagotomy, cardia hernia repair, four episodes of pancreatitis, cholecystectomy, diabetes, and mild diarrhea. Patient was diagnosed with ZES in 1987. According to the information submitted, ZES was based on "basal gastric acid hypersecretion, fasting hypergastrinemia, positive secretin test, and duodenitis with ulcerations. Medications taken prior to study entry included lansoprazole PO (from 1994 to 1996), and Zantac PO, (October 4, 1996 to October 10, 1996). **He had been treated for one year with 60 mg rabeprazole before he developed an ADE.**

- ***Study J0811-016*** *(Vol 226).* The following is a brief summary of the study protocol and study descriptive.

This protocol was **designed by Eisai in Japan in 1991** with the aim to **ascertain appropriate rabeprazole dose and safety profile in four patients with ZES.**

The protocol planned for an open label, dose-range investigation. It required enrollment of males 18 y-74 y, and a **diagnosis of ZES based on high fasting serum gastrin (≥1000 pg/ml), high BAO (≥15 meq/l), or tumor confirmed by CT and angiography.** Excluded by protocol were patients with impaired thyroid function, or serious heart, liver, or kidney complications. The other two exclusion criteria were pregnancy or women who may become pregnant, and drug allergies.

The protocol established a **study duration of up to 6 months** (it could be extended at the investigator discretion) and the following **rabeprazole dose: one 20 mg tablet after breakfast. If no improvement was observed after 1 month therapy, the dose was to be increased to 40 mg or above (maximum of 80 mg/day)** at the discretion of the investigator.

The sponsor submitted the narrative of two ZES patients, who were enrolled in this small rabeprazole investigation between, **1991 and 1993.** The following is the narrative for one of these two ZES cases. This patient was a 31 year old Japanese male. His symptoms started in 1986 with upper abdominal pain. According to the narrative *ulcerous lesions were noted in the duodenum*, and the patient was given cimetidine, 800 mg/day for a period of one month. The patient symptoms improved. Between the period of 1986 to 1990, he was treated three more times for the same abdominal symptomatology. On May 1990, while on ranitidine treatment,

300 mg/day, he was found to have a **fasting serum gastrin of 10,400 pg/ml.** The diagnosis of ZES was confirmed by further elevation of serum gastrin levels, from ±10,000 to ±18,000 pg/ml, after pancreatic stimulation with a secretin load test. A subsequent CT scan and echography revealed tumors in the tail of the pancreas and in the liver. He underwent resection of the tail of the pancreas and splenectomy, and was started on famotidine 160 mg/day. The patient improved temporarily, but his symptoms recurred in October 1992. An upper GI endoscopy revealed ulcers in the retrobulbar region and anterior wall of the duodenum. He was started on rabeprazole 40 mg per day. Two days after initiation of rabeprazole therapy, the epigastric pain and heartburn disappeared and follow-up endoscopies done 2-3 weeks later showed marked reduction of ulcer size, with some ulcers healed. Rabeprazole therapy, 40 mg/day, was given for a total period of 51 weeks.

iii. Reviewer Comments.

The efficacy data submitted in these two small studies provide documented information on the treatment of rabeprazole in gastric acid hypersecretion and ZES. My review of the CRFs revealed that most of the cases were gastric hypersecretory states with only a few fulfilling the strict criteria needed to establish the diagnosis of gastrinoma. Many of the patients were on H_2-Blockers or other PPI treatment at the time of enrollment. One patient (007), who carried the diagnosis of ZES since 1988 by virtue of a high BAO=51.6 mmol/h and a positive secretin test, revealed a low baseline BAO (2.8 mmol/h) , borderline gastrin levels (134-194 pg/ml), and a negative secretin test.

In his letter, Dr Gardner (an expert in ZES) states that ***In eight of the ten patients, the 60 mg rabeprazole dose produced satisfactory inhibition of gastric acid hypersecretion and complete resolution of preexisting signs and symptoms of acid-peptic disease. In these eight patients, this dose also prevented recurrence of gastric hypersecretion and manifestations of acid-peptic disease. The remaining two patients required daily doses of 100 mg and 120 mg (60 mg bid) rabeprazole to produce satisfactory inhibition of gastric acid hypersecretion as well as resolution and prevention of signs and symptoms of acid-peptic disease.*** My review of the CRFs and narratives confirmed Dr. Gardner's statement.

