Table 19 Summary of Demographic and Baseline Characteristics ---- Protocol NRRQ

Characteristic	Omeprazole (N=83)	Rabeprazole 10 mg (N= 82)	Rabeprazole 20 mg (N=78)	Total (N =243)	Between Treatment p-value[a]
Sex					0.637
Male	52 (63%)	56(68%)	54 (69%)	162 (67%)	
Female	31 (37%)	26 (32%)	24 (31%)	81 (33%)	
Race					0.317
Caucasian	80 (96%)	79 (96%)	77 (99%)	236 (97%)	
African	0 (0%)	0 (0%)	1 (1%)	1 (<1%)	
Other	3 (4%)	3 (4%)	0 (0%)	6 (2%)	
Age (yr)					0.547
Mean	54.0	51.9	52.4	52.7	
S.D.	15.0	13.5	14.4	14.3	
Minimum	20	25	20	20	
Maximum	83	76	75	83	
Tobacco Consumption					0.785
No	63 (76%)	64 (78%)	63 (81%)	190 (78%)	
Yes	20 (24%)	18 (22%)	15 (19%)	53 (22%)	
Alcohol Consumption					0.730
No	38 (46%)	37 (45%)	41 (53%)	116 (48%)	
Yes	45 (54%)	45 (55%)	37 (47%)	127 (52%)	
Caffeine Consumption					0.132
No	2 (2%)	8 (10%)	7 (9%)	17 (7%)	
Yes	81 (98%)	74 (90%)	71 (91%)	226 (93%)	

Copied from Table NRRQ 6.1, page 71 Vol. 210

[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 19 Summary of Demographic and Baseline Characteristics ---- NRRQ (continued)

Characteristic	Omeprazole (N=83)	Rabeprazole 10 mg (N= 82)	Rabeprazole 20 mg (N=78)	Total (N =243)	Between Treatment p-value[a]
Antacid Use					0.589
No	73 (88%)	76 (93%)	71 (91%)	220 (91%)	
Yes	10 (12%)	6 (7%)	7 (9%)	23 (9%)	
Number of Doses of Antacid Used per Day (based on average of last three days)					0.231
Mean	0.31	0.11	0.23	0.22	
S.D.	0.987	0.445	0.772	0.770	
Minimum	0	0	0	0	
Maximum	6	3	4	6	
Baseline Endoscopy Modified Hetzel-Dent Esophagitis Grade					0.632
0	61 (73%)	63 (77%)	64 (82%)	188(77%)	
1	22 (27%)	18 (22%)	14 (18%)	54 (22%)	
2+[b]	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Missing	0 (0%)	1 (1%)	0 (0%)	1 (<1%)	
Baseline GERD Heartburn Frequency Grade					0.133
0=None	44 (53%)	45 (55%)	49 (63%)	138 (57%)	
1=Few	20 (24%)	17 (21%)	18 (23%)	55 (23%)	
2=Several	19 (23%)	19 (23%)	11 (14%)	49 (20%)	
3=Many	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
4=Continual	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Missing	0 (0%)	1 (0%)	0 (0%)	1 (<1%)	

Copied from Table NRRQ 6.1, page 72, Vol. 210.

[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.

Figure 21 Cumulative Proportion of Patients Who Remained Free of GERD Relapse --- Protocol NRRQ

