CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020973

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION — NDA

NDA #: 20-973

Date: NOV 9 1998

Applicant: Eisai Incorporated

Drug Class: 1S

Name of Drug: Aciphex (Rabeprazole Sodium) Delayed-release Tablet

Indication: GERD Maintenance
(Separate reviews for treatment of GU, DU, and GERD)

Documents Reviewer: NDA Vol. 1.1,1.147-1.281, 1.283 Dated March 31, 1998
SAS data sets in diskettes Dated April 10, 1998
Response to FDA's Request for Additional Information
Dated June 30, 1998

User Fee Date: 3/31/99 (12 mos), 1/31/99 (10 mos)

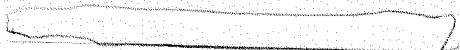**Statistical Reviewer:** Milton C. Fan, Ph.D.

Medical Reviewer: This review has been discussed with the medical officer,
John Senior, MD.

Key Words: Relapse, life table, Cutler-Ederer, cumulative point prevalence

A. Background

Rabeprazole, a substituted benzimidazole proton pump inhibitor (PPI), is structurally and pharmaceutically similar to the marketed compound omeprazole (approved for gastric ulcer, duodenal ulcer, GERD, erosive esophagitis, maintenance of healing of erosive esophagitis, and pathological hypersecretary conditions) and lansoprazole (approved for duodenal ulcer, maintenance of healed duodenal ulcer, gastric ulcer, erosive esophagitis, maintenance of healing erosive esophagitis, and pathological hypersecretary conditions).

In the current NDA, the sponsor seeks approval of rabeprazole tablet in four primary indications:

2). the healing of duodenal ulcers

3). the healing of erosive or ulcerative gastroesophageal reflux disease (GERD)

4). the long-term maintenance of healing of erosive GERD

Additionally, data have been presented in support of the usefulness of rabeprazole in treatment of pathological hypersecretory disorder including Zollinger-Ellison syndrome.

This review addresses only maintenance of GERD healing. Separate reviews address the other three indications.

B. Long-term Maintenance of GERD

The sponsor has submitted three clinical trials (E3810-A001-304 (NRRK-Odd), E3810-A001-304 (NRRK-Even), E3810-A001-304 (NRRQ)) in support of the proposed claim: GERD maintenance.

Protocol E3810-A001-304 (NRRK) was a U.S. multicenter, placebo-controlled comparison of the efficacy and safety of 10 mg and 20 mg rabeprazole. This protocol was prospectively segmented in two studies (even and odd sites, NRRK-Even and NRRK-Odd, respectively) to provide two placebo-controlled trials. Before the trial was split, the sample size was doubled to maintain adequate power to determine efficacy. Since NRRK- Odd and NRRK- Even came from the same protocol, it was agreed that the individual study results would be considered as two adequate and well-controlled studies not independent studies. The two studies would be analyzed both separately and combined.

Protocol E3810-E044-308 (NRRQ) was a European multicenter, active-controlled comparison of the efficacy and safety of 10 mg and 20 mg rabeprazole versus 20 mg omeprazole.

Patients enrolled into the two maintenance studies included men and women, 18 years of age or older, who were previously diagnosed with erosive and/or ulcerative GERD and who were healed as demonstrated by an endoscopy performed within 90 days prior to enrollment. Patients were eligible either if they successfully completed a rabeprazole GERD healing study or if they had documented erosive and ulcerative GERD and had been healed by successful anti-secretory therapy.

I. E3810-A001-304 (NRRK)

1. Description of Study

This was a randomized, double-blind, placebo-controlled, parallel-group, dosing ranging, multicenter (41 investigators) study. The objective of this study was to compare the efficacy of rabeprazole 20 mg once daily in the morning (QAM) with rabeprazole 10 mg QAM and with placebo in the prevention of relapse in patients who were previously diagnosed with erosive or ulcerative gastroesophageal reflux disease (GERD) and at the time of study entry were healed.

This study was prospectively planned to be analyzed as two different studies based on odd and even investigator numbers (NRRK-ODD and NRRK-EVEN).

