was a 2-arm study including only 20 mg regimen for rabeprazole group. Patients who were healed at Visit 2 (Week 4) were not required to return for Visit 3 (Week 8) and were considered to have completed the study. The concern for possible relapses raised in study NRRI also holds here.

The study was designed to include approximately 310 patients divided into two treatment groups. This sample size would produce at least 80% power to detect a significant difference (α=0.05, two-tailed test) between rabeprazole and ranitidine, assuming 8-week healing response rates of 70% for rabeprazole and 54% for ranitidine.

2. Sponsor's Analysis

A total of 338 patients were enrolled (169 patients for rabeprazole and 169 for ranitidine). Of the 338 patients enrolled, 27 patients (8%) were discontinued from the study (15 in the rabeprazole group and 12 in the ranitidine group). Of these 27 patients, six patients in the rabeprazole group and two patients in the ranitidine group were discontinued from the study because of protocol violations; of these eight patients, patients ([31]-8211 and [31]-8213 reclassified to rabeprazole) were excluded from all efficacy analyses because of study medication crossover.

2.1 Treatment Group Comparability

The demographic and baseline characteristics of the two 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, endoscopy modified Hetzel-Dent esophagitis grade, and GERD heartburn frequency grade (See Attachment Table 8).

2.2 Sponsor's Analysis of Primary Endpoint

The primary endpoint was the GERD healing rate at Week 8. The results for the ITT and ENDO analyses are shown in the tables below.

Protocol NRRJ
Summary of GERD Healing Rates
ITT Analysis

Analysis	Week	Treatment	Healing Rate	(Rab-Ran) %	vs. Ranidine p-value
ITT	4	Rab 20 mg	98/167 (59%)	23	<0.001
		Ran 150 mg	60/169 (36%)		
	8	Rab 20 mg	146/167 (87%)	21	<0.001
		Ran 150 mg	112/169 (66%)		

Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square statistics.
Copied from Table NRRJ.6.2, page 70, vol. 164

ENDO Analysis

Analysis	Week	Treatment	Healing Rate	(Rab-Ran) %	vs. Ranitidne p-value
ENDO	4	Rab 20 mg	98/163 (60%)	23	<0.001
		Ran 150 mg	60/162 (37%)		
	8	Rab 20 mg	146/158 (92%)	21	<0.001
		Ran 150 mg	112/158 (71%)		

Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square statistics.
Copied from Table NRRJ.6.2, page 70, vol. 164

As seen from the tables above, at both Weeks 4 and 8, the healing rates were significantly higher in the rabeprazole group than in the ranitidine in both ITT and ENDO analyses.

2.3 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.

The number and percentage of patients with improvement and complete resolution in GERD heartburn frequency at Weeks 4 and 8 for the ITT analysis is given in Attachment Table 9.

As seen from Table 9 (attached), at both Weeks 4 and 8, the improvement rates were significantly higher in the rabeprazole group than in the ranitidine group. At both Weeks 4 and 8, the complete resolution rates were significantly higher in the rabeprazole group than in the ranitidine group.

The number and percentage of patients with improvement and complete resolution in GERD daytime and nighttime heartburn severity at Weeks 4 and 8 for the ITT analysis is given in Attachment Tables 10 and 11, respectively.

As seen from Tables 10 and 11 (attached), there were no significant differences between the two treatment groups in the proportion of patients with improvement in GERD daytime and nighttime heartburn severity, respectively at either Week 4 or Week 8. At both Weeks 4 and 8, the proportion of patients with complete resolution in GERD daytime and nighttime heartburn severity, respectively was significantly higher in the rabeprazole group than in the ranitidine group.

The number and percentage of patients who had improvement and normalization of overall well-being at Weeks 4 and 8 for the ITT analysis is given in Attachment Table 12.

As seen from Table 12 (attached), at Week 4, the improvement rates were significantly higher in the rabeprazole group than in the ranitidine group. At Week 8, the difference

proportion of patients with normalization in overall well-being was significantly higher in the rabeprazole group than in the ranitidine group.

