Table NRRC.6.3

Summary of Improvement Rates in Duodenal Ulcer Pain Frequency - Intent to Treat

				p-value[a]		
		Rabeprazole		Placebo vs Rabeprazole		Rabeprazole 20 mg vs
Week	Placebo	20 mg	40 mg	20 mg	40 mg	40 mg
Improvement						
2	15/32 (47%)	24/31 (77%)	24/31 (77%)	.010	.011	.924
4	19/32 (59%)	26/31 (84%)	26/31 (84%)	.029	.032	.920
Complete Resolution						
2	4/32 (13%)	12/31 (39%)	9/31 (29%)	.018	.094	.481
4	5/32 (16%)	17/31 (55%)	15/31 (48%)	<.001	.005	.612

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

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

Improvement: Frequency evaluation grade lower than baseline evaluation.

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

Both **rabeprazole doses were also significantly better than placebo in improving daytime and nighttime duodenal ulcer pain**, but in both analyses, **only a subset of patients were included**. The following Table NRRC.6.5 illustrates this point.

Table NRRC.6.5

Summary of Improvement Rates in Duodenal Ulcer Nighttime Pain Severity - Intent to Treat

				p-value[a]		
		Rabeprazole		Placebo vs Rabeprazole		Rabeprazole 20 mg vs
	Placebo	20 mg	40 mg	20 mg	40 mg	40 mg
Improvement						
Day 7	15/25 (60%)	21/24 (88%)	18/20 (90%)	.025	.054	.853
Week 2	20/27 (74%)	21/24 (88%)	20/23 (87%)	.143	.208	1.000
Week 4	18/27 (67%)	22/24 (92%)	21/23 (91%)	.053	.040	1.000
Complete Resolution						
Day 7	7/25 (28%)	18/24 (75%)	16/20 (80%)	.003	.003	.878
Week 2	11/27 (41%)	20/24 (83%)	17/23 (74%)	.003	.035	.249
Week 4	10/27 (37%)	20/24 (83%)	19/23 (83%)	.001	.003	.686

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

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

Improvement: Severity evaluation grade lower than baseline evaluation.

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

3. Antacid Consumption. Reduction in antacid consumption paralleled DU healing rates and pain improvement, since it was significantly lower in the rabeprazole groups, as shown in the next Table NRRC.6.8.

Table NRRC.6.8
Summary of Antacid Use (Doses/Day) - Intent to Treat

				p-value[a]		
		Rabeprazole		Placebo vs Rabeprazole		Rabeprazole 20 mg vs
Week	Placebo	20 mg	40 mg	20 mg	40 mg	40 mg
Baseline						
N	33	34	32			
Mean	1.94	1.32	1.59			
S.D.	2.52	1.43	1.68			
Range	0.0-10.0	0.0-5.0	0.0-5.0			
Week 2						
N	33	34	32			
Mean	1.83	0.39	0.62			
S.D.	2.11	0.56	0.81			
Range	0.0-10.0	0.0-2.3	0.0-2.6			
Week 4						
N	33	34	33			
Mean	1.50	0.34	0.38			
S.D.	1.96	0.54	0.63			
Range	0.0-10.0	0.0-2.3	0.0-2.4			
Week 2 Change from Baseline						
N	33	34	32			
Mean	-0.11	-0.93	-0.97	<.001	<.001	.633
S.E.	0.32	0.24	0.28			
Week 4 Change from Baseline						
N	33	34	32			
Mean	-0.44	-0.98	-1.20	<.001	<.001	.893
S.E.	0.30	0.26	0.30			

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

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 and 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.

4. Helicobacter Pylori Infection. Only a subset of patients, 72 total patients, were tested for *H. pylori* at the end of the study period. **There was no successful eradication of the microorganism by any of the treatment groups**, though the proportion of negative *H. pylori* patients was significantly lower in the rabeprazole treated group, i.e., 2/22 (9%) for PBO, 5/22 (23%) for the 20 mg Rabeprazole, and 8/18 (44%) for the 40 mg Rabeprazole.

iii. Reviewer Comments.

