Protocol NRRK
Cumulative Point Prevalence Analysis of Relapse Rates

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	14/126 (11%)	8/133 (6%)	64/114 (56%)	<0.001	<0.001	0.142
26	16/120 (13%)	9/130 (7%)	72/107 (67%)	<0.001	<0.001	0.092
39[1]	18/37 (49%)	11/30 (37%)	72/78 (92%)	<0.001	<0.001	0.329
52	23/99 (23%)	12/114 (11%)	72/100 (72%)	<0.001	<0.001	0.013

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

As seen from the table above, both rabeprazole 10 mg and 20 mg were superior to the placebo in terms of relapse rate at each visit week (4, 13, 26, 39 and 52). Relapse rate for rabeprazole 20 mg was smaller than that for rabeprazole 10 at visit week. However, statistical significance was reached at Week 52 only.

2.5.1.4 Relapse Rate by Baseline Hetzel-Dent Grade

To evaluate the impact of baseline Hetzel-Dent grade on relapse, this reviewer re-analyzed the relapse rates at Week 52 using the Mantel-Haenszel method adjusting for baseline Hetzel-Dent grade. The results are given below.

Protocol NRRK
Relapse Rate at Week 52 by Baseline Hetzel-Dent Grade

Baseline Hetzel-Dent Grade	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
0	30/118 (25%)	16/118 (14%)	83/117 (71%)	0.001	0.001	0.006
1	9/41 (22%)	4/42 (10%)	37/52 (71%)			

*P-value was obtained by this reviewer using the Mantel-Haenszel method adjusting for baseline Hezel-Dent grade.
This table was compiled by this reviewer.

The data suggested no significant effect of baseline Hetzel-Dent grade on relapse (p=0.583). As seen from the table above, the relapse rates were still significantly higher in the placebo group than in either rabeprazole 10 mg or 20 mg group even after adjusting for baseline Hetzel-Dent grade. There was a statistically significantly lower rate of relapse observed at Week 52 in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group.

2.5.1.5 Relapse Rate by Patient Group

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

The sponsor did not provide sufficient information to link the acute treatment to maintenance treatment. Particularly, for "Starter" group of patients, the sponsor did not provide the treatment with which a patient was treated and healed successfully before entry into the maintenance study. There was more "Starter" patients than "Rollover" patients (331 vs. 166).

To evaluate the impact of patient group on relapse, this reviewer re-analyzed relapse rates at Week 52 using the Mantel-Haenszel method adjusting for patient groups. The results are given below.

Protocol NRRK
Relapse Rate at Week 52 by Patient Groups

Patient Group	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
Rollover	15/51 (29%)	8/52 (15%)	40/59 (68%)	0.001	0.001	0.006
Starter	24/108 (22%)	12/108 (11%)	80/110 (73%)			

*P-value was obtained by this reviewer using the Mantel-Haenszel method adjusting for patients' categories.
This table was compiled by this reviewer.

The data suggested no significant effect of patient groups on relapse (p=0.624). As seen from the table above, the relapse rate was still significantly higher in the placebo group than in either rabeprazole 10 mg or 20 mg group even after adjustment for patient groups. There was a statistically significantly lower rate of relapse observed at Week 52 in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group.

2.5.1.6 Relapse Rate by Acute Treatment for "Rollover" Group of Patients

There was a slightly disproportionate acute treatment for treatment assignment for the "Rollover" group of patients (p=0.173). To evaluate the impact of this imbalance in acute treatment for "Rollover" group of patients, this reviewer re-analyzed the relapse rates at Week 52 using the Mantel-Haenszel method adjusting for acute treatment assignment for "Rollover" group of patients. The results are given below.

Protocol NRRK

Relapse Rate at Week 52 by Acute Treatment Assignment for "Rollover" Patients

Acute Treatment	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
Rabeprazole	11/34 (32%)	4/25 (16%)	25/33 (76%)	0.001	0.001	0.118
Ranitidine	4/17 (24%)	4/27 (15%)	15/26 (57%)			

*P-value was obtained by this reviewer using the Mantel-Haenszel method adjusting for acute treatment assignment.