The mean and mean change in antacid use from baseline during the study for the ITT analysis is given in Attachment Table 13.

As seen from Table 13 (attached), no significant differences were observed between the two treatment groups in the mean reduction in antacid consumption from baseline.

3. **Reviewer's Evaluation**

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

The sponsor's ITT analysis did not include all randomized patients. Two patients ([31]-8211 and [31]-8213) randomized to receive rabeprazole treatment were excluded from the sponsor's ITT analysis because of study medication crossover.

Including these two patients as "no healed" in the ITT analysis would not affect the sponsor's results since p-values were extremely small (<0.001) and the sample size per treatment was large (n=169).

This study showed that rabeprazole 20 mg QAM was more effective than ranitidine 150 mg QID in terms of GERD healing at Week 8.

3.2 **Erosive Esophagitis Grade at Endoscopies**

Per medical officer's request, this reviewer tabulated erosive esophagitis grade at Weeks 4 and 8 by baseline esophagitis grade for each treatment group. The results are given in Table 14. This reviewer also performed treatment comparisons using Mantel-Haenszel test for erosive esophagitis grade at Weeks 4 and 8 adjusted for baseline esophagitis grade.

In terms of erosive esophagitis at both Weeks 4 and 8, all three rabeprazole groups were significantly higher than in the placebo ($p<0.001$) adjusted for baseline esophagitis grade.

III. **H4M-MC-NRRP**

1. **Description of Study**

This was a randomized, double-blind, parallel group, multicenter (27 investigators) active-controlled study. The objective of this study was to compare rabeprazole 20 mg once daily in the morning (QAM) with omeprazole 20 mg QAM in the treatment of patients with erosive or ulcerative gastroesophageal reflux disease (GERD).

The study design of this study was similar to that of study NRRI. The main differences were that this study was an active-controlled instead of placebo controlled. This study was a 2-arm study including only 20 mg regimen for rabeprazole group.

Although not specified in the protocol, patients who were healed at Week 4 were considered to have completed the study. The concern for relapse raised in the previous two studies also holds here.

The study was designed to include approximately 200 patients divided into two treatment groups. This sample size would provide at least 80% power (according to the sponsor) to "rule out" a difference of at least 15% between rabeprazole and omeprazole, assuming 8-week healing response rates of 84% for both rabeprazole and omeprazole.

2. Sponsor's Analysis

A total of 202 patients were enrolled (100 patients for rabeprazole and 102 for omeprazole). Of the 202 patients enrolled, 10 patients (5%) were discontinued from the study (5 in the rabeprazole group and 5 in the omeprazole group). Of 10 patients, two patients in the rabeprazole group and two patients in the omeprazole group were discontinued from the study because of protocol violations.

2.1 Treatment Group Comparability

The two treatment groups were comparable in all demographic and baseline characteristics except for gender and alcohol consumption (see Attachment Table 15).

There was significant treatment difference for gender; more males and fewer females in the omeprazole group than in the rabeprazole group. There was significant treatment difference for alcohol consumption; more patients in the omeprazole group consumed alcohol than in the rabeprazole group (68% vs. 51%).

2.2 Sponsor's Analysis of Primary Endpoint

The primary endpoint was the GERD healing rate at Week 8. The results for the ITT and ENDO analyses are shown in the tables below.

Protocol NRRP
Summary of GERD Healing Rates
ITT Analysis

Analysis	Week	Treatment	Healing Rate	(Rab-Ome) %	vs. Omeprazole p-value
ITT	4	Rab 20 mg	81/100 (81%)	0	0.957
		Ome 20 mg	83/102 (81%)		
	8	Rab 20 mg	92/100 (92%)	-2	0.557
		Ome 20 mg	96/102 (94%)		

Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square statistics.
Copied from Table NRRP.6.2, page 70, vol. 187

ENDO Analysis

Analysis	Week	Treatment	Healing Rate	(Rab-Ome) %	vs. Ranitidne p-value
ENDO	4	Rab 20 mg	81/99 (82%)	-1	0.884
		Ome 20 mg	83/100 (83%)		
	8	Rab 20 mg	92/97 (95%)	-1	0.701
		Ome 20 mg	96/100 (96%)		

Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square statistics.
Copied from Table NRRJ.6.2, page 70, vol. 187

As seen from the tables above, at both Weeks 4 and 8, there were no significant differences in rates between the two treatment groups in both ITT and ENDO analyses.