Cumulative Proportion of Patients Who Remained Free of GERD Relapse

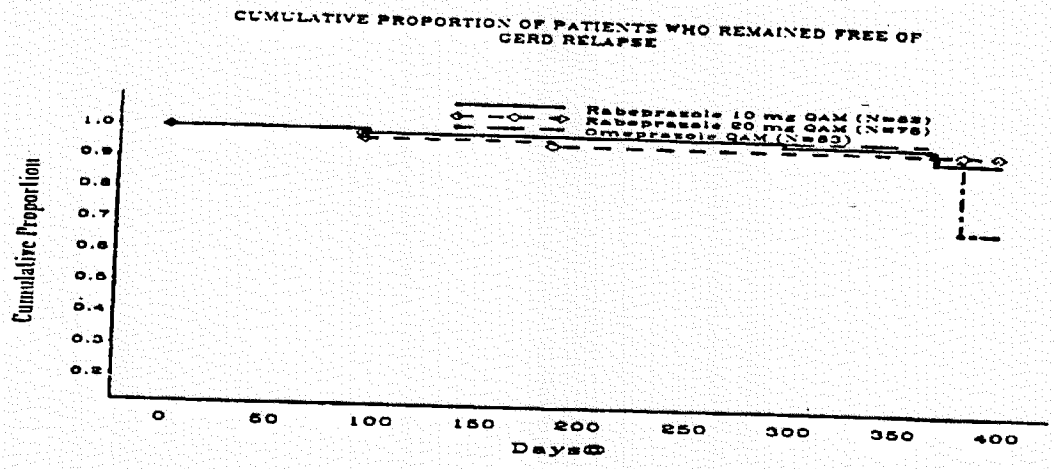

Table 22 Life Table Survival Estimates of Relapse --- Protocol NRRQ

Life Table Survival Estimates of Relapse
Pairwise Comparison
Rabeprazole Sodium 10 mg QAM vs. Rabeprazole Sodium 20 mg QAM

Interval (weeks) (Lower, Upper)		Number with Relapse	Number Censored	Effective Sample Size	Probability of No Relapse	Probability of Relapse
Rabeprazole Sodium 10 mg QAM (N=82)						
0	8	0	9	78	1.000	0.000
8	17	1	0	73	1.000	0.000
17	34	0	0	72	0.986	0.014
34	43	1	0	72	0.986	0.014
43	52	0	15	64	0.973	0.027
52		2	54	29	0.973	0.027
Rabeprazole Sodium 20 mg QAM (N=78)						
0	8	0	9	74	1.000	0.000
8	17	2	0	69	1.000	0.000
17	34	1	0	67	0.971	0.029
34	43	0	0	66	0.957	0.044
43	52	0	10	61	0.957	0.044
52		0	56	28	0.957	0.044
Omeprazole QAM (N=83)						
0	8	0	11	78	1.000	0.000
8	17	1	0	72	1.000	0.000
17	34	0	0	71	0.986	0.014
34	43	0	0	71	0.986	0.014
43	52	1	12	65	0.986	0.014
52		2	56	30	0.971	0.029

Life Table survival estimates extracted from Life-Test Model using Table method.
Cross Reference: Table 3.6

Comparison	Log rank p-value	Wilcoxon p-value
Rab 10 mg QAM vs Omeprazole QAM	0.9775	0.6972
Rab 20 mg QAM vs Omeprazole QAM	0.9051	0.7644
Rab 10 mg QAM vs Rab 20 mg QAM	0.7582	0.9487

Copied from Tables TRRK-Even 6.3.1 – 6.3.3.

Table 23 Summary of Relapse Rates for GERD Heartburn Frequency --- Protocol NRRQ

Summary of Relapse Rates for Heartburn Frequency

Week	Rabeprazole Sodium 10 mg QAM	Rabeprazole Sodium 20 mg QAM	Omeprazole QAM	p-value[a] Omeprazole vs. Rabeprazole Sodium 10 mg	20 mg	Rabeprazole Sodium 10 mg vs. 20 mg
4	13/62 (21%)	10/67 (15%)	15/64 (23%)	0.631	0.284	0.552
13	9/62 (15%)	6/67 (9%)	10/64 (16%)	0.922	0.266	0.405
26	10/62 (16%)	10/67 (15%)	14/64 (22%)	0.418	0.247	0.704
39	10/62 (16%)	10/67 (15%)	10/64 (16%)	0.937	0.763	0.759
52	11/62 (18%)	8/67 (12%)	11/64 (17%)	0.985	0.331	0.287

Relapse in Heartburn Frequency was defined as 2 (several), 3 (many), or 4 (continual); patients with baseline grades of 2 (several), 3 (many), or 4 (continual) were excluded from the analysis.

[a] Treatment p-value is adjusted for investigator and baseline value; obtained using the Cochran-Mantel-Haenszel statistic.