This table was compiled by this reviewer.

The data suggested a slight effect of acute treatment assignment on relapse for "Rollover" group of patients (p=0.163). As seen from the table above, for "Rollover" group of patients, the relapse rate at Week 52 was still significantly higher in the placebo group than in either rabeprazole 10 mg or 20 mg group even after adjustment for acute treatment. Lower relapse rate was observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group. But, the difference did not reach statistical significance, probably due to small sample size.

2.5.1.7 Relapse Rate by Week of Acute Healing for "Rollover" Patients

To evaluate the impact of the week of acute healing on relapse rate for "Rollover" group of patients, this reviewer re-analyzed the relapse rates at Week 52 using the Mantel-Haenszel method adjusting for week of acute healing for "Rollover" group of patients. The results are given below.

Protocol NRRK

Relapse Rate at Week 52 by Week of Acute Healing for "Rollover" Patients

Week of Acute Healing	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	1/28 (36%)	6/31 (19%)	24/34 (71%)	0.001	0.001	0.107
8	4/22 (18%)	2/21 (10%)	16/25 (64%)			

*P-value was obtained by this reviewer using the Mantel-Haenszel method adjusting for week of acute healing.

This table was compiled by this reviewer.

The data suggested a slight effect of week of acute healing on relapse for "Rollover" group of patients (p=0.111). As seen from the table above, for "Rollover" group of patients, the relapse rate at Week 52 was still significantly higher in the placebo group than in either rabeprazole 10 mg or 20 mg group even after adjustment for week of acute healing. Lower relapse rate was observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group. But, the difference did not reach statistical significance, probably due to small sample size.

In conclusion, by the point prevalence analysis of relapse rate, a more appropriate analysis of this endpoint, either rabeprazole 10 mg or 20 group was significant better than placebo at weeks 4, 13, 26, 39, and 52. The relapse rates were lower in the rabeprazole 20 mg group as compared to the rabeprazole 10 mg group. The difference for the comparison between the rabeprazole 10 mg and the rabeprazole 20 mg reached statistical significance at Week 52.

II. E3810-A001-308 (NRRQ)

1. Description of Study

This was a randomized, double-blind, parallel group, multicenter (21 investigators) active-controlled study. The objective of this study was to compare rabeprazole 10 mg and 20 mg once daily in the morning (QAM) with omeprazole 20 mg QAM 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.

The design of this study was similar to the design for Protocol NRRK.

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

Patients were assigned by random allocation to one of three treatment groups: rabeprazole 20 mg QAM, rabeprazole 10 mg QAM, or omeprazole 20 mg QD.
Duration of the study was approximately 52 weeks. A maximum of six visits, at Visit 1 - Week 0, Visit 2 - Week 4 (28 ± 3 days), Visit 3- Week 13 (91 ± 7 days), Visit 4 - Week 26 (182 ± 7 days), Visit 5 - Week 39 (273 ± 7 days), and Visit 6 - Week 52 (364 ± 7 days) were scheduled. Each patient had an endoscopy performed at Visits 3, 4 and 6 to determine if a relapse had occurred. Endoscopies were also performed at Visit 1 if necessary and at Visit 5 if clinically indicated.

The primary efficacy variable was endoscopic evidence of relapse of erosive or ulcerative GERD.

The secondary efficacy variables were frequency and severity of heartburn, use of antacids and overall well-being.

The study was designed to include approximately 240 patients randomly divided into three treatment groups. This sample size would provide at least 80% power to "rule out" a difference of at least 18% between rabeprazole and omeprazole, assuming a relapse rate of 20% for both rabeprazole and omeprazole after six months.

2. Sponsor's Analysis

A total of 243 patients were enrolled (82 patients in the 10 mg rabeprazole group, 78 patients in the 20 mg rabeprazole group and 83 in the omeprazole group).