After successful treatment with rabeprazole or ranitidine, in the GERD efficacy study (Protocol H4M-MC-NRRJ), or any other erosive or ulcerative GERD therapy, healed patients were eligible for entry into the maintenance study.

Duration of each study was up to 52 weeks. Six visits were scheduled: Visit 1 - Baseline, Visit 2 - Week 4 (Day 28 ± 3 days), Visit 3 - Week 13 (91 ± 7 days), Visit 4 - Week 26 (Day 182 ±7 days), Visit 5 - Week 39 (Day 273 ±7 days) and Visit 6 - Week 52 (Day 364 ± 7 days).

Each patient had an endoscopy at Visits 2, 3, 4, and 6 to determine if relapse had occurred. If endoscopic evidence of relapse (esophagitis grade 2 or more was present), patient was to be discontinued.

Patients were allowed to use NSAIDs, aspirin, or acetaminophen for relief of pain. Patients were given Mylanta tablets at Visits 1 through 5 and were instructed to take the tablets as needed per label recommendation for relief of their GERD symptoms.

The primary efficacy variable was the continued absence of esophageal erosions or ulcerations upon follow-up endoscopic examination. The endoscopic examination at Week 39 was performed only if clinically indicated. Relapse was defined as a score of two or greater on the modified Hetzel-Dent grading scale (2, 3, 4, or 5).

The secondary efficacy variables were relief of daytime and nighttime heartburn (based on frequency and severity), improvement in well-being, and the patients' daily antacid use. These data were taken from the patients' daily log. The severity of heartburn was rated using a 0-4 scale (0=none, 4=terrible). The frequency of symptoms was rated using a 0-4 scale (0=none, 4=continual). Patients' well-being was rated using a 0-4 scale (0=very good, 4=very poor). Secondary efficacy variables were analyzed using data from the patient diary cards.

The study was designed to include approximately 480 patients randomized into three treatment groups. This sample size would produce at least 80% power to detect at least a 24% absolute difference between rabeprazole and placebo, independent of hypothesized relapse rates and length of treatment period.

2. Sponsor's Analysis

2.1 Treatment Assignment

Patients enrolled in this GERD maintenance trial came from two groups of patients: "Rollover", and "Starter." The "Rollover" group constituted those patients who received

rabeprazole sodium or ranitidine and whose GERD was healed during the acute trial NRRJ. The de novo group of patients that could start in the GERD maintenance studies were referred to as "Starter"; they had not received any prior exposure to active or placebo drug in any of these sponsor's trials. This study included 166 "Rollover" patients and 331 "Starter" patients.

The treatment assignment for combined NRRK-Odd and NRRk-Even from "Rollover" and "Starter" groups of patients is given below.

Treatment Assignment — Combined NRRK-Odd and NRRK-Even

Patient Group	Rab 10 mg QAM	Rab 20 mg QAM	Placebo
Rollover	53 (32%)	54 (33%)	59 (35%)
Starter	112 (68%)	109 (67%)	110 (65%)

Copied from Table 3B, page 203, Vol. 249

As seen from the table above, the three treatment groups were comparable with regard to patient assignment from the two patient groups (p=0.861).

Summary of GERD patients who received acute treatment ("Rollover" group) is given below.

Treatment Assignment by Acute GERD Treatment
"Rollover" Group of Patients — Combined NRRK-Odd and NRRK-Even

Acute Treatment	Maintenance Treatment		
	Rab 10 mg QAM	Rab 20 mg QAM	Placebo
Rab 20 mg QAM	35 (66%)	26 (48%)	33 (56%)
Ranitidine 150 mg QID	18 (34%)	28 (52%)	26 (44%)

Copied from Table 3C, page 204, Vol. 249

As seen from the table above, there was a slight disproportionate distribution of patients in the acute treatment phase rolled over into the maintenance phase (p=0.173).

2.2 Sponsor's Analysis of NRRK-ODD

A total of 209 patients were enrolled (70 in the rabeprazole 10 mg group, 69 in the rabeprazole 20 mg group, and 70 in the placebo group).

Of the 209 patients enrolled, 101 (48%) discontinued from the study [43% (30/70), 23% (16/69), and 79% (55/70) in the rabeprazole 10 mg QAM, rabeprazole 20 mg QAM, and placebo treatment groups, respectively].