2.3 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.

The number and percentage of patients with improvement and complete resolution in GERD heartburn frequency at Weeks 4 and 8 for the ITT analysis is given in Attachment Table 16.

As seen from Table 16 (attached), the proportions of patients with improvement and the proportions of patients with complete resolution of GERD heartburn frequency were comparable for the two treatment groups at both Weeks 4 and 8. There were no significant differences between rabeprazole and omeprazole groups.

The number and percentage of patients with improvement and complete resolution in GERD daytime and nighttime heartburn severity at Weeks 4 and 8 for the ITT analysis is given in Attachment Tables 17 and 18, respectively.

As seen from Tables 17 and 18 (attached), there were no significant differences between the two treatment groups in the proportions of patients with improvement and with complete resolution in GERD daytime heartburn severity and in the proportions of patients with improvement and with complete resolution in GERD nighttime heartburn severity, respectively at either Week 4 or Week 8.

The number and percentage of patients who had improvement and normalization of overall well-being at Weeks 4 and 8 for the ITT analysis is given in Attachment Table 19.

As seen from Table 19 (attached), the two treatment groups were comparable in the proportions of patients with improvement and normalization in overall well-being at Weeks 4 and 8. There were no significant differences between the rabeprazole and omeprazole treatment groups.

The mean and mean change in antacid use from baseline during the study for the ITT analysis is given in Attachment Table 20.

As seen from Table 20 (attached), no significant differences were observed between the two treatment groups in the mean reduction in antacid consumption from baseline.

3. Reviewer's Evaluation

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

There was significant imbalance in gender; more males and fewer females in the omeprazole group than in the rabeprazole group (p=0.006). This reviewer re-analyzed the GERD healing rates by adjusting gender using Mantel-Haenszel method. The results showed that there was no gender effect (Breslow and Day p=0.519). This imbalance had no significant impact on the sponsor's finding.

This study was designed as an "equivalence" trial to show rabeprazole was comparable to omeprazole in terms of GERD healing rate at Week 8. The GERD healing rate by treatment groups and 95% confidence interval for the treatment differences are given below.

Protocol NRRP
95% Confidence Interval for Treatment Difference
for GERD Healing Rate at Week 8

Analysis	Rab 20 mg QAM	Ome 20 mg QAM	(Rab – Ome) %	95% C. I.
ITT	92/100 (92%)	96/102 (94%)	-2	(-9.1%, 4.9%)
ENDO	92/97 (95%)	96/100 (96%)	-1	(-7.0%, 4.7%)

95% confidence interval was obtained by this reviewer.

As seen from the table above, the upper limit of 95% confidence interval for treatment difference between rabeprazole and omeprazole groups for GERD at Week 8 was less than 15% (pre-specified in protocol) for the ITT and ENDO analyses. The lower limit of 95% confidence interval for treatment difference between rabeprazole and omeprazole groups for GERD healing at Week 8 was greater than -15% for both ITT and ENDO analyses. So, this study showed that rabeprazole 20 mg QAM was equivalent to omeprazole 20 mg QAM in terms of GERD healing at Week 8.

C. **Overall Summary and Recommendation**

In Study NRRI, the GERD healing rates at Weeks 4 and 8 were significantly higher in all rabeprazole groups (10 mg, 20 mg and 40 mg) than in the placebo group in both ITT and ENDO analyses. The rabeprazole 10 mg QAM might be the minimum effective dose for GERD healing at Week 8.