- This reviewer concurs with the sponsor in that rabeprazole tablets, either at a dose of 20 mg/day or 40 mg/day, taken for a period of 4 weeks, are significantly better than placebo in healing duodenal ulcers. **Based on the presented results, the 4 week duration of treatment is a requirement, since the data revealed lack of rabeprazole efficacy in the initial two week treatment.** The results also showed absence of dose response, i.e., patients placed on the high 40 mg rabeprazole dose did not show significantly higher healing rates than patients placed on the 20 mg low dose.

- Not surprisingly, **improvement in symptomatology did not follow DU healing rates; patients required only 2 weeks of rabeprazole treatment to show significant reductions in pain.** The significant improvement in abdominal pain was largely due to a reduction in pain frequency and in nighttime pain. Nighttime pain is a common complaint exhibited by DU patients, and is usually a consequence of the high nocturnal gastric acid hypersecretion found in a variable proportion of duodenal ulcers[1]. Hence, the rapid improvement in symptomatology observed in rabeprazole DU patients was very likely due to very strong neutralization of gastric acid hypersecretion by this powerful H_2-proton pump inhibitor.

- Aside from the clear superiority of rabeprazole over placebo, there were a few baseline imbalances in risk factors, i.e., tobacco or smoking, and sex (males), that were unfavorable to the 40 mg rabeprazole and the placebo treatment arms (*see Table NRRC.6.1 in my Descriptive of this trial*). Both of these variable have been reported in the DU literature as high risk factors that may contribute to a delay in duodenal ulcer healing[2,3,4]. Of these two imbalanced risk factors at baseline, smoking had no impact on healing results. In contrast, the higher proportion of females in the rabeprazole treatment arms may have somewhat influenced the proportion of healing patients, as can be seen in the following comparison between sex and healing rates (taken from the sponsor Table 12.1, Page 35, Vol. 171). As noticed, female rabeprazole patients had a higher healing rates than their male counterparts.

Table 12.1
Summary of Relationship of Baseline Characteristics to Week 4 Duodenal Ulcer Healing Rates
Intent to Treat

Characteristic	Placebo QAM	Rabeprazole 20 mg QAM	Rabeprazole 40 mg QAM	p-value*
Sex				
Male	11/26 (42%)	16/22 (73%)	19/22 (86%)	0.066
Female	2/ 7 (29%)	11/12 (92%)	11/11(100%)	

- Noteworthy to point is the overall high healing rates observed across all treatment groups, including placebo. After 4 weeks of exposure to placebo, the all–treated patient population reached almost 40 % healing rates, which is rather high if we take into consideration the low antacid consumption (1/day). A variable that may have strongly affected this high healing rate is the small duodenal ulcer size, ±0.45-0.5 cm, seen in the enrolled patients.

Twelve patients had baseline DUs below the allotted 0.3 cm limit: 3 Placebo, Healed=1/3 (1061, 1065, 1072); **4 rabeprazole 20 mg, Healed=3/4** (1015, 1158, 1070, 1097); **5 rabeprazole 40 mg, Healed=5/5** (1001, 1014, 1023, 1069, 1077). Large ulcer size, e.g., ≥1.0 cm, is another important risk factor in duodenal ulcer healing[5].

References Consulted by this Reviewer .

1. Jones DB et al. Acid suppression in duodenal ulcer: a meta-analysis to define optimal dosing with antisecretory drugs. Gut; 28:1120-1127, 1987.

2. Kurata HJ, Elashoff JD, et al. Sex and smoking differences in duodenal ulcer mortality. AJPH; 76:700-702, 1986.

3. Massarrat S et al. Risk factors for healing of duodenal ulcer under antacid treatment: do ulcer patients need individual treatment? Gut; 29:291-297, 1988.

4. Sontag S et al. Cimetidine, cigarette smoking, and recurrence of duodenal ulcer. NEJM; 311:689-693, 1984.

5. Reynolds JC. Famotidine therapy for active duodenal ulcers. A multivariate analysis of factors affecting early healing. Ann Int Med; 111:7-14, 1989.

Study NRRL. Rabeprazole vs Omeprazole.