E. SAFETY.

In the following paragraphs, I will summarize the safety information collected in the three pivotal duodenal ulcer trial and complete the safety information from the gastric acid hypersecretion/ZES syndrome ADEs.

First, I will sequentially include a brief descriptive of relevant information for each of the three duodenal pivotal studies. Subsequent to these descriptives, I will include my comments.

Study NRRC.

The sponsor reports that there were no deaths or discontinuations due to ADEs during this study.

1. Serious Adverse Events. The sponsor reported three patients with 5 serious adverse events; two patients had received rabeprazole 40 mg, and 1 had received placebo. Included were the following narratives for the three relevant ADEs.

Patient 5-1169 was a 77 y male treated with rabeprazole 40 mg for 15 days and had an unhealed ulcer at week 2. The patient was prematurely discontinued due to lack of efficacy The rabeprazole medication was stopped on March 21, 1994, and patient was started on Prilosec® the next day. On April 5, the patient called the office complaining of nausea, vomiting and upper abdominal distention. He was admitted to the hospital where a surgical intervention revealed a pancreatic carcinoma with duodenal obstruction.

Patient 12-1071 was a 74 y male treated with rabeprazole 40 mg for 26 days. He completed the study March 17, 1994 with an unhealed duodenal ulcer. He was placed on Axid® 150 mg bid. On March 28, 1994, the patient was admitted to the hospital with upper gastrointestinal bleeding originated from a large duodenal ulcer that had malignant characteristics. The PI described it as pancreatic carcinoma.

Patient 9-1052 was a 41 y Hispanic male treated with placebo for 30 days (Jan 30 '94 to Feb 28 '94). The patient had a history of melena and was anemic at the time of enrollment (Hb 9.5 g/dl, Hct 27.9%). The patient had moderate abdominal pain, dizziness. and two episodes of mild vomiting on Feb 1, 1994. All episodes were considered to be serious and the patient was hospitalized on Feb 1, 1994. The patient was treated with RBCs on Feb 3, '94; Hb and Hct improved but remained below the normal range at week 4. The abdominal pain and dizziness subsided on Feb 5, '94. The patient completed the study with an unhealed DU. The three ADEs were considered to be unrelated to study medication.

2. Treatment-Emergent Signs and Symptoms (TESS). The sponsor reports that there were no significant differences in TESS between rabeprazole doses and placebo. According to the report, there was only one ophtalmic TESS reported during the study: **Patient 13-1075** in the 40 mg group experienced mild amblyopia for 1 day that was ***considered to be remotely related to the study medication.***

The following Table NRRC.7.4, illustrates TESS events by body systems.

Table NRRC.7.4
Treatment-Emergent Signs and Symptoms (TESS) by Body System Reported by at Least 2 Patients in One or More Treatment Groups

Event Classification Term	Placebo (N=33)	Rabeprazole 20 mg (N=34)	Rabeprazole 40 mg (N=33)	p-value[a] Placebo vs Rabeprazole 20 mg	p-value[a] Placebo vs Rabeprazole 40 mg	p-value[a] Rabeprazole 20 mg vs 40 mg
BODY SYSTEM: Body as a Whole						
Patients with at Least One Event	5 (15%)	8 (24%)	10 (30%)	.386	.142	.532
Headache	2 (6%)	1 (3%)	4 (12%)	.537	.392	.153
Abdominal pain	1 (3%)	3 (9%)	1 (3%)	.317	-	.317
Flu syndrome	2 (6%)	1 (3%)	2 (6%)	.537	1.000	.537
Chills	0 (0%)	2 (6%)	0 (0%)	.157	-	.157
Pain	0 (0%)	0 (0%)	2 (6%)	-	.151	.145
BODY SYSTEM: Digestive System						
Patients with at Least One Event	8 (24%)	8 (24%)	7 (21%)	.945	.769	.820
Vomiting	4 (12%)	2 (6%)	2 (6%)	.371	.392	.975
Nausea	2 (6%)	3 (9%)	1 (3%)	.667	.555	.317
Diarrhea	0 (0%)	1 (3%)	2 (6%)	-	.151	.537
Gastrointestinal carcinoma	0 (0%)	0 (0%)	2 (6%)	-	.151	.145
Stomach ulcer	2 (6%)	0 (0%)	0 (0%)	.145	.151	-
BODY SYSTEM: Nervous System						
Patients with at Least One Event	4 (12%)	0 (0%)	2 (6%)	.036	.392	.145
Dizziness	3 (9%)	0 (0%)	1 (3%)	.072	.302	-
BODY SYSTEM: Respiratory System						
Patients with at Least One Event	1 (3%)	1 (3%)	4 (12%)	-	.163	.153
Rhinitis	1 (3%)	1 (3%)	3 (9%)	-	.302	.288