Of the 243 patients enrolled, 33 (14%) discontinued from the study [13% (11/82), 13% (10/78), and 14% (12/83) in the rabeprazole 10 mg, rabeprazole 20 mg groups and omeprazole groups, respectively].

Three patients in the rabeprazole 10 group, no patient in the rabeprazole 20 mg group, and five patients in the omeprazole group were discontinued from the study because of protocol violations.

More patients in rabeprazole 10 mg group had their Week 52 visit failing outside the specified window than either patients in the rabeprazole 20 mg group or in the omeprazole group (18 for rabeprazole 10 mg vs. 10 and 8 for rabeprazole 20 and omeprazole, respectively).

2.1 Treatment Group Comparability

The patients who enrolled in this GERD maintenance trial came from two groups of patients: "Rollover", and "Starter." The "Rollover" group constituted patients who received rabeprazole sodium or omeprazole and whose GERD was healed during the acute trial NRRP. 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 any of these sponsor's trials. This study included 124 "Rollover" patients and 119 "Starter" patients.

The treatment assignment for NRRQ from "Rollover" and "Starter" groups of patients is given below.

Treatment Assignment by Patient Group— NRRQ

Patient Group	Rab 10 mg QAM	Rab 20 mg QAM	Ome 20 mg QAM
Rollover	40 (49%)	41 (53%)	43 (52%)
Starter	42 (51%)	37 (47%)	40 (48%)

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

As seen from the table above, the three treatment groups were comparable with regard to treatment assignment from the two patient groups (p=0.878).

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

Treatment Assignment by Acute GERD Treatment Assignment
"Rollover" Group of Patients--- NRRQ

Acute Treatment	Maintenance Treatment		
	Rab 10 mg QAM	Rab 20 mg QAM	Ome 20 mg QAM
Rab 20 mg QAM	15 (38%)	24 (59%)	19 (44%)
Ome 20 mg QAM	25 (63%)	17 (41%)	24 (56%)

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 rolled over into the maintenance phase (p=0.151).

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, number of doses of antacid used per day and baseline endoscopy modified Hetzel-Dent Esophagitis grade (See Attachment Table 19).

A slight significant difference among treatments was observed for GERD heartburn frequency grade (p=0.133).

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.

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

Protocol NRRQ
Summary of GERD Relapse Rate
Intent-to-Treat Analysis

Week	Rab 10 mg	Rab 20 mg	Ome 20 mg	P-value Rab 10 mg vs. Ome 20 mg	P-value Rab 20 mg vs. Ome 20 mg	P-value Rab 10 mg vs. Rab 20 mg
13	1/82 (1%)	2/78 (3%)	1/83 (1%)	0.807	0.410	0.557
26	1/82 (1%)	3/78 (4%)	1/83 (1%)	0.807	0.181	0.297
52	4/82 (5%)	3/78 (4%)	4/83 (5%)	0.833	0.962	0.738

P-value was adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistics.
Copied from Table NRRQ- 6.2, page 74, Vol. 210.

ENDO Analysis

Week	Rab 10 mg	Rab 20 mg	Ome 20 mg	P-value Rab 10 mg vs. Ome 20	P-value Rab 20 mg vs. Ome 20 mg	P-value Rab 10 mg vs. Rab 20 mg
13	1/76 (1%)	2/74 (3%)	1/79 (1%)	0.807	0.381	0.541
26	1/71 (1%)	3/69 (4%)	1/74 (1%)	0.849	0.167	0.270
52	4/72 (6%)	3/87 (4%)	4/72 (6%)	0.709	0.931	0.688

P-value was adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistics.
Copied from Table NRRQ 6.2, page 74, Vol. 210.

As seen from the tables above, at all visit weeks, the relapse rates for the three treatment groups did not differ significantly. 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 20. Cumulative proportion of patients who remained free of GERD relapse is given in Attachment Figure 21.

As seen from Figure 21 (attached), on the basis of the Kaplan-Meier estimates, there were no inter-treatment group differences in the probability of maintaining healing.