Cross Reference: Table 4.2

Table 24 Summary of Relapse Rates for GERD Daytime Heartburn --- Protocol NRRQ

Summary of Relapse Rates for Daytime Heartburn
Intent to Treat

Week	Rabeprazole Sodium 10 mg QAM	Rabeprazole Sodium 20 mg QAM	Omeprazole QAM	p-value[a] Omeprazole vs. Rabeprazole Sodium 10 mg	p-value[a] Omeprazole vs. Rabeprazole Sodium 20 mg	p-value[a] Rabeprazole Sodium 10 mg vs. 20 mg
4	1/69 (1%)	1/73 (1%)	2/70 (3%)	0.510	0.475	0.893
13	3/69 (4%)	1/73 (1%)	3/70 (4%)	0.974	0.243	0.294
26	5/69 (7%)	1/73 (1%)	3/70 (4%)	0.443	0.374	0.143
39	4/69 (6%)	2/73 (3%)	4/70 (6%)	0.946	0.342	0.634
52	5/69 (7%)	2/73 (3%)	4/70 (6%)	0.742	0.286	0.298

Relapse in Daytime Heartburn Severity was defined as 2 (moderate), 3 (severe), or 4 (terrible); patients with baseline grades of 2 (moderate), 3 (severe), or 4 (terrible) were excluded from the analysis.

[a] Pairwise treatment p-value is adjusted for investigator and baseline value; obtained using the Cochran-Mantel-Haenszel statistic.

Cross Reference: Table 5.2

Table 25 Summary of Relapse Rates for GERD Nighttime Heartburn --- Protocol NRRQ

Summary of Relapse Rates for Nighttime Heartburn
Intent to Treat

Week	Rabeprazole Sodium 10 mg QAM	Rabeprazole Sodium 20 mg QAM	Omeprazole QAM	p-value[a] Omeprazole vs. Rabeprazole Sodium 10 mg	p-value[a] Omeprazole vs. Rabeprazole Sodium 20 mg	p-value[a] Rabeprazole Sodium 10 mg vs. 20 mg
4	1/77 (1%)	2/74 (3%)	1/77 (1%)	1.000	0.466	0.387
13	4/77 (5%)	1/74 (1%)	2/77 (3%)	0.454	0.554	0.191
26	5/77 (6%)	3/74 (4%)	0/77 (0%)	0.026	0.126	0.597
39	5/77 (6%)	1/74 (1%)	2/77 (3%)	0.262	0.410	0.153
52	5/77 (6%)	1/74 (1%)	2/77 (3%)	0.201	0.693	0.165

Relapse in Nighttime Heartburn Severity was defined as 2 (moderate), 3 (severe), or 4 (terrible); patients with baseline grades of 2 (moderate), 3 (severe), or 4 (terrible) were excluded from the analysis.

[a] Pairwise treatment p-value is adjusted for investigator and baseline value; obtained using the Cochran-Mantel-Haenszel statistic.

Cross Reference: Table 6.2

Table 26 Summary of Relapse Rates in Patients' Overall Well-Being --- Protocol NRRQ

Summary of Relapse Rates in Patients' Overall Well-Being
Intent to Treat

Week	Rabeprazole Sodium 10 mg QAM	Rabeprazole Sodium 20 mg QAM	Omeprazole QAM	p-value[a] Omeprazole vs. Rabeprazole Sodium 10 mg	p-value[a] Omeprazole vs. Rabeprazole Sodium 20 mg	p-value[a] Rabeprazole Sodium 10 mg vs. 20 mg
4	4/61 (7%)	2/69 (3%)	5/73 (7%)	0.804	0.247	0.361
13	3/61 (5%)	2/69 (3%)	7/73 (10%)	0.261	0.063	0.638
26	2/61 (3%)	4/69 (6%)	6/73 (8%)	0.375	0.468	0.809
39	4/61 (7%)	8/69 (12%)	6/73 (8%)	0.935	0.757	0.632
52	4/61 (7%)	3/69 (4%)	6/73 (8%)	0.860	0.231	0.376

Relapse in patients' Overall Physical Well-Being was defined as 2 (fair), 3 (poor), or 4 (very poor); patients with baseline grades of 2 (fair), 3 (poor), or 4 (very poor) were excluded from the analysis.