Study Protocol H4M-MC-NRRL.

i. This protocol, finalized on August 12, 1994, was designed to show comparability between rabeprazole tablets and omeprazole capsules in safety and efficacy on duodenal ulcer healing. Basically, **the design of this protocol is identical to the design described in protocols NRRC** and NRRD, with the exception of sample size and dose of omeprazole. **Protocol H3M-MC-NRRL planned for an enrollment of approximately 200 duodenal ulcer patients.** Dosages were rabeprazole tablets 20 mg qam, and omeprazole capsules, 20 mg qam. Omeprazole 20 mg/day is the approved dose for treatment of duodenal ulcer. To protect blinding and mask for study distribution of tablets and capsules, the protocol added the distribution of double-dummy placebo tablets and capsules.

Descriptive of Study H4M-MC-NRRL.

ii. This randomized, double-blind, parallel trial was conducted in 9 European countries between April 4, 1995, and January 6, 1996. In this period, **25 investigators enrolled**

205 patients, with endoscopically diagnosed duodenal ulcer. Of the 295 enrolled patients, **102 were randomized to rabeprazole and 103 to omeprazole.**

(a) Patient Disposition. Ninety-eight of rabeprazole patients and 96% of omeprazole patients completed the study, as seen in sponsor Table NRRL.5.1, Vol. 179.

Table NRRL.5.1

Summary of Patient Disposition

Disposition	Rabeprazole (n=102)	Omeprazole (n=103)	Treatment p-value[a]
Completed Study	100 (98%)	99 (96%)	0.401
Dropped out of Study	2 (2%)	4 (4%)	
Adverse Event	0 (0%)	2 (2%)	
Protocol Violation	2 (2%)	0 (0%)	
Patient Decision	0 (0%)	2 (2%)	

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

The sponsor states that one patient in the rabeprazole group had gastric ulceration.. One rabeprazole patient and one omeprazole patient were identified as having esophageal erosions, but none of these patients were excluded from efficacy or safety analyses. Two rabeprazole patients were discontinued on study Day 16, because of noncompliance with study medication. Both patients were included in the efficacy analyses.

According to the sponsor, there were 13 omeprazole vs. 2 rabeprazole week 2 endoscopies that fell outside the allotted window (Days 12-18). At the week 4 endoscopy visit, 2 rabeprazole and 5 omeprazole were outside the allotted specified day ranges (26-32).

(b) Patient Demographics. The **102 rabeprazole and 103 omeprazole** patients had similar characteristics of age (47.3 and 47.8), race (aver. 95% Caucasian), males (65% and 69%), smoking (47% and 52%), alcohol consumption (54% and 56%), and antacid use (83% and 85%).

The following section of Table NRRL.6.1, depicts baseline ulcer size and ulcer pain of enrolled patients which had a balance distribution in both treatment groups.

Table NRRL.6.1 (continued)
Summary of Demographic and Baseline Characteristics

Characteristic	Rabeprazole (n=102)	Omeprazole (n=103)	Total (n=205)
Baseline Number of Duodenal Ulcers			
Mean	1.1	1.0	1.1
SD	0.3	0.2	0.3
Minimum	1	1	1
Maximum	3	2	3
Baseline Ulcer Size[a]			
≥0.3 - <0.50 cm	2 (2%)	2 (2%)	4 (2%)
≥0.50 cm	99 (97%)	101 (98%)	200 (98%)
Missing	1 (1%)	0 (0%)	1 (<1%)
Baseline Duodenal Ulcer Pain Frequency Grade			
0 = None	2 (2%)	0 (0%)	2 (1%)
1 = Few	10 (10%)	9 (9%)	19 (9%)
2 = Several	24 (24%)	29 (28%)	53 (26%)
3 = Many	34 (33%)	32 (31%)	66 (32%)
4 = Continual	32 (31%)	33 (32%)	65 (32%)

[a] The greater value between the width and length dimensions of the largest ulcer.

(c) Efficacy Results.

1. Ulcer Healing. Next Table NRRL.6.2, shows the sponsor summary of weeks 2 and 4 healing results. As observed in the table, the rabeprazole and omeprazole treatment groups had comparable 2 and 4 week healing rates, either in the ITT comparison or in the group of patients enrolled with DUs ≥0.50 cm. As noticed in the sponsor's table, the ENDO analysis also show comparable healing rates in both treatment groups.