[a] Treatment p-value is obtained using Pearson's Chi-Square Statistic.
-=Not calculated.
Note: Treatment comparison performed only if there were ≥2 patients in ≥1 treatment.

3. Clinical Laboratory Evaluations. Aside from a numerical difference in the incidence of elevated creatinine phosphokinase in plasma, i.e., PBO=1/31(3%), Rabe 20 mg=4/34 (12%), Rabe 40=1/33 (3%), p-Value between PBO vs. Rabe 20=0.197, between Rabe 20 vs. 40=0.174, there were no other relevant differences among treatment groups.

4. Serum Gastrin, At endpoint, and as expected, there was a rabeprazole dose-dependent significant increases in serum gastrin levels, as seen in the following Table NRRC.7.12.

Table NRRC.7.12
Summary of Serum Gastrin (pg/mL)

Week	Placebo	Rabeprazole 20 mg	Rabeprazole 40 mg	p-value[a] Placebo vs Rabeprazole 20 mg	Placebo vs Rabeprazole 40 mg	Rabeprazole 20 mg vs 40 mg
Baseline						
N	32	34	32			
Mean	62.8	63.1	74.8			
S.D.	23.2	20.3	39.9			
Range	29-134	35-111	25-233			
Endpoint						
N	31	34	33			
Mean	61.4	102.8	141.0			
S.D.	27.8	42.7	99.3			
Range	28-172	41-258	36-505			
Change from Baseline to Endpoint						
N	30	34	32			
Mean	3.0	39.7	69.3	.013	<.001	.053
S.E.	3.9	6.9	16.1			

[a] Pairwise treatment p-value is adjusted for baseline value and investigator; obtained from ANCOVA (baseline value, investigator, and treatment effects).

5. Vital Signs Evaluations. At the 2 and 4 week visits, there was a significant change in the diastolic BP in patients on Rabe 20 (Week 2) and borderline significant in patients on Rabe 40 (Week 2), and, significant increases in pulse in patients on Rabe 40 (Week 4). These changes were not considered clinically significant see next Table NRRC.7.13).

Table NRRC.7.13
Mean Changes in Vital Signs from Baseline to Posttherapy

Parameter	Placebo	Rabeprazole 20 mg	Rabeprazole 40 mg	p-value[a] Placebo vs Rabeprazole 20 mg	Placebo vs Rabeprazole 40 mg	Rabeprazole 20 mg vs 40 mg
Systolic BP (mmHg)						
Week 2 Change from Baseline						
N	31	34	33			
Mean	2.8	-0.6	0.0	.162	.309	.699
S.E.	3.3	2.0	2.2			
Week 4 Change from Baseline						
N	22	16	19			
Mean	-4.1	-1.5	4.5	.816	.158	.249
S.E.	3.3	4.1	3.7			
Diastolic BP (mmHg)						
Week 2 Change from Baseline						
N	31	34	33			
Mean	3.0	-0.2	-1.1	.049	.061	.935
S.E.	1.8	1.2	2.1			
Week 4 Change from Baseline						
N	22	16	19			
Mean	1.9	-1.0	-1.4	.220	.533	.530
S.E.	2.0	2.4	3.6			
Pulse (beats per minute)						
Week 2 Change from Baseline						
N	31	34	33			
Mean	-1.7	1.1	0.7	.062	.033	.743
S.E.	1.8	2.1	2.0			
Week 4 Change from Baseline						
N	22	16	19			
Mean	-1.5	-2.8	0.9	.603	.106	.273
S.E.	2.2	2.7	2.5			

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6. EKG Changes. As noticeable in the next Table NRRC.7.15, there were 4 patients on rabeprazole (3 on 40 mg; 1 on 20 mg) vs. 1 on PBO with EKG changes compatible with myocardial infarction at study endpoint. However, the sponsor comparative review of these EKG changes, i.e., from baseline to endpoint, revealed no significant clinical abnormalities.