[a] Pairwise treatment p-value is adjusted for investigator and baseline value; obtained using the Cochran-Mantel-Haenszel statistic.

Cross Reference: Table 7.2

Table 27 Summary of Antacid Use (Doses per Day) --- Protocol NRRQ

Summary of Antacid Use (Doses per Day)

Week	Rabeprazole Sodium 10 mg QAM	Rabeprazole Sodium 20 mg QAM	Omeprazole QAM	p-value[a] Omeprazole vs. Rabeprazole Sodium 10 mg	p-value[a] Omeprazole vs. Rabeprazole Sodium 20 mg	p-value[a] Rabeprazole Sodium 10 mg vs. 20 mg
Week 4 Change from Baseline						
n	82	75	82			
Mean	-0.06	-0.14	-0.25	0.927	0.917	0.989
S.E.	0.049	0.070	0.109			
Week 13 Change from Baseline						
n	78	76	79			
Mean	-0.04	-0.19	-0.28	0.369	0.596	0.716
S.E.	0.050	0.082	0.112			
Week 26 Change from Baseline						
n	75	72	74			
Mean	-0.06	-0.08	-0.26	0.825	0.279	0.387
S.E.	0.050	0.130	0.123			
Week 39 Change from Baseline						
n	66	64	72			
Mean	-0.04	-0.20	-0.31	0.153	0.166	0.973
S.E.	0.061	0.100	0.120			
Week 52 Change from Baseline						
n	73	67	71			
Mean	-0.07	-0.22	-0.27	0.728	0.762	0.970
S.E.	0.050	0.094	0.097			

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

Cross Reference: Table 9 and Patient Data Listing 8

STATISTICAL REVIEW AND EVALUATION — NDA

NDA #: 20-973

Date: OCT 26 1998

Drug Class: 1S

Applicant: Eisai Incorporated

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

Indication: Healing of GERD
(Separate reviews for treatment of [redacted] DU, GERD maintenance)

Documents Reviewed: 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 (12mos), 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: Healing rate, Intent-to-Treat

A. Background

Rabeprazole, a substituted benzimidazole proton pump inhibitor (PPI) is structurally and pharmaceutically similar to the marketed compound omeprazole (approved for [redacted] 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, [redacted] 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:

[redacted]

2). the healing of duodenal ulcers (DU)

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 the treatment of pathological hypersecretory disorder including Zollinger-Ellison syndrome.

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

B. **Healing of GERD**

The sponsor has submitted three clinical trials (H4M-MC-NRRI, H4M-MC-NRRJ, H4M-MC-NRRP) in support of the proposed claim: for treatment of GERD.

Outpatients with a history of GERD over a minimum period of 3 months prior to enrolling in the study were enrolled in the study. Endosocopic evidence of erosive or ulcerative esophagitis (Grade 2 or above) as defined using the modified Hezel-Dent grading scale.

Duration of the entire study was approximately 8 weeks. A maximum of three visits, at Weeks 0 (baseline; Day -1), 4 (28 ± 3 days), and 8 (56± 3 days), was scheduled. Efficacy and safety were evaluated at all follow-up visits.

Among three studies, two were North American trials (H4M-MC-NRRI, H4M-MC-NRRJ) and one was a European trial (H4M-MC-NRRP). One was a placebo-controlled trail (NRRI). The other two were active-controlled trials. In NRRJ study ranitidine 150 mg QID was used as a control. In NRRP study omeprazole 20 mg QAM was used as a control.

I. **H4M-MC-NRRI**

1. **Description of Study**

This was a randomized, double-blind, placebo-controlled, parallel-group, dosing ranging, multicenter (20 investigators) study. The objective of this study was to compare the efficacy of rabeprazole doses 10 mg, 20 mg, and 40 mg once daily in the morning (QAM) with each other and with placebo in the treatment of patients with erosive or ulcerative gastroesophageal reflux disease (GERD).