The percentages of patients who completed the study in both rabeprazole groups were significantly greater than in the placebo group (p<0.001). This was due primarily to a

large difference in the number of dropouts due to lack of efficacy, 66%, 20%, and 7% for the placebo, 10 mg, and 20 mg rabeprazole groups, respectively.

Seven patients in the rabeprazole 10 mg QAM group, four patients in the rabeprazole 20 mg QAM group, and two patients in the placebo group were discontinued from the study because of protocol violation.

Four patients in the rabeprazole 10 mg QAM group [(9)-9058, (9)-9059, (59)-9412 and (59)-9413] and two patients in the rabeprazole 20 mg QAM group [(55)-9380 and (55)-9381] were not evaluable for efficacy because of misrandomization of study drug.

2.2.1 Treatment Group Comparability

The demographic and baseline characteristics of the three treatment groups were comparable with regard to distribution by gender, age, tobacco consumption, alcohol consumption, caffeine consumption, and number of doses of antacid used per day (See Attachment Table 1).

Slightly significant differences among treatments were observed for endoscopy modified Hetzel-Dent esophagitis grade (p=0.107). Significant differences among treatments were also observed for GERD heartburn frequency grade (p=0.040). Significantly more patients in the placebo group reported daytime and night heartburn than did patients in the rabeprazole groups.

2 2.2 Sponsor's Analysis of Primary Endpoint

The primary endpoint was endoscopic evidence of relapse of erosive or ulcerative GERD. Relapse was defined by a score of two or greater on the modified Hetzel-Dent grading scale. Relapse rates were evaluated using data collected at Weeks 4, 13, 26, 39, and 52 of the study and were analyzed using three different methods of analyses:

1. ITT (intent-to-treat) analysis

   The primary analysis was the "intent-to-treat" (ITT) analysis. With the ITT analysis, if a patient has a missing endoscopy at any visit, the most recent non-missing endoscopy result will be used in place of the missing value.

2. ENDO (endoscopies performed) analysis

   The second analysis was the "endoscopies performed" (ENDO) analysis. The ENDO analysis is similar to the ITT analysis except that only missing values following treatment failures are replaced by the previous endoscopy result (i.e. GERD relapse).

3. Survival Analysis

The third analysis was the survival analysis. The Kaplan-Meier product limit estimate of relapse was used. The response variable was the amount of time between randomization and the first occurrence of relapse of GERD.

The additional Cutler-Ederer analysis was requested by this reviewer. This method is similar to the Kaplan-Meier method. The study period was grouped into intervals with each study visit week as the midpoint. Unlike the Kaplan-Meier technique, an assumption is made that patients who relapse or drop out of the study are uniformly distributed over an interval.

The results for the ITT and ENDO analyses are shown in the tables below.

Protocol NRRK-ODD
Summary of GERD Relapse Rate
Intent-to-Treat Analysis

Week	Rab 10 mg	Rab 20 mg	Placebo	P-value Rab 10 mg vs. Placebo	P-value Rab 20 mg vs. Placebo	P-value Rab 10 mg vs. Rabe 20 mg
4	11/66 (17%)	3/67 (4%)	39/70 (56%)	<0.001	<0.001	0.038
13	14/66 (21%)	5/67 (7%)	43/70 (61%)	<0.001	<0.001	0.028
26	15/66 (23%)	5/67 (7%)	48/70 (69%)	<0.001	<0.001	0.015
39	16/66 (24%)	6/67 (9%)	49/70 (70%)	<0.001	<0.001	0.032
52	18/66 (27%)	7/67 (10%)	50/70 (71%)	<0.001	<0.001	0.027

P-value was adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistics.
Copied from Table NRRK-Odd 6.2, page 76, Vol. 192.