Table NRRC.7.15
Patients with ECG Abnormalities[a]

Investigator No.	Patient No.	Study Drug	Week	Parameter	Abnormality
1	1001[b]	40 mg	4	T-Waves	T-Waves Abnormal
2	1007	40 mg	4	Rhythm	Sinus Bradycardia
2	1010	20 mg	4	Rhythm	Sinus Bradycardia
2	1011	40 mg	4	Myocardial Infarction	Antero Lateral V3-V6
2	1012	Placebo	4	Rhythm	Sinus Bradycardia
4	1160	Placebo	2	T-Waves	T-Waves Abnormal
5	1030	40 mg	4	Myocardial Infarction	Anterior V3, V4
5	1169	40 mg	2	T-Waves	T-Waves Abnormal
				Myocardial Infarction	Septal V1, V2, (V3)
8	1196	Placebo	4	Rhythm	Sinus Bradycardia
10	1058	Placebo	4	Rhythm	Sinus Bradycardia
10	1060	20 mg	4	Rhythm	Sinus Bradycardia
12	1069	40 mg	2	Conduction	Intraventricular Conduction Delay
12	1072	Placebo	2	Axis	QRS < -30°
17	1097	20 mg	4	Myocardial Infarction	Anterior V3, V4[c]
17	1100	40 mg	4	Myocardial Infarction	Septal V1, V2, (V3)[c]
18	1104	40 mg	2	Conduction	1st Degree Block
19	1112	20 mg	2	Rhythm	Sinus Bradycardia
				Conduction	1st Degree Block[e]
19	1161	Placebo	2	Conduction	1st Degree Block
				Myocardial Infarction	Inferior (2), 3, F
				Morphology	Right Ventricular Hypertrophy
19	1162	40 mg	4	Conduction	WPW[f]

[a] Includes patients who had normal ECG results for a particular parameter at baseline, but who had abnormal results for that parameter at the endpoint visit. Patients who had an abnormality in a given parameter at baseline, but who had a different abnormality in that same parameter at the endpoint visit, are also presented.
[b] Missing baseline T-wave results.
[c] Patient had evidence of myocardial infarction at baseline (septal V1, V2, [V3]).
[d] Patient had evidence of myocardial infarction at baseline (anterior V3, V4).
[e] Patient had a conduction abnormality at baseline (right bundle branch block).
[f] Patient had a conduction abnormality at baseline (intraventricular conduction delay).

(continued)

Table NRRC.7.15 (concluded)
Patients with ECG Abnormalities[a]

Investigator No.	Patient No.	Study Drug	Week	Parameter	Abnormality
20	1119	20 mg	4	Rhythm	Sinus Bradycardia
21	1124	20 mg	4	Myocardial Infarction	Antero Lateral V3-V6
22	1127[g]	20 mg	2	T-Waves	T-Waves Abnormal
				U-Waves	U-Waves Abnormal

[a] Includes patients who had normal ECG results for a particular parameter at baseline, but who had abnormal results for that parameter at the endpoint visit. Patients who had an abnormality in a given parameter at baseline, but who had a different abnormality in that same parameter at the endpoint visit, are also presented.
[g] Missing baseline ECG.

Study NRRL.