The inclusion criteria were: 1) outpatients with a history of GERD over a period 3 months prior to enrolling in this study, and 2) endoscopic evidence of erosive or ulcerative esophagitis.

Each patient was randomly assigned to one of four treatment groups: 1) rabeprazole 10 mg QAM, 2) rabeprazole 20 mg QAM, 3) rabeprazole 40 mg QAM or 4) placebo QAM.

Although not specified in the protocol, patients who were healed at Week 4 were considered to have completed the study, and treatment drug was discontinued for these patients. Patients were not reevaluated at Week 8 for possible relapses.

The primary efficacy variable was erosive or ulcerative GERD healing. Erosive or ulcerative GERD healing is defined as the absence of esophageal erosions or ulcerations upon posttherapy endoscopic examination (i.e., grades 0 or 1 on the modified Hetzel-Dent grading scale).

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 100 patients divided into four 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 placebo, assuming 8-week healing response rates of 71% for rabeprazole and 28% for placebo.

2. Sponsor's Analysis

A total of 103 patients were enrolled (27 in the rabeprazole 10 mg group, 25 in the rabeprazole 20 mg group, 26 in the rabeprazole 40 mg group, and 25 in the placebo group). Of the 103 patients enrolled, 8 patients (8%) were discontinued from the study (5 in the placebo group, 0 in the 10 mg group, 2 in the 20 mg group, and 1 in the 40 mg group). The percentage of patients who discontinued from the study was significantly higher (p=0.022) in the placebo group (5/25, 20%) than in the 10 mg group (0/27, 0%).

The sponsor analyzed GERD healing rates using two methods. The primary method was an intent-to-treat (ITT) or last-observation-carried-forward (LOCF). This method incorporates data from all randomized patients who had at least one postdose measurement of any of the efficacy variables. Endoscopy results were carried forward to the next scheduled time point if data for that time point were missing.

The second method used to evaluate healing-response rates was based on complete visits, or endoscopies performed (referred to as the ENDO method). In this method, if endoscopy results were not available for a particular time point, the missing value was

not filled with the results of the previous endoscopic evaluation unless the previous result indicated that healing had occurred.

The significance of differences in healing rates between the treatment groups was assessed using stratified Mantel-Haenszel Chi-Square statistics.

2.1 Treatment Group Comparability

The demographic and baseline characteristics of the four 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 1).

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 NRRI
Summary of GERD Healing Rates
ITT Analysis

Analysis	Week	Treatment	Healing Rate	(Rab – Placebo) %	vs. Placebo p-value
ITT	4	Rab 10 mg	17/27 (63%)	63	<0.001
		Rab 20 mg	14/25 (56%)	56	<0.001
		Rab 40 mg	14/26 (54%)	54	<0.001
		placebo	0/25 (0%)		
	8	Rab 10 mg	25/27 (93%)	81	<0.001
		Rab 20 mg	21/25 (84%)	72	<0.001
		Rab 40 mg	22/26 (85%)	73	<0.001
		placebo	3/25 (12%)		

Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square statistics.
Copied from Table NRRI.6.2, page 55, vol. 176

ENDO Analysis

Analysis	Week	Treatment	Healing Rate	(Rab – Placebo) %	vs. Placebo p-value
ENDO	4	Rab 10 mg	17/27 (63%)	63	<0.001
		Rab 20 mg	14/24 (58%)	58	<0.001
		Rab 40 mg	14/25 (56%)	56	<0.001
		placebo	0/24 (0%)		
	8	Rab 10 mg	25/27 (93%)	78	<0.001
		Rab 20 mg	21/24 (88%)	73	<0.001
		Rab 40 mg	22/25 (88%)	73	<0.001
		placebo	3/20 (15%)		

Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-Square statistics.
Copied from Table NRRI.6.2, page 55, vol. 176.

As seen from the tables above, at both Weeks 4 and 8, the healing rates were significantly higher in all three rabeprazole groups than in the placebo 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 2.