The results for Cutler-Ederer analysis are given in Attachment Table 22.

As seen from Table 22 (attached), pairwise comparison showed that overall, there was no statistically significant difference in life table survival estimates of relapse between patients on rabeprazole 20 mg and patients on omeprazole. The overall survival estimates of relapse between patients on rabeprazole 20 mg and patients on omeprazole were comparable.

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. 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 23.

As seen from Table 23 (attached), at all visit weeks, the relapse rates were similar among the three treatment 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 24 and 25, respectively.

As seen from Table 24 (attached), at all visit weeks the relapse rates were similar among the three treatment groups for GERD daytime heartburn.

As seen from Table 25 (attached), the nighttime heartburn relapse rates observed among treatment groups were comparable at Week 52. There was a lower rate of relapse observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group at Weeks 13, 26, 39, and 52, although a statistical significance was not reached.

The numbers and percentages of patients who relapsed in patients' overall well-being at each study week are given in Attachment Table 26.

As seen from Table 26 (attached), at all visit weeks, the relapse rates in patients' overall well-being were comparable among the three treatment groups.

The mean change in antacid use for all study visits is given in Attachment Table 27.

As seen from Table 27 (attached), the mean changes in antacid use from baseline were comparable between the omeprazole and rabeprazole groups at each study visit.

3. Reviewer's Evaluation

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

3.1.1 Reviewer's Endoscopy Analysis

LOCF (last observation carried forward) method was used in the sponsor's ITT and ENDO analyses. However, in the protocol, it did not specified that "if endoscopic evidence of relapse (esophagitis grade 2 or more was present), patient was to discontinued." Patients were supposed to remain in the study. This reviewer re-analyzed relapse rates based on patient's endoscopy data without using "LOCF" method.

Protocol NRRQ
Summary of GERD Relapse Rate
Reviewer's Endoscopy Analysis

Week	Rab 10 mg	Rab 20 mg	Ome 20 mg	P-value Rab 10 mg vs. Ome 20 mg	P-value Rab 20 mg vs. Ome 20 mg	P-value Rab 10 mg vs. Rab 20 mg
13	1/76 (1%)	2/74 (3%)	1/79 (1%)	1.000	0.610	0.617
26	1/71 (1%)	2/68 (3%)	0/74 (0%)	0.490	0.228	0.614
52	4/72 (6%)	0/68 (0%)	4/72 (6%)	1.000	0.120	0.120

P-value was obtained using Fisher's Exact test.
The table was compiled by this reviewer

As seen from the table above, there were no treatment differences at Weeks 13 and 26. Lower rate of relapse was observed at Week 52 in the rabeprazole 20 mg group as compared with either the rabeprazole 10 mg group or the omeprazole 20 mg group.

3.1.2 Comparison between Rabeprazole and Omeprazole

This study was designed as an "equivalence" trial to show that rabeprazole 10 mg and rabeprazole 20 mg were comparable to omeprazole in terms of GERD relapse rate at Month 6. In the protocol, it was assumed relapse rates for both rabeprazole and omeprazole after six months was 20%. The delta to "rule out" a difference was specified in the protocol as 18%. However, the results from this study turned out the relapse rates at week 26 ranged from 1% to 4%, which was much smaller than 20% specified in the protocol. So, the delta of 18% specified in the protocol seems too large. The sample size seems to be too small if it was assumed relapse rates were about 5% or 10% and the delta was 10%.

Therefore, there was a design problem. The selection of delta and the expected relapse rate for both test drug and comparator seem to have little scientific rationale.

3.1.3 Relapse Rate by Patient Group

The patients who enrolled in this GERD maintenance trial were came from two groups of patients: "Rollover" and "Starter." The "Rollover" group constituted those patients who received rabeprazole sodium or omeprazole and whose GERD was healed during the acute trial NRRP. 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.

The sponsor did not provide sufficient information to link the acute treatment to maintenance treatment. Particularly, for "Starter" group of patients, the sponsor did not provide the treatment with which patient was treated and healed successfully before entry

into the maintenance study. The number of the patients in "Starter" group was about the same as the number of the patients in "Rollover" group.