There were few ADEs in this comparative PPI study. The next paragraphs , taken from **Page 71, Vol. 179**, best summarizes all these safety events.
"

> One patient in the omeprazole group reported a serious adverse event for which he was discontinued from the study. However, it was considered by the investigator to be unrelated to study medication. Another patient in the omeprazole group prematurely discontinued from the study because of an adverse event considered by the investigator to be unrelated to study medication. At least one TESS was reported by 21% of patients (21/102) in the rabeprazole group and by 21% of patients (22/103) in the omeprazole group.
>
> A statistically significant difference was observed between the two treatment groups in mean change from baseline to endpoint in total bilirubin ($p=0.034$), urine pH ($p=0.030$), and urine protein ($p=0.025$). However, none of the mean changes of any of the laboratory parameters was considered clinically meaningful. The mean values for all the laboratory parameters remained within normal limits.
>
> There was a statistically significant ($p=0.020$) difference between treatment groups in the mean change in fasting serum gastrin from baseline to endpoint: 39.8 pg/mL in the rabeprazole group versus 18.9 pg/mL in the omeprazole group. The mean values at endpoint were well within normal limits for both groups.
>
> At Weeks 2 and 4, there were no statistically significant differences between treatment groups in mean changes from baseline for vital signs evaluations. There were also no clinically meaningful differences between treatment groups in mean changes from baseline for body weight and ECG measurements.

The two serious ADEs were: 1. Back Pain/Herinated Disk; and 2. Prostatic Disorder.

Study NRRD.

1. Deaths and Serious Adverse Events. Sponsor Tables NRRD.7.2, and NRRD.7.3, shown below, list the serious ADEs and discontinuations due to ADEs. the sponsor summarizes these ADEs in the following two paragraphs:

No deaths occurred during the study; one patient in the rabeprazole group died of lung cancer approximately four months after the treatment period. This adverse event was considered unrelated to study medication by the investigator. Five patients in the rabeprazole group and one patient in the ranitidine group reported other serious adverse events. Of the five rabeprazole patients, the adverse events in two patients were considered by the investigators to be only remotely related to study medication. The remaining serious adverse events (three in the rabeprazole group and one in the ranitidine group) were considered by the investigators to be unrelated to study medication.

Four patients in the rabeprazole group and one patient in the ranitidine group prematurely discontinued from the study because of adverse events. Of the five patients who discontinued, two patients in the rabeprazole group had events that the investigators considered remotely or probably related to study medication; the other three patients' events were considered unrelated to study medication.

Table NRRD.7.2
Serious Adverse Events

Investigator Number	Patient Number	Serious Adverse Event(s) COSTART/Verbatim Terms	Reason Serious	Days on Study Medication at Onset
		Rabeprazole		
7	5045	Convulsion/Seizure[a,b]	Hospitalization	NA
10	5064	Cholelithiasis/Gallstones[a] Angina Pectoris/Unstable Angina[a]	Hospitalization Hospitalization	NA
10	5500	Carcinoma of Lung/Lung Cancer[a,c]	Cancer	NA
20	5134	Myalgia/Myalgia Nausea/Nausea Vomiting/Vomiting	Hospitalization Hospitalization Hospitalization	14
42	5285	Embolus/Bilateral Arterial Embolism Thrombosis[d]	Life-threatening	-1 (baseline)
62	5423	Hypertension/Uncontrolled Hypertension	Hospitalization	9
		Ranitidine		
26	5180	Pyelonephritis/Pyelonephritis	Hospitalization	15

[a] Serious adverse event reported after patient's participation in the study.

[b] Patient was discontinued from treatment due to lack of efficacy and compliance with study medication.

[c] Patient died four months after completion of the study.

[d] Patient prematurely discontinued because of the serious adverse event.

NA = Not applicable.

Table NRRD.7.3
Patients Who Prematurely Discontinued from the Study Because of Adverse Events

Investigator Number	Patient Number	Reason for Discontinuation COSTART/Verbatim Terms	Severity/Relationship to Study Medication	Days Study Medication
		Rabeprazole		
22	5148	Arrhythmia/ Heartbeats irregular	Mild/None	4
42	5285	Embolus/Bilateral Arterial Embolism Thrombosis[a]	Moderate/None	3
43	5290	Rash/Skin Rash	Moderate/Probable	4
57	5388	Anxiety/Acute Anxiety Reaction	Moderate/Remote	14
		Ranitidine		
47	5479	Arthritis/Arthritis	Severe/None	12

[a] Adverse event was reported on Day -1 and was considered serious.