As seen from Table 2 (attached), at both Weeks 4 and 8, the improvement rates were significantly higher in all three rabeprazole groups than in the placebo group. At both Weeks 4 and 8, the complete resolution rates were significantly higher in all three rabeprazole groups than in the placebo 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 3 and 4, respectively.

As seen from Table 3 (attached), at Week 8, the improvement rates in GERD daytime heartburn severity were significantly higher in all three rabeprazole groups than in the placebo group. At both Weeks 4 and 8, the complete resolution rates were significantly higher in all three rabeprazole groups than in the placebo group.

As seen from Table 4 (attached), at Week 8, the improvement rates in GERD nighttime heartburn severity for 40 mg group was significantly higher than in the placebo group. At Week 8, the complete resolution rates were significantly higher in 10 mg and 40 mg

groups than in the placebo group. There were no significant differences between rabeprazole 20 mg and placebo.

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 5.

As seen from Table 5 (attached), at week 8, the improvement rates were significantly higher in all three rabeprazole groups than in the placebo group. No significant differences were observed between rabeprazole (10 mg, 20mg, or 40 mg) and placebo in overall well-being normalization rates.

The mean and mean change in antacid use from baseline during the study for the ITT analysis is given in Attachment Table 6.

As seen from Table 6 (attached), at both Weeks 4 and 8, the mean reductions in antacid consumption from baseline were significantly greater in all three rabeprazole groups compared to the placebo group.

3. Reviewer's Evaluation

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

The sponsor's ITT analysis included all randomized patients. This study was designed to show the superiority of rabeprazole groups over placebo. The sample size was inadequate to detect the differences among rabeprazole doses.

However, there were disproportionate withdrawals. Among eight patients who were discontinued from the study, there were five patients in the placebo group, zero in the 10 mg group, two in the 20 mg group, and one in the 40 mg group. The percentage of patients who were discontinued from the study was significantly higher ($p=0.022$) in the placebo group (5/25, 20%) than in the 10 mg group (0/27, 0%). Four of five placebo patients who were discontinued from the study were endoscopied at Week 4 and found not healed and were withdrawn after Week 4 (relative days 24, 29, 29, and 31, respectively) for reasons of lack of efficacy or adverse event. In the sponsor's efficacy analysis, these patients were considered not healed at Week 8 evaluation. The sponsor's results might be biased against placebo.

To evaluate the impact of this biased, this reviewer performed a "worst case" analysis at Week 8 assuming "withdrawal" as "healed" for the placebo group. The results are given below.

Summary of GERD Healing Rates
Reviewer's "Worst Case" Analysis

Analysis	Week	Treatment	Healing Rate	(Rab – Placebo) %	vs. Placebo p-value
	8	Rab 10 mg	25/27 (93%)	61	<0.001
		Rab 20 mg	21/25 (84%)	52	<0.001
		Rab 40 mg	22/26 (85%)	53	<0.001
		placebo	8/25 (32%)		

Pairwise treatment p-value is obtained using Fisher's exact test.

As seen from table above, even in the "worst case" analysis, the healing rates at Week 8 were significantly higher in all three rabeprazole groups than placebo. The results were robust.

Furthermore, there was a slight imbalance in antacid use at baseline among treatment groups (p=0.079). This reviewer re-analyzed the GERD healing rates by adjusting baseline antacid use using Mantel-Haenszel method. The results reconfirmed sponsor's finding. The sponsor's results were robust as seen from the huge treatment differences between the rabeprazole groups and the placebo and the extremely small p-value (<0.001).

This study showed that the rabeprazole 10 mg QAM might be the minimum effective dose for 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 7. 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.

H4M-MC-NRRJ

1. **Description of Study**

This was a randomized, double-blind, parallel group, multicenter (63 investigators) active-controlled study. The objective of this study was to compare rabeprazole 20 mg once daily in the morning (QAM) with ranitidine 150 mg four times a day (QID) in the treatment of patients with erosive or ulcerative gastroesophageal reflux disease (GERD).

The design of this study was similar to that of study NRRI above. The main differences were that this study was an active-controlled instead of placebo controlled. This study