ENDO Analysis

Week	Rab 10 mg	Rab 20 mg	Placebo	P-value Rab 10 mg vs. Placebo	P-value Rab 20 mg vs. Placebo	P-value Rab 10 mg vs. Rabe 20 mg
4	11/66 (17%)	3/67 (4%)	39/70 (56%)	<0.001	<0.001	0.038
13	14/60 (23%)	5/64 (8%)	43/66 (65%)	<0.001	<0.001	0.015
26	15/60 (25%)	5/63 (8%)	48/64 (75%)	<0.001	<0.001	0.009
39[a]	16/32 (50%)	6/22 (27%)	49/52 (94%)	0.003	<0.001	0.199
52	18/56 (32%)	7/59 (12%)	50/70 (79%)	<0.001	<0.001	0.012

P-value was adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistics.
[a] Endoscopy performed only if clinically indicated.
Copied from Table NRRK-Odd 6.2, page 76, Vol. 192.

As seen from the tables above, for ITT analysis at all visit weeks, the relapse rates were significantly higher in the placebo group than in either rabeprazole group. There was a statistically significantly lower rate of relapse observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group.

The results from the ENDO analysis were very similar to those from the ITT analysis. There were statistically significantly lower GERD relapse rates in the rabeprazole 20 mg group as compared to the rabeprazole 10 mg group for all visit weeks except Week 39. At Week 39, results did not show a statistically significant difference in GERD relapse; however, the GERD relapse rate for the rabeprazole 20 mg group was numerically lower than that for the rabeprazole 10 mg group (27% vs. 50%).

The results for the Kaplan-Meier analysis are given in Attachment Table 2. Cumulative proportion of patients who remained free of GERD relapse is given in Attachment Figure 3.

As seen from Figure 3 (attached), there was a clear and large separation in the probability curves. Based on the Kaplan-Meier estimate of cumulative probability of GERD relapse, both 10 mg and 20 mg doses of rabeprazole group were statistically significantly superior to placebo in maintaining healing over the 52-week study period. There was a clear dose-response between placebo, 10 mg, and 20 mg rabeprazole group. The rabeprazole 20 mg was significantly superior to the 10 mg dose in maintaining healing.

The results for Cutler-Ederer analysis are given in Attachment Table 4.

As seen from Table 4 (attached), pairwise comparison showed that there was a statistically significant difference in the survival estimates of relapse between patients on 10 mg rabeprazole and patients on 20 mg rabeprazole. Patients who received 20 mg rabeprazole were more likely to remain healed than patients who received 10 mg rabeprazole from study Week 8 to 52. The overall survival estimate of relapse between patients on either 10 mg or 20 mg rabeprazole and patients on placebo was statistically significantly different. Patients who received either 10 mg or 20 mg rabeprazole were more likely to remain healed than patients who received placebo from study Week 8 to 52.

2.2.3 Sponsor's Analysis of Secondary Endpoint

The secondary endpoints were relapse rates in GERD heartburn frequency, relapse rates in GERD daytime and nighttime heartburn severity, relapse rates of patients' overall rating of well-being and mean changes in antacid use.

Relapse in GERD symptoms and overall well-being were summarized for the three treatment groups by the number and percentage of patients who were classified as symptomatic (grade of 2, 3, or 4). Only patients who were asymptomatic (grade 0 or 1) at baseline were included in these analyses.

The numbers and percentages of patients who were asymptomatic at baseline and relapsed in GERD heartburn frequency at each study week is given in Attachment Table 5.

As seen from Table 5 (attached), at all visit weeks, the relapse rates were significantly higher in the placebo group than in the two rabeprazole groups for GERD heartburn frequency.

The numbers and percentages of patients who relapsed in daytime and nighttime GERD heartburn severity at each study weeks are given in Attachment Tables 6 and 7, respectively.

As seen from Tables 6 and 7 (attached), at all visit weeks the relapse rates were significantly higher in the placebo than in the rabeprazole 10 mg group and the rabeprazole 20 mg group for GERD daytime and nighttime heartburn severity. The numbers and percentages of patients who relapsed in patients' overall well-being at each study week are given in Attachment Table 8.

As seen from Table 8 (attached), at all visit weeks, the relapse rates were statistically significantly higher in the placebo group than in the 20 mg rabeprazole group for patients' overall well-being. The relapse rates were higher in the placebo group than in the rabeprazole 10 mg group at all visits; however, the difference only reached significance at Weeks 4 and 52.