To evaluate the impact of patient group on relapse, this reviewer re-analyzed the relapse rates at Week 52 using the Mantel-Haenszel method adjusting for patient group. The results are given below.

Protocol NRRQ
Relapse Rate at Week 52 by Patient Categories

Patient Group	Rab 10 mg	Rab 20 mg	Ome 20 mg	P-value* Rab 10 mg vs. Ome 20 mg	P-value*[1] Rab 20 mg vs. Ome 20 mg	P-value*[2] Rab 10 mg vs. Rab 20 mg
Rollover	3/40 (8%)	0/41 (0%)	2/40 (5%)	0.990	0.802	0.763
Starter	1/42 (2%)	3/37 (8%)	2/43 (5%)			

*P-value was obtained by this reviewer using the Mantel-Haenszel method adjusting for patients' groups.
This table was compiled by this reviewer.
[1] p=0.116 for Breslow-Day statistics for testing interaction between treatment and patients' category.
[2] p=0.034 for Breslow-Day statistics for testing interaction between treatment and patients' category.

The data suggested no significant effect of patient group on relapse (p=0.780). But, interaction between treatment and patient group was slightly significant (p=0.103). As seen from the table above, there were no statistically significant differences among treatment groups after adjusting for patient groups. In the pairwise comparisons, significant interactions between patient group and treatment were observed for the comparisons between rabeprazole 20 mg and omeprazole 20 mg and between rabeprazole 20 mg and omeprazole 20 mg.

3.1.4 Relapse Rate by Acute Treatment Assignment for "Rollover" Group

There was a slightly disproportionate acute treatment for treatment assignment for the "Rollover" group of patients (p=0.151). To evaluate the impact of this imbalance in the acute treatment for "Rollover" group of patients, this reviewer re-analyzed the relapse rates at Week 52 using the Mantel-Haenszel method adjusting for acute treatment for "Rollover" group of patients. The results are given below.

Protocol NRRQ
Relapse Rate at Week 52 by Acute Treatment for "Rollover" Patients

Acute Treatment	Rab 10 mg	Rab 20 mg	Ome 20 mg	P-value*[1] Rab 10 mg vs. Ome 20 mg	P-value* Rab 20 mg vs. Ome 20 mg	P-value* Rab 10 mg vs. Rab 20 mg
Rabeprazole	2/15 (13%)	0/24 (0%)	0/19 (0%)	0.592	0.228	0.051
Omeprazole	1/25 (4%)	0/17 (0%)	2/24 (8%)			

*P-value was obtained by this reviewer using the Mantel-Haenszel method adjust
This table was compiled by this reviewer.
[1] p=0.093 for Breslow-Day statistics for testing interaction between treatment and acute treatment.

The data suggested no significant effect of acute treatment on relapse for "Rollover" group of patients (p=0.994). But, the interaction between treatment and acute treatment was significant (Breslow-Day p=0.092). As seen from the table above, for "Rollover" group of patients, there was no statistically significant difference between rabeprazole 20 mg and omeprazole 20 mg and between rabeprazole 10 mg and omeprazole 20 mg after adjusting for acute treatment for "Rollover" group of patients. The difference between rabeprazole 10 mg and rabeprazole 20 mg almost reached statistical significance (p=0.051).

3.1.5 Relapse Rate by Week of Acute Healing for "Rollover" Patients

To evaluate the impact of the week of acute healing on relapse rate for "Rollover" group of patients, this reviewer re-analyzed the relapse rates at Week 52 using the Mantel-Haenszel method adjusting for week of acute healing for "Rollover" group of patients. The results are given below.