Table NRRL.6.2
Summary of Duodenal Ulcer Healing Rates

Week	Analysis	Rabeprazole	Omeprazole	p-value[a]
	Intent to Treat			
2	Overall[b]	70/102 (69%)	63/103 (61%)	0.231
	≥0.50	70/99 (71%)	62/101 (61%)	0.161
4	Overall[c]	100/102 (98%)	96/103 (93%)	0.083
	≥0.50	97/99 (98%)	94/101 (93%)	0.093
	ENDO			
2	Overall	70/101 (69%)	63/101 (62%)	0.247
	≥0.50	70/98 (71%)	62/99 (63%)	0.174
4	Overall	100/101 (99%)	96/100 (96%)	0.162
	≥0.50	97/98 (99%)	94/98 (96%)	0.173

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

[b] Overall duodenal ulcer healing rate.

[c] Duodenal ulcer healing rate for ulcers ≥0.50 cm at baseline (the greater value between the width and length dimensions of the largest ulcer).

Healed: Complete regeneration of the mucosa (re-epithelialization) at the site of all ulcers identified during the study.

(d) Duodenal Ulcer Pain. The following Tables NRRL/6.3, NRRL.6.4, NRRL.6.5, illustrate improvement of ulcer pain in frequency, daytime, and nighttime. With the exception of week 4 daytime improvement, i.e., rabeprazole was superior to omeprazole; all the other pain improvement analyses revealed no differences between rabeprazole and omeprazole.

Table NRRL.6.3
Summary of Improvement in Duodenal Ulcer Pain Frequency Grades
Intent to Treat[a]

Frequency Evaluation	Week	Rabeprazole	Omeprazole	p-value[b]
Improvement[c]	2	70/100 (70%)	66/103 (64%)	0.372
	4	76/100 (76%)	70/103 (68%)	0.192
Complete Resolution[d]	2	28/100 (28%)	28/103 (27%)	0.843
	4	43/100 (43%)	37/103 (36%)	0.233

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

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

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

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

Table NRRL.6.4
Summary of Improvement in Severity Grades for Duodenal Ulcer Daytime Pain
Intent to Treat[a]

Severity Evaluation	Week	Rabeprazole	Omeprazole	p-value[b]
Improvement[c]	2	89/98 (91%)	86/101 (85%)	0.159
	4	90/98 (92%)	84/101 (83%)	0.038
Complete Resolution[d]	2	65/98 (66%)	62/101 (61%)	0.368
	4	70/98 (71%)	69/101 (68%)	0.530

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

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

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

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

Table NRRL.6.5
Summary of Improvement in Severity Grades for Duodenal Ulcer Nighttime Pain
Intent to Treat[a]

Severity Evaluation	Week	Rabeprazole	Omeprazole	p-value[b]
Improvement[c]	2	78/83 (94%)	80/83(96%)	0.525
	4	79/83 (95%)	80/83 (96%)	0.742
Complete Resolution[d]	2	66/83 (80%)	67/83 (81%)	0.737
	4	67/83 (81%)	69/83 (83%)	0.610

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

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

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

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

iii. Reviewer Comments.

- Omeprazole was the first proton-pump inhibitor approved for the treatment of active duodenal ulcer. Approval was based on one USA placebo-controlled and one USA

active-active controlled trial that compared omeprazole vs. ranitidine, and one foreign small International trial that also compared efficacy in DU healing between omeprazole vs. ranitidine (***PDR, 51th Edt., 1997)***. Week 4 healing rates with omeprazole 20 mg qam ranged between 75% in the two USA studies to 97% in the International study. **In this NRRL** trial, the **sponsor compared the efficacy of rabeprazole 20 mg qam to omeprazole 20 mg qam**. The week 4 DU healing results seen in this NRRL study are very similar to the healing result observed in the omeprazole International study, i.e., 98% healed in the rabeprazole and omeprazole group, respectively. Hence, **based on this controlled, multicenter, European study, we may conclude that rabeprazole and omeprazole administered for four weeks, have comparable efficacy** in healing active duodenal ulcers. Overall, the trial was adequate; there were protocol violations but these did not impact the efficacy results. In addition to DU healing, this trial showed comparability between rabeprazole and omeprazole in improvement of frequency of pain, nighttime pain and complete ulcer pain resolution. Only the efficacy on improvement of daytime pain appeared to favor rabeprazole, though this was a single event among 12 different comparisons of pain improvement. Similar to the complete comparability seen in healing, there was **no** difference between these two PIPs in reduction of antacid consumption (-0.73 rabeprazole and –0.65 omeprazole, p-Value=0.817).