The mean change in antacid use for all study visit is given in Attachment Table 9. As seen from Table 9 (attached), patients in the placebo group increased their antacid use at each study Week. The differences in mean changes in antacid use from baseline were significant between the placebo and rabeprazole groups at each study visit, whereas no significant differences were observed between the two rabeprazole groups.

2.2.4 Safety Summary

Compared to placebo patients, patients treated with 10 mg or 20 mg rabeprazole had a significantly higher incidence rate of hypergastrinemia. In addition, patients treated with 20 mg rabeprazole had a significantly higher incidence rate of hypergastrinemia than those treated with 10 mg rabeprazole.

A significant difference was observed between the rabeprazole 20 mg QAM and the placebo groups in the percentage of patients with normal endpoint ECG rhythm results.

2.3 Sponsor's Analysis of NRRK-EVEN

A total of 288 patients were enrolled (95 in the rabeprazole 10 mg group, 94 in the rabeprazole 20 mg group, and 99 in the placebo group). Of the 288 patients enrolled, 135 (47%) discontinued from the study [33% (31/95), 27% (25/94) and 80% (79/99) in the rabeprazole 10 mg QAM, rabeprazole 20 mg QAM, and placebo groups, respectively].

The percentages of patients who completed the study in both rabeprazole groups were significantly greater than in the placebo group (p<0.001). This was due primarily to a

large difference in the number of dropouts due to lack of efficacy, 73%, 17%, and 9% for the placebo, 10 mg, and 20 mg rabeprazole groups, respectively.

Two patients in the rabeprazole 10 mg QAM group [(34)-9578 and (60)-9417] and one patient in the rabeprazole 20 mg QAM group [(56)-9386] were not evaluable for efficacy because of misrandomization of study drug.

Two patients in the rabeprazole 20 mg group and three patients in the placebo group were discontinued from the study due to protocol violations.

2.3.1 Treatment Group Comparability

The demographic and baseline characteristics of three treatment groups were comparable with regard to distribution by gender, age, tobacco consumption, alcohol consumption, caffeine consumption, baseline endoscopy modified Hetzel-Dent esophagitis grade and baseline GERD heartburn frequency grade (See Attachment Table 10).

The mean number of doses of antacid was significant higher in the rabeprazole 10 mg group than in the rabeprazole 20 mg group and placebo group.

2.3.2 Sponsor's Analysis of Primary Endpoint

The primary endpoint was endoscopic evidence of relapse of erosive or ulcerative GERD. Relapse was defined by a score of two or greater on the modified Hetzel-Dent grading scale.

The results for the ITT and ENDO analyses are shown in the tables below.

Protocol NRRK-EVEN
Summary of GERD Relapse Rate
Intent-to-Treat Analysis

Week	Rab 10 mg	Rab 20 mg	Placebo	P-value Rab 10 mg vs. Placebo	P-value Rab 20 mg vs. Placebo	P-value Rab 10 mg vs. Rab 20 mg
4	10/93 (11%)	6/93 (6%)	59/99 (60%)	<0.001	<0.001	0.375
13	13/93 (14%)	8/93 (9%)	66/99 (67%)	<0.001	<0.001	0.274
26	14/93 (15%)	10/93 (11%)	69/99 (70%)	<0.001	<0.001	0.399
39	15/93 (16%)	11/93 (12%)	70/99 (71%)	<0.001	<0.001	0.537
52	21/93 (23%)	13/93 (14%)	70/99 (71%)	<0.001	<0.001	0.110

P-value was adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistics.
Copied from Table NRRK-Even 6.2, page 74, Vol. 200.

ENDO Analysis

Week	Rab 10 mg	Rab 20 mg	Placebo	P-value Rab 10 mg vs. Placebo	P-value Rab 20 mg vs. Placebo	P-value Rab 10 mg vs. Rab 20 mg
4	10/93 (11%)	6/93 (6%)	59/99 (60%)	<0.001	<0.001	0.375
13	13/90 (14%)	8/90 (9%)	66/94 (70%)	<0.001	<0.001	0.251
26	14/87 (16%)	10/87 (11%)	69/93 (74%)	<0.001	<0.001	0.422
39*	15/24 (63%)	11/26 (42%)	70/75 (93%)	<0.001	<0.001	0.878
52	21/80 (26%)	13/79 (16%)	70/90 (78%)	<0.001	<0.001	0.164

P-value was adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistics.
* Endoscopy performed only if clinically indicated.
Copied from Table NRRK-Even 6.2, page 74, Vol. 200.