In Study NRRJ, the rabeprazole 20 mg QAM was significantly better than the ranitidine 150 mg QID in terms of GERD healing at Weeks 4 and 8 in both ITT and ENDO analyses.

In Study NRRP, it was shown that the rabeprazole 20 mg QAM was equivalent to the omeprazole 20 mg QAM in terms of GERD healing at Week 8 in both ITT and ENDO analyses.

In conclusion, the rabeprazole 10 mg QAM might be the minimum effective dose for GERD healing at Week 8. But, it was studied in one study (NRRI) only. The efficacy of rabeprazole 20 mg QAM for GERD healing at Week 8 is also supported in all three studies (NRRI, NRRJ, and NRRP) (for the primary endpoint).

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 14 pages of text and 23 pages of tables.

Concur: Dr. Sankoh /S/ 10/26/98
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. Sankoh
HFD-715/Dr. Fan
Dr. Fan/x73088/mcf/10/26/98

Table 1

Summary of Demographic and Baseline Characteristics ---- Protocol NRRI

Characteristic	Placebo (N=25)	Rabeprazole 10 mg (N= 27)	Rabeprazole 20 mg (N=25)	Rabeprazole 40 mg (N = 26)	Total (N=103)	Between Treatment p-value[a]
Sex						0.770
Male	19 (76%)	20 (74%)	17 (68%)	21 (81%)	77 (75%)	
Female	6 (24%)	7 (26%)	8 (32%)	5 (19%)	26 (25%)	
Race[b]						0.556
Caucasian	25 (100%)	27 (100%)	24 (96%)	25 (96%)	101 (98%)	
African Descent	0 (0%)	0 (0%%)	1 (4%)	1 (4%)	2 (2%)	
Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Age (yr)						0.623
Mean	49.5	52.3	47.1	49.5	49.6	
S.D.	11.8	15.5	13.1	15.8	14.1	
Minimum	21	24	28	20	20	
Maximum	75	77	71	71	77	
Tobacco Consumption						0.331
No	20 (80%)	24 (89%)	18 (72%)	23 (88%)	85(83%)	
Yes	5 (20%)	3 (11%)	7 (28%)	3 (12%)	18 (17%)	
Alcohol Consumption						0.288
No	17 (68%)	21 (78%)	18 (72%)	14 (54%)	70 (68%)	
Yes	8 (32%)	6 (22%)	7 (28%)	12 (46%)	33 (32%)	
Caffeine Consumption						0.291
No	2 (8%)	2 (7%)	3 (12%)	6 (23%)	13 (13%)	
Yes	23 (92%)	25 (93 %)	22 (88 %)	20 (77%)	90 (87%)	
Antacid Use						0.079
No	5 (20%)	7 (26%)	12 (48%)	5 (19%)	29 (28%)	
Yes	20 (80%)	20 (74%)	13 (52%)	21 (81%)	74 (72%)	
Number of Doses of Antacid Used per Day (based on average of last three days)						0.685
Mean	3.3	3.1	2.6	2.2	2.8	
S.D.	3.5	4.8	3.3	1.5	3.4	
Minimum	0	0	0	0	0	
Maximum	12	25	10	5	25	

Copied from Table NRRI 6.1, page 52, Vol. 176

[a]P-values were obtained by this reviewer using Mantel-Haenszel Chi-Square for endoscopy modified Hetzel-Dent esophagitis grade and gastric ulcer pain frequency grade, using anova for age and number of antacid used per day, and using Chi-Square test for other variables.

[b]Tabulated by this reviewer from sponsor's supplied dataset NRRIFDA.DAT.