Study NRRD. Rabeprazole vs Ranitidine.

i. Study Protocol H4M-MC-NRRD.

As in the previous placebo-controlled protocol NRRC, [redacted] designed this protocol, and finalized it on September 9, 1994.

The design of this protocol NRRD is IDENTICAL to the previously described NRRC protocol, with the exception of patient population, comparative drug dosage, and blinding. This **NRRD protocol planned for an enrollment of 370 duodenal ulcer patients,** to be randomized to either rabeprazole 20 mg tablets, **ranitidine 150 mg capsules** (twice a day or **bid**). Ranitidine 150 mg bid is the approved dose for duodenal ulcer treatment. To protect blinding and mask for study distribution of tablets and capsules. the protocol included the use of a double-dummy placebo technique.

ii. Descriptive of Study H4M-MC-NRRD.

This USA study started on February 9, 1995, and ended on December 22, 1995. **Sixty two investigators** participated in the study and **enrolled a total of 376 duodenal ulcer patients**; 2 investigators enrolled 22-26 patients, 4 investigators enrolled a range of 12-15 patients, 3 investigators enrolled 10 patients each, and the remaining investigators enrolled between 2 to 9 patients each.

(a) Patient Disposition. Of the total **376 DU patients, 188 were randomized to rabeprazole and 188 to ranitidine.** The sponsor notes that *although the primary method for determining the efficacy of the study medication was an ITT approach, one patient was excluded from all efficacy analyses because of study medication crossover. Patient ([31]-5213), randomized to receive rabeprazole treatment, was erroneously given ranitidine for Weeks 1 and 2, then received the assigned rabeprazole treatment for Weeks 3 and 4. As a result, this patient was included in the safety analyses in the rabeprazole group, but excluded from all efficacy analyses.* Of the 376 enrolled patients, 16 (4%) discontinued from the study (11 in the rabeprazole and 5 in the ranitidine group). The proportion of completed patients was comparable, 94% in the rabeprazole and 97% in the ranitidine group. The following Table NRRD 5.1, lists the reasons for withdrawals.

Table NRRD.5.1
Summary of Patient Disposition

Disposition	Rabeprazole (n=188)	Ranitidine (n=188)	p-value[a]
Completed Study	177(94%)	183 (97%)	0.119
Dropped out of Study	11 (6%)	5 (3%)	
Adverse Event	4 (2%)	1 (1%)	
Lack of Efficacy	1 (1%)	0 (0%)	
Protocol Violation	6 (3%)	0 (0%)	
Lost to Follow-up	0 (0%)	3 (2%)	
Patient Decision	0 (0%)	1 (1%)	

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

(b) Patient Demographics. Next table NRRD 6.1, reveals **no** imbalances in demographics.

Table NRRD.6.1
Summary of Demographic and Baseline Characteristics

Characteristic	Rabeprazole (n=188)	Ranitidine (n=188)	Total (n=376)
Sex			
Male	122	127	249
Female	66	61	127
Race			
Caucasian	144	136	280
African Descent	21	33	54
Other	23	19	42
Age (yr)			
Mean	51.5	49.0	50.2
SD	14.8	14.7	14.8
Minimum	18	18	18
Maximum	87	81	87
Tobacco Consumption			
No	111	116	227
Yes	77	72	149
Alcohol Consumption			
No	130	127	257
Yes	58	61	119
Caffeine Consumption			
No	47	55	102
Yes	141	133	274
Antacid Use			
No	104	96	200
Yes	84	91	175
Missing	0	1	1
Number of Doses of Antacid Used Per Day (based on average of last three days)			
n	188	187	375
Mean	1.59	1.70	1.65
SD	2.58	3.00	2.80
Minimum	0	0	0
Maximum	20	24	24