As seen from the tables above, for ITT analysis at all visit weeks, the relapse rates were significantly higher in the placebo group than in either rabeprazole group. A consistently lower rate of relapse was observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group at each visit week. The results from the ENDO analysis were very similar to those from the ITT analysis.

The results for Kaplan-Meier analysis are given in Attachment Table 11. Cumulative proportion of patients who remained free of GERD relapse is given in Attachment Figure 12.

As seen from Figure 12 (attached), there was a clear and large separation in the probability curves. Based on the Kaplan-Meier estimate of cumulative probability of GERD relapse, both 10 mg and 20 mg doses of rabeprazole group were statistically significantly superior to placebo in maintaining healing over the 52-week study period. There was no significant difference between 10 mg and 20 mg rabeprazole groups.

The results for Cutler-Ederer analysis are given in Attachment Table 13.

As seen from Table 13 (attached), pairwise comparison showed that the overall survival estimates of relapse between patients on either 10 mg or 20 mg rabeprazole and patients on placebo was statistically significantly different. Patients who received either 10 mg or 20 mg rabeprazole were more likely to remain healed than patients who received placebo from study Week 8 to 52. No significant difference was observed between rabeprazole 10 mg and 20 mg groups.

2.3.3 Sponsor's Analysis of Secondary Endpoint

The secondary endpoints were improvement rates in GERD heartburn frequency, improvement rates in GERD daytime and nighttime heartburn severity, patients' overall rating of well-being improvement rates and mean changes in antacid use.

Relapse in GERD symptoms and overall well-being were summarized for the three treatment groups by the number and percentage of patients who were classified as symptomatic. Only patients who were asymptomatic at baseline were included in these analyses.

The numbers and percentages of patients who had no symptoms at baseline and relapsed in GERD heartburn frequency at each study week is given in Attachment Table 14.

As seen from Table 14 (attached), at all visit weeks, the relapse rates were significantly higher in the placebo group than in the two rabeprazole groups for GERD heartburn frequency.

The numbers and percentages of patients who relapsed in GERD daytime and nighttime heartburn severity at each study weeks are given in Attachment Tables 15 and 16, respectively.

As seen from Table 15 (attached), at all visit weeks the relapse rates were significantly higher in the placebo than in the rabeprazole 10 mg group and the rabeprazole 20 mg group for GERD daytime heartburn severity.

As seen from Table 16 (attached), at all visit weeks the relapse rates were significantly higher in the placebo than in the rabeprazole 20 mg group for GERD nighttime severity. The relapse rates were higher in the placebo group than in the rabeprazole 10 mg group at all time points; the differences reached significance at Week 13 (p=0.022). A consistently lower rate of relapse was observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group at each visit; the differences were statistically significant at Week 13 (p=0.02) and at Week 26 (p=0.01).

The numbers and percentages of patients who relapsed in patients' overall well-being at each study week are given in Attachment Table 17.

As seen from Table 17 (attached), at all visit weeks, the relapse rates were statistically significantly higher in the placebo group than in the rabeprazole 20 mg group for patients' overall well-being. The relapse rates were higher in the placebo group than in the rabeprazole 10 mg group at all visits; however, the difference only reached significance at Week 26 (p=0.049). A consistently lower rate of relapse was observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group at each visit; the differences were statistically significant at Week 4 (p=0.042) and at Week 52 (p=0.037).

The mean change in antacid use for all study visit is given in Attachment Table 18.

As seen from Table 18 (attached), the differences in mean changes in antacid use from baseline were significant between the placebo and rabeprazole groups at each study visit, whereas no significant differences were observed between the two rabeprazole groups.

2.3.4 Safety Summary

Significantly fewer patients reported treatment-emergent signs and symptom (TESS) in the placebo group than in either rabeprazole group.