Table 1 (continued)

Summary of Demographic and Baseline Characteristics ---- Protocol NRRI

Characteristic	Placebo (N=25)	Rabeprazole 10 mg (N= 27)	Rabeprazole 20 mg (N=25)	Rabeprazole 40 mg (N = 26)	Total (N=103)	Between Treatment p-value[a]
Endoscopy Modified Hetzel-Dent Esophagitis Grade[c]						0.360
0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
2	12 (48%)	14 (52%)	17 (68%)	14 (54%)	57 (55%)	
3	9 (36%)	12 (44%)	6 (24%)	10 (38%)	37 (36%)	
4	4 (16%)	1 (4%)	2 (8%)	2 (8%)	9 (9%)	
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
GERD Heartburn Frequency Grade						0.662
0=None	0 (0%)	1 (4%)	0 (0%)	0 (0%)	1 (1%)	
1=Few	1 (4%)	0 (0%)	2 (9%)	2 (8%)	5 (5%)	
2=Several	4 (16%)	7 (26%)	5 (20%)	4 (15%)	20 (19%)	
3=Many	5 (20%)	8 (30%)	6 (24%)	6 (23%)	25 (24%)	
4=Continual	15 (60%)	11 (41%)	12 (48%)	14 (54%)	52 (50%)	

Copied from Table NRRI 6.1, page 53, Vol. 176

[a]P-values were obtained by this reviewer using Mantel-Haenszel Chi-Square for endoscopy modified Hetzel-Dent esophagitis grade [redacted] pain frequency grade, using anova for age and number of antacid used per day, and using Chi-Square test for other variables.

[b]Tabultated by this reviewer from sponsor's supplied dataset NRRCFDA.DAT.

[c]0=Normal mucosa;1=No macroscopic erosions, but presence of erythema, hperemia, and/or friability of the esophageal mucosa; 2=Superficial ulceration or erosions involving < 10% of the mucosal surface of the last 5 cm of the esophageal squamous mucosa; 3= Superficial ulceration or erosions involving 10% but <50% of the mucosal surface of the last 5 cm of the esophageal squamous mucosa; 4=Deep ulceration anywhere in the esophagus or confluent erosion of > 50% of the mucosal surface of the last 5 cm of the esophageal squamous mucosa; 5=Stricture.

Table 2

Summary of Improvement Rates in GERD Heartburn Frequency - Intent to Treat[a] ---- Protocol NRRI

		Rabeprazole			P-Value[b] Placebo vs Rabeprazole			Rabeprazole 10 mg vs		Rabeprazole 20 mg vs
	Placebo	10 mg	20 mg	40 mg	10 mg	20 mg	40 mg	20 mg	40 mg	40 mg
Improvement[c]										
Week 4	10/25 (40%)	23/26 (88%)	20/26 (80%)	23/26 (88%)	< 0.001	0 .005	< 0.001	0.442	0.936	0.414
Week 8	12/25 (48%)	24/26 (92%)	20/25 (80%)	25/26 (96%)	<0 .001	0 .025	<0 .001	0.219	0.458	0.072
Complete Resolution[d]										
Week 4	1/25 (4%)	13/26 (50%)	7/25 (28%)	14/26 (54%)	<0.001	0.026	<0.001	0 .089	0.745	0.077
Week 8	1/25 (4%)	15/26 (58%)	10/25 (40%)	19/26 (73%)	< 0.001	0.003	< 0.001	0.175	0.249	0.018

Copied from Table NRRI 6.3, page 57, Vol. 176.

[a]Patient with normal (grade=0) or missing baseline values were excluded from the analysis.

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

[c] Improvement: Frequency evaluation grade lower than baseline evaluation.

[d] Complete resolution: Frequency evaluation grade of 0 (none).