Protocol NRRQ
Relapse Rate at Week 52 by Week of Acute Healing
"Rollover" Group of Patients

Week of Acute Healing	Rab 10 mg	Rab 20 mg	Ome 20 mg	P-value* Rab 10 mg vs. Ome 20 mg	P-value* Rab 20 mg vs. Ome 20 mg	P-value* Rab 10 mg vs. Rab 20 mg
4	2/33 (6%)	0/38 (0%)	2/39 (5%)	0.626	0.160	0.102
8	1/7 (14%)	0/3 (0%)	0/4 (0%)			

*P-value was obtained by this reviewer using the Mantel-Haenszel method adjusting for week of acute healing..
This table was complied by this reviewer.

The data suggested no significant effect of week of acute healing on relapse for "Rollover" group of patients (p=0.703). As seen from the table above, for "Rollover" group of patients, there were no statistically significant differences between rabeprazole 10 mg and omeprazole 20 mg and between rabeprazole 20 mg and omeprazole 20 mg. Lower relapse rate was observed in the rabeprazole 20 mg group as compared with the

rabeprazole 10 mg group. But, the difference did not reach statistical significance due to small sample size.

In summary, for "Rollover" group of patients, the relapse rate for rabeprazole 20 mg was numerically smaller than that for rabeprazole 10 mg (3/40 (8%) vs. 0/41 (0%)). The difference did not reach statistical significance due to small sample size.

C. **Overall Summary and Recommendation**

For studies NRRK-Odd and NRRK-Even, sponsor's analysis results showed that for both ITT and ENDO analyses, the relapse rates were significantly higher in the placebo group than in either rabeprazole 10 mg or 20 mg group at all visit weeks

For study NRRK-Odd, it was also shown that there was a statistically significantly lower rate of relapse observed in the rabeprazole 20 mg group as compared with the rabeprazole 10 mg group at all visit weeks. For study NRRK-Even, a numerical trend in favor of the rabeprazole 20 mg group over the rabeprazole 10 mg group was observed at each visit week.

The combined results showed significant results in favor of the rabeprazole 20 mg over rabeprazole 10 mg.

Similar results were observed in both studies, separately and combined, by the more appropriate point prevalence analysis method.

Study NRRQ had design problem. The selection of the delta (18%) and the expected relapse rate (20%) for both test drug and the comparator and this sample size appeared to be faulty.

In conclusion, both rabeprazole 10 mg QAM and rabeprazole 20 mg QAM are effective in the maintenance treatment for healed GERD. The equivalence between rabeprazole and omeprazole in Study NRRQ cannot be concluded on the basis of the efficacy evidence provided.

/S/

Milton C, Fan, Ph.D.
Mathematical Statistician

This review consists of 27 pages of text and 30 pages of tables.

Concur: Dr. Sankoh /S/ 4-9-98
Dr. Welch /S/

cc:

Archival NDA 20-973
HFD-180
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres
HFD-180/Dr. Senior
HFD-180/Dr. Prizont
HFD-180/Ms. Walsh
HFD-344/Dr. Barton
HFD-715/Dr. Nevius
HFD-715/Dr. Welch
HFD-715/Dr. Sarkoh
HFD-715/Dr. Fan
Dr. Fan/x73088/mcf/011/05/98

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Table 1 Summary of Demographic and Baseline Characteristics ---- Protocol NRRK-ODD

Characteristic	Placebo (N=70)	Rabeprazole 10 mg (N= 70)	Rabeprazole 20 mg (N=69)	Total (N =209)	Between Treatment p-value[a]
Sex					0.611
Male	39 (56%)	43 (61%)	44 (64%)	126 (60%)	
Female	31 (44%)	27 (39%)	25 (36%)	83 (40%)	
Race					0.392
Caucasian	64 (91%)	62 (89%)	56 (81%)	182 (87%)	
African	3 (4%)	5 (7%)	9 (13%)	17 (8%)	
Other	3 (4%)	3 (4%)	4 (6%)	10 (5%)	
Age (yr)					0.406
Mean	55.4	58.3	57.4	57.0	
S.D.	12.9	14.8	13.6	13.8	
Minimum	28	22	36	22	
Maximum	79	83	83	83	
Tobacco Consumption					0.955
No	61 (87%)	62 (89%)	60 (87%)	183 (88%)	
Yes	9 (13%)	8 (11%)	9 (13%)	26 (12%)	
Alcohol Consumption					0.686
No	55 (79%)	51 (73%)	50 (72%)	156 (75%)	
Yes	15 (21%)	19 (27%)	19 (28%)	53 (25%)	
Caffeine Consumption					0.522
No	18 (26%)	24 (34%)	20 (29%)	62 (30%)	
Yes	52 (74%)	46 (66%)	49 (71%)	147 (70%)	