2. TESS. There were no significant differences in TESS between rabeprazole, 98/188 (52%), and ranitidine, 108/188 (57%). The most frequent TESS were headaches (14%), diarrhea (10%), nausea (6%), abdominal pain (5%), and asthenia (5%).

There were a few pharmacological episodes which PIs considered related to study drugs. The following is the sponsors narrative of these eye ADRs:

> Three patients in the rabeprazole group reported ophthalmic events: mild eye irritation (conjunctivitis) (patient [22]-5148) on Day 5 of the study, mild dryness in both eyes (patient [50]-5341) for eight study days, and worsening of eyesight (patient [52]-5351) for 19 study days. Two patients in the ranitidine group reported ophthalmic events: moderate conjunctivitis (patient [10]-5497) for 18 study days and mild itchiness of eye (patient [21]-5144) for 14 study days. The investigators considered the conjunctivitis to be unrelated to either treatment, the dryness and worsening of eyesight to be possibly related to rabeprazole treatment, and the itchiness to be probably related to ranitidine treatment.

3. Laboratory Abnormalities and Gastrin Levels. With the exception of low total WBC in 1 rabeprazole vs. 9 ranitidine patients (p=0.011), and elevated GGTP levels in 5 ranitidine vs 0 rabeprazole patients (p=0.005), at study endpoint, there were no other significant laboratory abnormalities of clinical relevance. Low WBC values ranged from 2.9-3.7 $x10^3$ µl, and elevated GGTP values ranged from 71-142 U/l.

By the end of the study period, patients on rabeprazole had a significantly higher mean change in serum gastrin levels (+40.5 pg/ml), than the mean change in serum gastrin observed in patients given ranitidine (+5.2 pg/ml). This difference was significant (p<0.001).

4. EKG Changes. As seen in the following sponsor paragraph, there were significantly more patients on rabeprazole than on ranitidine, that had EKG changes at endpoint compatible with myocardial infarction. The sponsor states that these EKG changes were reviewed and were considered not clinically significant. The following is the **aforementioned sponsor paragraph** *(scanned and copied directly from Page 100, Vol. 149)* and Table NRRD.7.14.

> There was a significant difference between treatment groups in the percentages of patients who were reported by the core ECG reading facility to have normal ECGs at baseline and evidence of myocardial infarction at endpoint. Four patients who received rabeprazole and no patient who received ranitidine were reported to have evidence of myocardial infarction at endpoint (p=0.048).

Table NRRD.7.14
Patients with ECG Abnormalities[a]

Investigator Number	Patient Number	Week	Parameter	Abnormality
			Rabeprazole	
5	5032	4	Axis	QRS < -30
10	5453	4	T-Waves	T-Waves Abnormal
			Myocardial Infarction	Anterior V3, V4[b]
10	5500	4	T-Waves	T-Waves Abnormal
17	5114	4	Conduction	Left Anterior Hemiblock
			Axis	QRS < -30
20	5136	4	Myocardial Infarction	Septal V1, V2, (V3)
25	5650	2	Myocardial Infarction	Inferior (Z), 3, F
26	5178	4	Conduction	Intraventricular Conduction Delay
34	5616	4	Conduction	First Degree Block
37	5247[d]	2	Rhythm	Wenckebach Mobitz I
			Conduction	Left Anterior Hemiblock
			Axis	QRS < -30
		4	Conduction	First Degree Block/Left Anterior Hemiblock
			Axis	QRS < -30
			Myocardial Infarction	Inferior (Z), 3, F
40	5268	4	Conduction	First Degree Block
45	5635	2	Conduction	First Degree Block
47	5522	2	T-Waves	T-Waves Abnormal
			Myocardial Infarction	Anterior V3, V4
49	5331	2	Conduction	First Degree Block
53	5473	4	Conduction	First Degree Block
57	5387	4	Conduction	Right Bundle Branch Block/ Left Anterior Hemiblock[c]
60	5407	2	Rhythm	Atrial Premature Contractions
67	5241	4	Rhythm	Paired Ventricular Premature Contraction
			Myocardial Infarction	Septal V1, V2, (V3)

[a] With the exception of sinus bradycardia and tachycardia, the table includes patients who had normal ECG results for a particular parameter at baseline, but who had abnormal results for that parameter at endpoint. Patients who had abnormalities in a given parameter at baseline, but who had different abnormalities in that same parameter at the endpoint visit, are also presented.