Compared to placebo patients, patients treated with 10 mg or 20 mg rabeprazole had a significantly higher incidence rate of hypergastrinemia. In addition, patients treated with 20 mg rabeprazole had a significantly higher incidence rate of hypergastrinemia than those treated with 10 mg rabeprazole.

A significant difference was observed between the rabeprazole 10 mg (90%) and rabeprazole 20 mg (74%) groups in the percentage of patients with normal endpoint ECG rhythm results.

2.4 Sponsor's Analysis of Dose Response for Primary Endpoint

Results from Study NRRK-Odd showed that the 20 mg dose was statistically significantly more effective than the 10 mg dose in preventing GERD relapse at each visit. Although the difference in efficacy between the 20 mg and 10 doses did not reach statistical significance in study NRRK-Even, the 20 mg dose was consistently numerically better than the 10 mg dose at all study visit. The sponsor stated that although speculative regarding the lack of statistical significance in this trial, is the observation that patients in study NRRK-Even had greater esophageal pathology severity at baseline than did patients in study NRRK-Odd.

The results from the combined NRRK-Odd and NRRK-Even trial for primary endpoint are given below.

Combined Protocols NRRK-ODD and NRRK-EVEN
Summary of GERD Relapse Rate
Intent-to-Treat Analysis

Week	Rab 10 mg	Rab 20 mg	Placebo	P-value Rab 10 mg vs. Rabe 20 mg
4	21/159 (13%)	9/160 (6%)	98/169 (58%)	0.021
13	27/159 (17%)	13/160 (8%)	109/169 (64%)	0.017
26	29/159 (18%)	15/160 (9%)	117/169 (69%)	0.022
39	31/159 (19%)	17/160 (11%)	119/169 (70%)	0.027
52	39/159 (25%)	20/160 (13%)	120/169 (71%)	0.006

P-value was adjusted for baseline Hetzel-Dent grade; obtained using the Cochran-Mantel-Haenszel statistics.
Copied from Table 4.16, page 92, Vol. 228.

As seen from the table above, the rabeprazole 20 mg was statistically significantly more effective than the rabeprazole 10 mg in preventing GERD relapse at each visit for the combined NRRK-Odd and NRRK-Even studies. This appears to support the superiority

of the 20 mg over the 10 mg dose in preventing recurrence of esophageal erosions and ulcerations.

2.5 Reviewer's Evaluation

This study was analyzed as two different studies (NRRK-ODD and NRRK-EVEN) based on odd and even investigator numbers. The protocol did state the intent to split the two studies based on investigator number (odd/even). But, this turned out to be problematic. It was observed that there were statistically significant discrepancies among treatment groups in baseline endoscopy modified Hetzel-Dent Esophagitis grade (p=0.034, sponsor's reported p=0.107 was incorrect.) and baseline GERD heartburn frequency grade (0.040) for Study NRRK-ODD. There was a slight discrepancy among treatment groups in antacid use and number of doses of antacid used per day for Study NRRK-EVEN. This discrepancy might be due to the fact that the two sub-studies were not totally independent.

It was also observed that there were inconsistent results for primary endpoint between two studies NRRK-ODD and NRRK-EVEN in comparing rabeprazole 20 mg with rabeprazole 10 mg. The sponsor showed that in Study NRRK-ODD, there was a statistically significantly lower rate of relapse observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group for each visit week. In Study NRRK-EVEN, a consistently numerically lower rate of relapse was observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group at each visit week. But, the difference did not reach statistical significance.

For completeness, however, this reviewer evaluated the combined efficacy results for NRRK-ODD and NRRK-EVEN.

2.5.1 Reviewer's Comments on Sponsor's Analysis of Primary Endpoint

2.5.1.1 Scheduled and Unscheduled Endoscopy at Week 4

A disproportionate number of patients had their Week 4 visit falling outside the specified day range among treatment groupss. The window for Week 4 endoscopy was specified in the protocol as Day 28 ± 3 days. This reviewer compiled the data from sponsor supplied data diskette. The patient who had Week 4 endoscopy performed within the specified day range (Day 28 ± 3) is defined as "scheduled." The patient who had Week 4 endoscopy performed outside the specified day range is defined as "unscheduled." The patient who did not have Week 4 endoscopy performed is defined as "missing."