Table NRRD.6.1 (continued)
Summary of Demographic and Baseline Characteristics

Characteristic	Rabeprazole (n=188)	Ranitidine (n=188)	Total (n=376)
Baseline Number of Duodenal Ulcers			
n	187[a]	188	375
Mean	1.14	1.15	1.14
SD	0.42	0.39	0.40
Minimum	1	1	1
Maximum	3	3	3
Baseline Ulcer Size[b]			
n	187	188	375
≥0.3 - <0.50 cm	19 (10%)	21 (11%)	40 (11%)
≥ 0.50 cm	168 (90%)	167 (89%)	335 (89%)
Baseline Duodenal Ulcer Pain Frequency Grade			
0 = None	28 (15%)	24 (13%)	52 (14%)
1 = Few	18 (10%)	11 (6%)	29 (8%)
2 = Several	35 (19%)	23 (12%)	58 (15%)
3 = Many	31 (17%)	36 (19%)	67 (18%)
4 = Continual	75 (40%)	92 (49%)	167 (45%)
Missing	0 (0%)	2 (1%)	2 (1%)

[a] One patient ([31]-5213) was randomized to the rabeprazole treatment group, but erroneously received ranitidine treatment during Weeks 1 and 2. This patient received rabeprazole treatment during Weeks 3 and 4. Therefore, he was excluded from all efficacy analysis, but was included in the safety analysis under the rabeprazole group.

[b] The greater value between the width and length dimensions of the largest ulcer.

The sponsor notes that **7 enrolled patients had esophageal erosions/ulcer diagnosed at baseline endoscopy (65 rabeprazole and 2 ranitidine).** These patients were not excluded from the efficacy or safety analyses.

(c) Efficacy Results.

1. Ulcer Healing. In Table NRRD.6.2, the sponsor presents the proportion of patients who healed at weeks 2 and 4, for both, the intent-to-treat (ITT) and endoscopies (ENDO) only analyses. The table also includes the healing rates in the subset of patients enrolled with ulcer size ≥0.50 cm. **In all analyses. DU healing rates in rabeprazole patients are significantly superior than DU healing rates observed in ranitidine patients.**

The sponsor states that *in the ITT population, the overall duodenal ulcer healing rate at Week 2 was 40% (75/187) in the rabeprazole group compared with 26% (49/188) in the ranitidine group. At Week 4, the overall healing rate was 93% (156/187) for the rabeprazole group compared with 73% in the ranitidine group.* Very similar healing rates were observed in patients with duodenal ulcers equal or greater than 0.50 cm in size.

Table NRRD.6.2
Summary of Duodenal Ulcer Healing Rates

Week	Analysis	Rabeprazole	Ranitidine	p-value[a]
	Intent-to-treat			
2	Overall[b]	75/187 (40%)	49/188 (26%)	0.002
	≥ 0.50[c]	65/168 (39%)	41/167 (25%)	0.006
4	Overall	156/187 (83%)	138/188 (73%)	0.017
	≥ 0.50	139/168 (83%)	119/167 (71%)	0.009
	ENDO			
2	Overall	75/181 (41%)	49/185 (26%)	0.001
	≥ 0.50	65/162 (40%)	41/164 (25%)	0.004
4	Overall	156/178 (88%)	138/181 (76%)	0.005
	≥ 0.50	139/159 (87%)	119/161 (74%)	0.002

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

[b] Overall duodenal ulcer healing rate.

[c] Duodenal ulcer healing rate for ulcers ≥0.50 cm at baseline (the greater value between the width and length dimensions of the largest ulcer).

Healed: Complete regeneration of the mucosa (re-epithelialization) at the site of all ulcers identified during the study.

2. Duodenal Ulcer Pain. The sponsor submitted data on frequency of DU pain and complete resolution of DU pain in a subset of 318 patients (85% of total 376 patients). As noticeable in the following Table NRRD.6.3, **there were no differences between the rabeprazole and ranitidine groups, in the proportion of patients reporting improvement in frequency of DU pain after 2 or 4 weeks treatments**; appr. 64% and 74% of overall patients reported improvements at weeks 2 and 4, respectively. **The only significant difference between the two active treatments was observed in the proportion of patients reporting complete pain resolution at the week 2 visit: 39% rabeprazole vs. 25% ranitidine.** At the subsequent week 4 visit, the difference in complete pain resolution was not significant.