Table 3

Summary of Improvement Rates in GERD Daytime Heartburn Severity - Intent to Treat[a] ---- Protocol NRRI

					P-Value[b]					
		Rabeprazole			Placebo vs Rabeprazole			Rabeprazole 10 mg vs		Rabeprazole 20 mg vs
	Placebo	10 mg	20 mg	40 mg	10 mg	20 mg	40 mg	20 mg	40 mg	40 mg
Improvement[c]										
Week 4	15/23 (65%)	23/23 (100%)	17/19 (89%)	22/22 (100%)	0.003	0.099	0.004	0.225	-	0.225
Week 8	13/23 (57%)	23/23 (100%)	17/19 (89%)	21/22 (95%)	<0 .001	0 .034	0 .002	0.225	0.157	0.695
Complete Resolution[d]										
Week 2	8/23 (35%)	20/23 (87%)	14/19 (74%)	18/22 (82%)	<0.001	0.022	0.004	0 .254	0.770	0.499
Week 8	10/23 (43%)	21/23 (91%)	14/19 (74%)	19/22 (86%)	< 0.001	0.036	0.004	0.099	0.575	0.408

Copied from Table NRRI 6.4, page 58, Vol. 176.

[a]Patient with normal (grade=0) or missing baseline values were excluded from the analysis.

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

[c] Improvement: Severity evaluation grade lower than baseline evaluation.

[d] Complete resolution: Severity evaluation grade of 0 (none).

Table 4

Summary of Improvement Rates in GERD Nighttime Heartburn Severity - Intent to Treat[a] ---- Protocol NRRI

					P-Value[b]					
		Rabeprazole			Placebo vs Rabeprazole			Rabeprazole 10 mg vs		Rabeprazole 20 mg vs
	Placebo	10 mg	20 mg	40 mg	10 mg	20 mg	40 mg	20 mg	40 mg	40 mg
Improvement[c]										
Week 4	17/23 (74%)	24/25 (96%)	16/22 (73%)	22/23 (96%)	0.032	0.920	0.047	0.030	0.945	0.088
Week 8	18/23 (78%)	23/25 (92%)	17/22 (77%)	23/23 (100%)	0.178	0.972	0.022	0.169	0.340	0.025
Complete Resolution[d]										
Week 4	11/23 (48%)	21/25 (84%)	15/22 (68%)	21/23 (91%)	0.015	0.198	0.004	0.155	0.343	0.106
Week 8	10/23 (43%)	20/25 (80%)	15/22 (68%)	22/23 (96%)	0.015	0.074	<0.001	0.335	0.136	0.019

Copied from Table NRRI 6.5, page 59, Vol. 176.

[a]Patient with normal (grade=0) or missing baseline values were excluded from the analysis.

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

[c] Improvement: Severity evaluation grade lower than baseline evaluation.

[d] Complete resolution: Severity evaluation grade of 0 (none).

Table 5

Summary of the Patients' Overall Ratings of Well-Being Improvement Rates - Intent to Treat[a]
----Protocol NRRI

					P-Value[b]					
		Rabeprazole			Placebo vs Rabeprazole			Rabeprazole 10 mg vs		Rabeprazole 20 mg vs
	Placebo	10 mg	20 mg	40 mg	10 mg	20 mg	40 mg	20 mg	40 mg	40 mg
Improvement[c]										
Week 4	7/21 (33%)	17/24 (71%)	15/25 (60%)	16/25 (64%)	0.040	0 .056	0.057	0.516	0.673	0.737
Week 8	7/21 (33%)	16/24 (67%)	16/25 (64%)	16/25 (64%)	0 .051	0 .026	0 .029	0.969	1.000	0.968
Normalization[d]										
Week 4	5/21 (24%)	10/24 (42%)	11/25 (44%)	9/25 (36%)	0.200	0.163	0.344	0.938	0.728	0.611
Week 8	4/21 (19%)	9/24 (38%)	11/25 (44%)	8/25 (32%)	0.210	0.092	0.324	0.739	0.796	0.448

Copied from Table NRRC 6.6, page 60, Vol. 170.

Patient with normal (grade=0) or missing baseline values were excluded from the analysis.

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

[c] Improvement: Well-being exaltation grate lower than baseline evaluation.

[d] Normalization: Well-being evaluation grade of 0 (very good).