[b] Patient had a myocardial infarction at baseline (antero septal V1-V4).

[c] Patient had a conduction abnormality at baseline (intraventricular conduction delay).

[d] Patient did not have an ECG at baseline.

Gastric Acid Hypersecretion and ZE Cases; Study E3810-A001-501.

Patient 003 complete narrative was included in the efficacy section. The following are the ADEs descriptions for Patients 001 and 004.

Patient 001. This was a 75 y Caucasian male who entered in the study; started on rabeprazole 60 mg daily on September 5, 1996. On December 5, 1996, the investigator detected CK and ALT abnormal values. The patient was asymptomatic. Fractionation of CK was not done.. On March 5, 1997, CK was again raised but ALT was normal. CK-MB was <5% of the total CK. Thirteen days later, the plasma CK level was *"again elevated"* (CK-MB normal); this time plasma ALT and AST levels were also slightly elevated. There was no history of muscular injury, new exercise regimen, bruising, or intramuscular injections. The patient had complained of shortness of breath and ankle edema starting October 17, 1996. and resolving on December 5, 1996.

On March 19, 1997, rabeprazole was discontinued after 196 days of therapy. Next day, the patient was hospitalized for further observation. His EKG was found to be normal and no explanation could be found for the raised CK. Follow-up revealed normal ALT and AST, although CK remained elevated (June 5, 1997). No fractionation was performed. The severity of **the ADE was considered to be mild and possibly related to study medication**. On March 20, 1997, this patient was withdrawn from the study. The following sponsor table illustrates the laboratory abnormalities.

Date	CK normal: 24-295 IU/L, CK-MB up to 20 IU/L or 5%	ALT normal: 8-45 IU/L	AST normal: 5-43 IU/L
Sep. 5, 1996	175	31	26
Dec. 5, 1996	328	138	50
Mar. 5, 1997	417, CK-MB: 20	45	38
Mar. 18, 1997	508, CK-MB: 19	49	45
Jun. 5, 1997	377	27	25

Patient 004. This 57 y male entered the study on October 10, 1996 and was randomized to 60 mg rabeprazole daily. Approximately one year later, on October 22, 1997, the patient presented a complaint of abdominal pain. The pain was thought to be related to pancreatitis due to alcohol abuse. He was admitted to a hospital surgical ward. An abdominal CT scan revealed an edematous pancreatic gland with some *pancreatic effusion*. Treatment for his condition included morphine 20 mg sc, omeprazole 40 mg iv, thicolchicoside 4 mg po tid given for 2 days only, diazepam 10 mg po also prescribed for 2 days, *acid niflumique-gel*, paracetamol 4 g/day iv, tiapride 600 mg iv, phloroglucinol 120 mg iv, glibenclamide 2.5 mg po bid. The sponsor reports that ***further details of the patient's course in the hospital are not available***. This patient was continued in the study and was scheduled for Visit 7 on October 8, 1998. **The ADE was considered moderate in intensity and not related to study medication**. The table shown below lists the chronology of serum lab abnormalities.

Laboratory data for this patient included:

Date	Serum amylase normal range< 82 IU/L	Serum lipase normal range < 60 IU/L	Blood glucose normal range 4.2-5.8 mmol/L
Oct. 22, 1997	1790	–	9.6
Oct. 23, 1997	1096	–	13.3
Oct. 25, 1997	394	790	7.8
Oct. 27, 1997	319	545	–
Oct. 29, 1997	289	366	7.8
Nov. 7, 1997	143	179	–
Nov. 12, 1997	163	133	–

i. Reviewer Comments.

The **aforementioned three pivotal multicenter DU trials, and the small gastric acid hypersecretion-ZES study, encompassed a total of 367 patients treated with oral rabeprazole tablets.** The majority of these, 324 patients, were treated with 20 mg rabeprazole for up to 4 weeks.