Table NRRD.6.3
Summary of Improvement in Duodenal Ulcer Pain Frequency Grades
Intent to Treat[a]

Frequency Evaluation	Week	Rabeprazole	Ranitidine	p-value[b]
Improvement[c]	2	98/159 (62%)	106/162 (65%)	0.482
	4	116/159 (73%)	121/162 (75%)	0.824
Complete Resolution[d]	2	62/159 (39%)	41/162 (25%)	0.006
	4	81/159 (51%)	71/162 (44%)	0.166

[a] Patients with normal baseline values (grade = 0) were excluded from the analysis.
[b] Treatment p-value is adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistic.
[c] Improvement: Frequency evaluation grade lower than baseline evaluation.
[d] Complete resolution: Frequency evaluation grade of "0" (none).

Comparison between **the proportion of rabeprazole and ranitidine patients reporting daytime pain improvement disclosed no differences** (Table NRRD.6.4).

Table NRRD.6.4
Summary of Improvement in Severity Grades for Duodenal Ulcer Daytime Pain
Intent to Treat[a]

Severity Evaluation	Week	Rabeprazole	Ranitidine	p-value[b]
Improvement[c]	2	87/134 (65%)	88/143 (62%)	0.357
	4	99/134 (74%)	112/143 (78%)	0.514
Complete Resolution[d]	2	65/134 (49%)	62/143 (43%)	0.331
	4	81/134 (60%)	84/143 (59%)	0.925

[a] Patients with normal baseline values (grade = 0) were excluded from the analysis.
[b] Treatment p-value is adjusted for investigator; obtained using the Cochran-Mantel-Haenszel statistic.
[c] Improvement: Severity evaluation grade lower than baseline evaluation.
[d] Complete resolution: Severity evaluation grade of "0" (none).

The comparison of proportion of patients reporting improvement **in nighttime pain revealed significant superiority of rabeprazole at the week 2 visit, but this rabeprazole superiority was not observed at the week 4 visit.** Similarly, **no differences between DU treatments was observed in the proportion of patients reporting complete nighttime pain resolution.** The following Table NRRD.6.5, illustrates this point.

Table NRRD.6.5
Summary of Improvement in Severity Grades for Duodenal Ulcer Nighttime Pain
Intent to Treat[a]

Severity Evaluation	Week	Rabeprazole	Ranitidine	p-value[b]
Improvement[c]	2	100/132 (76%)	88/135 (65%)	0.044
	4	110/132 (83%)	110/135 (81%)	0.710
Complete Resolution[d]	2	73/132 (55%)	64/135 (47%)	0.185
	4	91/132 (69%)	86/135 (64%)	0.425

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

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

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

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

3. Antacid Consumption. The report states that the mean reduction in antacid consumption was significantly greater in the rabeprazole group, as illustrated in the next Table NRRD.6.7.

Table NRRD.6.7
Summary of Antacid Use (Doses Per Day)
Visit-Wise Analysis

Week	Rabeprazole	Ranitidine	p-value[a]
Baseline			
n	187	187	
Mean	1.60	1.70	
SD	2.59	3.00	
Range	0 - 20	0 - 24	
Missing	0	1	
Week 4			
n	97	120	
Mean	0.33	0.55	
SD	0.67	0.77	
Range	0 - 4	0 - 3	
Missing	5	10	
Week 4: Change from Baseline			
n	97	119	
Mean	-1.23	-0.88	0.037
S.E.	0.27	0.20	

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

Note: At baseline, the mean number of doses of antacid used per day is based on the number of doses taken for the previous three days. At Week 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.

iii. Reviewer Comments.

This reviewer agrees that the DU healing results, as presented by the sponsor, show that rabeprazole 20 mg qam is significantly better than ranitidine 150 mg bid. Careful examination of the center-by-center healing rates, reveals some inconsistencies.

a). The **largest center, Investigator 10, enrolled 26 DU patients**; 13 in the rabeprazole treatment arm, and 13 in the ranitidine treatment arm. **At the week 2 endoscopy, this center reported zero percent healing rates, 0/13 rabeprazole; 0/13 ranitidine** (information provided by the statistician reviewer, Dr. Milton Fan).