The summary of Week 4 endoscopy by treatment group is given below.

Protocol NRRK
Summary of Week 4 Endoscopy

Treatment	Scheduled	Unscheduled	Missing	P-value
Rab 10 mg QAM	133/165 (81%)	21/165 (13%)	11/165 (7%)	0.008
Rab 20 mg QAM	127/163 (78%)	31/163 (19%)	5/163 (3%)	
Placebo	113/169 (66%)	38/169 (23%)	18/169 (11%)	

P-value was computed by this reviewer using Chi-square test.

As seen from the table above, there was significant treatment difference in the number of patients who had Week 4 endoscopy performed in the specified day range (Day 28 ± 3). Even after excluding patients with no endoscopy performed at Week 4, rabeprazole 10 mg still had significantly more scheduled endoscopies than placebo ($p=0.011$).

2.5.1.2 Relapse in Scheduled Endoscopies

The results of relapse in scheduled endoscopies at Week 4, 13, 26, 39 and 52 are summarized below.

Protocol NRRK
Summary of GERD Relapse Rate
Scheduled Endoscopy

Week	Rab 10 mg	Rab 20 mg	Placebo	P-value Rab 10 mg vs. Placebo	P-value Rab 20 mg vs. Placebo	P-value Rab 10 mg vs. Rab 20 mg
4	9/133 (7%)	5/127 (4%)	54/113 (48%)	<0.001	<0.001	0.313
13	5/117 (4%)	3/128 (2%)	10/60 (17%)	0.005	<0.001	0.397
26	2/106 (2%)	1/121 (1%)	8/43 (19%)	<0.001	<0.001	0.486
39[1]	2/21 (10%)	2/21 (10%)	0/6 (0%)	1.000*	1.000*	1.000
52	5/81 (6%)	1/103 (1%)	0/28 (0%)	0.325*	1.000*	0.049

P-value was computed by this reviewer using Chi-square test.
[1] Endoscopy performed only if clinically indicated
*P-value was computed by this reviewer using Fisher's Exact test

As seen from the table above, both rabeprazole 10 mg and rabeprazole 20 mg had significantly fewer relapses than placebo at weeks 4, 13, and 26. No treatment differences were observed at weeks 39 and 52. A significant difference was observed between rabeprazole 10 and 20 at week 52.

2.5.1.3 Cumulative Point Prevalence Analysis of Relapse Rates

When one of the treatment groups in a maintenance trial is more effective in reducing the symptoms, then patients with relapse at an unscheduled endoscopy are a potential source of bias for treatment comparison. Since asymptomatic GERD can reheal before detection at a scheduled endoscopy, two treatments with equal relapse rates and equal rehealing rates could have different observed prevalences because treatment with better reduction

of symptoms would have fewer relapses detected by endoscopic evaluation at unscheduled visits (Elashoff, J.D. and Koch, G.G <u>Statistical Methods in Trials of Anti-Ulcer Drug</u>, 375-406, Ulcer Disease edited by Swabb and Szabo, 1991).

To evaluate the impact of this source of bias, this reviewer uses the cumulative point prevalence analysis for treatment comparison. The cumulative point prevalence analysis includes only the observed relapse at scheduled endoscopies in the study. The cumulative point prevalence method is defined below:

Probability of relapse for i^{th} time interval $= R_i/N_i$

With

R_i = Number of patients with endoscopically-verified erosive esophagitis relapse at the ith scheduled visit plus the number of patients with erosive esophagitis relapse at each previous scheduled endoscopy

N_i = Number of patients who had an endoscopy at the ith scheduled visit plus the number of patients with erosive esophagitis relapse at each previous scheduled endoscopy

and

i = 1 for the interval (0-4] weeks
2 for the interval (0-13] weeks
3 for the interval (0-26] weeks
4 for the interval (0-39] weeks
5 for the interval (0-52] weeks

Note: This cumulative point prevalence method puts more weight on relapse, that occurred in the first period, since there is evidence suggesting that preponderance of the observed relapse occurred early during the trial.

The results are given in below.