Overall, **the safety profile of rabeprazole tablets is good and acceptable, even when given in high doses and for long periods of time**, such as the >60 mg administered for 6 months-1 year to patients affected by gastric acid hypersecretion or ZES.

Unexpected was the rather high number of rabeprazole-treated patients who showed EKG changes compatible with myocardial infarction by the end of study periods. **The reported safety data revealed EKG changes compatible with MI in 8 rabeprazole patients (5 on 20 mg) vs. 1 PBO, 0 ranitidine and 0 omeprazole.** The sponsor reports that these patients did not show symptomatology associated with these EKG changes. This reviewer has been unable to find prior literature linking PPIs, specifically rabeprazole to myocardial ischemia and infarction Still, this observation ought to be commented because of the potential serious complications that might ensued by a silent MI[1,2,3].

References Consulted by this Reviewer.

1. Deedwania PC. Silent myocardial ischemia and its relationship to myocardial infarction. Cardiol Clin, 4:643-658, 1986.

2. Yano K et al. The incidence and prognosis of unrecognized myocardial infarction in the Honolulu, Hawaii, Heart {rogram/ Arch Int Med, 149:1528-1532, 1989.

3. Cohn PE. Indications for treatment of silent myocardial infarction. Cardiovasc Drugs Ther, 2:67-69, 1988.

F. REVIEWER SUMMARY, CONCLUSIONS AND RECOMMENDATIONS FOR REGULATORY ACTION.

The sponsor submitted three multicenter, randomized, double-blind trials in support of the claim of safety and effectiveness of rabeprazole tablets, administered in the single dose of 20 mg tablets after breakfast, in duodenal ulcer patients. Included in this application were narratives from 10 cases of gastric acid hypersecretion and ZES to support the claim of rabeprazole effectiveness in improving patients affected by gastric acid hypersecretion or gastrinomas.

i. Integrated Summary of Safety.

- **Based on my safety review of the three pivotal duodenal ulcer multi center studies, and gastric acid hypersecretion/ZES cases (GAH/ZES), I consider acceptable the safety exhibited by the 324 patient treated with rabeprazole 20-40 mg (DU) or >20 mg (GAH/ZES).**. The safety of these **324 rabeprazole**-treated patients was comparable to the safety margin observed in **33 placebo, 103 omeprazole, and 188 ranitidine treated patients**. There were no drug-related deaths in any of the DU studies or GAH/ZES cases. There were no significant differences in TESS among experimental treatments. **One patient on 40 mg and two on 20 mg rabeprazole** (13-075 in NRRC study; 50-5341and 52-5351 in NRRD study), **developed transient amblyopia, eye dryness, and eyesight worsening, that were considered as possibly related to** the **rabeprazole** treatment.

- **Five patients treated with 20 mg rabeprazole, vs 1 PBO, 0 omeprazole, 0 ranitidine patients, showed EKG changes consistent with the diagnosis of myocardial infarction** [rabeprazole 1124 (NRRC), 5136, 5650, 5522, 5241 (NRRD), placebo=1161]. **Three additional patients on rabeprazole 40 mg revealed similar EKG changes** [1011, 1030, 1169 (NRRC)]. All of these rabeprazole patients were asymptomatic. The relevance of these EKG changes, observed in a small subset of duodenal patients on 20 and 40 mg rabeprazole should now be carefully judged in the context of the overall rabeprazole safety, i.e., in conjunction with possible similar EKG changes revealed in patients treated with rabeprazole for GERD and gastric ulcer. If this overall safety renders no additional patients with EKG changes compatible with myocardial infarction, the aforementioned EKG findings should be considered incidental and not probably related to rabeprazole therapy.

ii. Integrated Summary of Efficacy.

- In support of the claim for rabeprazole effectiveness in healing active duodenal ulcers, the sponsor submitted three pivotal multi center, randomized, double-blind, controlled studies: **NRRC** (rabeprazole 20 mg and 40 mg vs. placebo), **NRRL** (rabeprazole 20 mg vs. omeprazole, 20 mg), and **NRRD** (rabeprazole 20 mg vs ranitidine 150 mg b.i.d.).