At **the week 4 endoscopy, this large center reported 12/13 (92%) rabeprazole patients healed, whereas only 7/13 (54%) ranitidine patients were reported as healed (see Appendix 1).** Hence, **this large center had an overall 73% healing gain in the last two weeks of therapy** This fast overall healing rate was clearly **driven by the 92% healing increase reported in the 13 rabeprazole** patients **(0%-92%)**. Contrasting this high fast rabeprazole healing is the rather low 4 week 54% ranitidine healing. The reasons behind the ±100% percent two week jump in healing reported in the 13 rabeprazole treated patients, and almost ±40% gain over ranitidine, are unclear. It is possible that in this center **all** ulcers treated with rabeprazole were decreasing rapidly in size and were already very small at the time of the week 2 endoscopy. The knowledge of ulcer size at the week 2 endoscopy visit was, therefore, of paramount importance. My examination of the submitted **Patient Data Listing 3.6, Vol. 153**, revealed no ulcer size for any follow up endoscopies in any of the enlisted centers. In view of the inconsistencies revealed in the 26 patients treated by Investigator 10, and in order to assess possible treatment-by-center interaction, I further compared 4 week healing rates excluding all 26 patients from Investigator 10. The following Reviewer Table 1, illustrates the results of this comparison.

Reviewer Table 1

NRRD: Four Week DU Healing After Exclusion of Investigator 10

Centers	Patient Population	Rabeprazole	Ranitidine	p-Values
All 62 Investigators	100% (375)	156/187 (87%)	138/188 (73%)	0.017
Minus Inv. 10 (61 Centers)	***93%*** (349)	144/174 (83%)	131/175 (75%)	***0.071***[1]

[1]Chi-Square method, as calculated by Dr. Milton Fan

The corrected healing rate comparison illustrated in Reviewer Table 1 reveals **comparable efficacy between rabeprazole and ranitidine, canceling**, thus, any **claim of rabeprazole superiority** over ranitidine. Superiority claim of rabeprazole over ranitidine was implicit by the significant p-values in favor of rabeprazole shown in the proposed annotated package (**Healing of Duodenal Ulcer** Section), and was stated as the rationale for the large patient sample population planned for this comparative active-active control trial (**Sample Size** section, study protocol **Appendix 2** of this reveiw).

Similar to my description of inconsistencies in the week 4 healing rates reported by Investigator 10, are the treatment-by-investigator interactions reported by the sponsor in the week 2 healing rates, as seen in the following sponsor Table 3.1, Vol 149.

Table 3.1
Summary of Duodenal Ulcer Healing Rates
Intent to Treat

Week	Baseline Ulcer Size+ (cm)	Rabeprazole 20 mg QAM	Ranitidine 150 mg BID	Delta++ (CI)	Treatment p-value#	Treatment by Investigator Interaction#
2	Overall	75/ 187 (40%)	49/ 188 (26%)	14% (5%,23%)	0.002	0.016
	>=.50	65/ 168 (39%)	41/ 167 (25%)	14% (4%,24%)	0.006	0.043
4	Overall	156/ 187 (83%)	138/ 188 (73%)	10% (2%,18%)	0.017	0.143
	>=.50	139/ 168 (83%)	119/ 167 (71%)	12% (3%,21%)	0.009	0.327

b). Submitted data on DU pain improvement or DU complete pain resolution encompassed a subset of 132-159 patients. Any claim of superiority over ranitidine in pain improvement should specify the subset of patient population in whom pain resolved by rabeprazole administration (**159 patients**) or in whom rabeprazole treatment resulted in improvement of nighttime pain (**132 patients**).

D. RABEPRAZOLE IN HYPERSECRETORY STATES AND ZES..

Study A001-501.

(a). Study Protocol *(Submitted in Vol. 227).* The protocol planned for an **open-label, multi center** study designed ***to determine the appropriate starting dose of rabeprazole for the management of patients with idiopathic gastric hypersecretion or ZES.***

(b). Dosage. The protocol states that ***at each visit the patients will receive sufficient medication to control gastric acid secretion below 10 meq/h for the last hour before next dose (or 5 meq/h in patients with prior gastric surgery). At any given visit, the prescribed dose may increase, remain unchanged or decrease. Initial dosing will be once daily in uncomplicated disease (60 mg QAM) or twice daily (40 mg BID) in patients with complicated disease.*** The subjects were provided with 20 mg rabeprazole tablets.

(c) Patient Population. Minimum of 40 to 60 patients. The protocol states that ***sample size is not critical for the purpose of this study, since only descriptive statistics will be used.***

(d) Efficacy Endpoints. The **Primary efficacy endpoint** is the control of gastric acid secretory rate below 10 meq/h during the last hour before the next dose of medication or below 5 meq/h in