Copied from Table NRRK-Odd 6.1, page 72 Vol. 192

[a] Treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square for categorical variables or using ANOVA (investigator and treatment effects) for continuous variables.

Table 1 Summary of Demographic and Baseline Characteristics — NRRK-ODD (continued)

Characteristic	Placebo (N=70)	Rabeprazole 10 mg (N= 70)	Rabeprazole 20 mg (N=69)	Total (N =209)	Between Treatment p-value[a]
Antacid Use					0.212
No	47 (67%)	56 (80%)	52 (75%)	155 (74%)	
Yes	22 (31%)	14 (20%)	16 (23%)	52 (25%)	
Missing	1 (1%)	0 (0%)	1 (1%)	2 (1%)	
Number of Doses of Antacid Used per Day (based on average of last three days)					0.258
n	69	70	68	207	
Mean	0.77	0.49	1.04	0.76	
S.D.	1.47	1.16	2.89	1.99	
Minimum	0	0	0	0	
Maximum	7	6	18	18	
Baseline Endoscopy Modified Hetzel-Dent Esophagitis Grade					0.034*
n	70	66	67	203	
0	44 (63%)	54 (82%)	53 (79%)	151(74%)	
1	26 (37%)	12 (18%)	14 (21%)	52 (26%)	
2_+[b]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Baseline GERD Heartburn Frequency Grade					0.040
n	70	66	67	203	
0=None	32 (46%)	42 (64%)	42 (63%)	116 (57%)	
1=Few	13 (19%)	13 (20%)	10 (15%)	36 (18%)	
2=Several	7 (10%)	4 (26%)	7 (10%)	18 (9%)	
3=Many	3 (4%)	2 (30%)	2 (3%)	7 (3%)	
4=Continual	14 (20%)	5 (8%)	6 (9%)	25 (12%)	
Missing	1 (1%)	0 (0%)	1 (1%)	2 (1%)	

Copied from Table NRRK-Odd 6.1, page 73, Vol. 192.

[a] Treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square for categorical variables or using ANOVA (investigator and treatment effects) for continuous variables.

[b] 2_+ combines Grade 2, 3, 4 and 5.

*p-value was obtained by this reviewer. The sponsor's reported p=0.107 was not correct.

Table 2 Kaplan-Meier Chance of GERD Relapse Over Time --- Protocol NRRK-ODD

Kaplan-Meier Chance of GERD Relapse Over Time

	Rabeprazole 10 mg QAM	Rabeprazole 20 mg QAM	Placebo QAM
Total Number of Patients	66	67	70
Total Number of Patients with Relapse	18	7	50
Total Number of Patients Censored	48	60	20
Mean Time to Relapse (Days)	285.7	339.1	132.8
Kaplan-Meier Probability at Day 365[a]	30%	12%	76%
Rabeprazole 10 mg vs Placebo			
DF=1			
Chi-Square *= 36.172			
p-value=<0.0001			
Rabeprazole 20 mg vs Placebo			
DF=1			
Chi-Square *= 56.681			
p-value=<0.0001			
Rabeprazole 10 mg vs 20 mg			
DF=1			
Chi-Square *= 5.814			
p-value=0.0159			

[a] The corresponding probabilities of remaining healed are 70% for rabeprazole sodium 10 mg, 88% for rabeprazole sodium 20 mg, and 24% for placebo-treated patients.

* Log-rank test for censored data; p-value adjusted for investigator.

Cross Reference: Table 3.4