Table 6

Summary of Antacid Use (Doses/day) – Intent to Treat ---- Protocol NRRI

					P-Value[b]					
		Rabeprazole			Placebo vs Rabeprazole			Rabeprazole 10 mg vs		Rabeprazole 20 mg vs
	Placebo	10 mg	20 mg	40 mg	10 mg	20 mg	40 mg	20 mg	40 mg	40 mg
Baseline										
N	25	27	25	26						
Mean	3.28	3.15	2.64	2.23						
S.D.	3.47	4.79	3.26	1.48						
Range	0-12.0	0-25.0	0-10.0	0-5.0						
Week 4										
N	25	27	25	26						
Mean	1.69	0.80	0.55	0.33						
S.D.	1.69	1.30	0.97	0.81						
Range	0-6.0	0-4.0	0-3.4	0-4.0						
Week 8										
N	25	27	25	26						
Mean	1.93	0.56	0.46	0.32						
S.D.	1.73	0.96	0.86	0.82						
Range	0-6.1	0-4.0	0-3.0	0-4.0						
Week 4 Change from Baseline										
N	25	27	25	26						
Mean	-1.59	-2.35	-2.09	-1.90	0.007	0.002	<0.001	0.576	0.286	0.619
S.E.	0.42	0.95	0.60	0.29						
Week 8 Change from Baseline										
N	25	27	25	26						
Mean	-1.35	-2.59	-2.18	-1.91	<0.001	<0.001	<0.001	0.918	0.685	0.767
S.E.	0.40	0.94	0.62	0.30						

Copied from Table NRRI 6.7, page 62, Vol. 176

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

Note: At baseline, the mean number of doses of antacid used per day is based on the number of doses taken for the previous 3 days. At Weeks 2 ant 4, the mean number of doses of antacid used per day is based on the total number of doses taken since the previous visit divided by the total number of days elapsed.

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Table 7

Summary of Esophagitis Grade at Weeks 4 and 8 by Baseline Esophagitis Grade
---- Protocol NRRI

Treatment	Baseline Grade	n	Esophagitis Grade at Week 4 0	1	2	3	4
Rab 10	2	14	10 (71%)	1 (7%)	3 (21%)	0 (0%)	0 (0%)
	3	12	5 (42%)	1 (8%)	6 (50%)	0 (0%)	0 (0%)
	4	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Rab 20	2	16	9 (56%)	2 (13%)	5 (31%)	0 (0%)	0 (0%)
	3	6	1 (17%)	2 (33%)	3 (50%)	0 (0%)	0 (0%)
	4	2	0 (0%)	0 (0%)	2 (100%)	0 (0%)	0 (0%)
Rab 40	2	14	10 (71%)	0 (0%)	4 (29%)	0 (0%)	0 (0%)
	3	10	3 (30%)	1 (10%)	6 (60%)	0 (0%)	0 (0%)
	4	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Placebo	2	11	0 (0%)	0 (0%)	10 (91%)	1 (9%)	0 (0%)
	3	9	0 (0%)	0 (0%)	6 (67%)	3 (33%)	0 (0%)
	4	4	0 (0%)	0 (0%)	0 (0%)	2 (50%)	2 (50%)

Treatment	Baseline Grade	n	Esophagitis Grade at Week 8 0	1	2	3	4
Rab 10	2	5	5 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	3	8	5 (63%)	2 (25%)	1 (13%)	0 (0%)	0 (0%)
	4	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Rab 20	2	8	6 (75%)	1 (13%)	1 (13%)	0 (0%)	0 (0%)
	3	5	3 (60%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)
	4	2	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rab 40	2	4	1 (25%)	2 (50%)	1 (25%)	0 (0%)	0 (0%)
	3	7	5 (71%)	1 (14%)	1 (14%)	0 (0%)	0 (0%)
	4	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Placebo	2	11	0 (0%)	1 (9%)	9 (82%)	1 (9%)	0 (0%)
	3	7	0 (0%)	2 (29%)	3 (43%)	2 (29%)	0 (0%)
	4	2	0 (0%)	0 (0%)	0 (0%)	1 (50%)	1 (50%)

Tables were compiled by the reviewer.