Investigator, City	*rabeprazole*	*ranitidine*	*total*
039/ J. McHattie, Regina, Saskatchewan	0	0	0
040/G. May, Calgary, Alberta	0	1	1
041/M. Moskowitz, Beaver PA	2	2	4
042/N. Nickl, Lexington KY	2	2	4
043/H. Offenburg, Gainesville FL	1	1	2
044/M. Oravec, Oshawa, Ontario	1	1	2
045/D. Pambianco, Charlottesville VA	2	2	4
046/F. Ramirez, Phoenix AZ	2	2	4
047/D. Riff, Anaheim CA	2	2	4
048/P. Rossos, Toronto, Ontario	0	1	1
049/W. M. Roufail, Winston-Salem NC	2	2	4
050/S. Sabesin, Chicago IL	6	6	12
051/S. Safevi, Irving TX	2	3	5
052/M. Safdi, Cincinnati OH	4	4	8
053/H. Schwartz, Miami FL	4	4	8
054/B. Scott, Baton Rouge LA	2	2	4
055/D. Scott, Shreveport LA	2	2	4
056/N. Shah, Leonardtown MD	3	4	7
057/B. Shivakumar, Davenport IA	1	1	2
058/M. Sklar, Bingham Farms MI	2	1	3
059/S. Sontag, Hines IL	2	2	4
060/L. Strong, Loveland CO	2	2	4
061/Z. Vlahcevic, Richmond VA	2	2	4
062/R. Soloway, Galveston TX	2	2	4
063/R. White, Sacramento CA	2	2	4
064/R. Willis, Harrogate TN	1	1	2
065/L. D. Wruble, Memphis TN	10	10	20
066/M. Shaukat, Phoenix AZ	0	0	0
067/T. Bianchi, Tallassee AL	2	2	4
total, 63 participating	*168*	*170**	*338*

Dr. Katz' patient 031-8211 was randomized to rabeprazole, and received the correct medication for the first 4 weeks, but by error received ranitidine for the second 4 weeks of the study (and was healed). His patient ***031-8313**** was randomized to ranitidine, but by error received rabeprazole for the first 4 weeks and then quit the study, ***and was reclassified as if randomized to rabeprazole***. Both patients were excluded from efficacy analyses (both improved from grade 3 to grade 2 on rabeprazole for 4 weeks, (*Patient Data Listing 4, Volume 167, pages 130-4*), and both were included in safety analyses as having been on rabeprazole.

Comment: The medication mixup at Dr. Katz' site in Great Neck NY resulted in an extra patient who had originally been randomized to ranitidine (Patient 031-8313) being "reclassified" as having been randomized to rabeprazole, since he did in fact get rabeprazole for 4 weeks. His esophageal erosions and ulcerations decreased from grade 3 to grade 2 but were not healed after 28 days on rabeprazole (see Patient Data Listing 4, Volume 167, pages 133-4). However,

the patient left the study despite heartburn frequency decreasing from "continual" and moderately severe to none (see Patient Data Listing 5, Volume 168, page 34). Patient 031-8211 randomized to rabeprazole healed partially on rabeprazole, and healed completely on a second 4 weeks of ranitidine. Excluding both patients from efficacy analysis favors rabeprazole.

The two randomized groups were similar in distribution, and no significant differences were seen between the randomized groups of 169 patients each, with respect to gender, age, race, weight, use of antacids, alcohol, tobacco, caffeine (*Table 2.1, Volume 164, pages 131-4*). Somewhat more of the patients randomized to rabeprazole were 65 or older, 40/169 (23.7%) than those randomized to ranitidine, 27/169 (16.0%), but the difference was not quite significant ($p = 0.074$). The distribution of endoscopic findings in the esophagus, stomach, and duodenum were similar (*Table 2.2, Volume 164, page 135*). The severity of the esophageal erosive lesions was not significantly different ($p = 0.875$:

SEVERITY OF EROSIVE ESOPHAGITIS BEFORE STUDY TREATMENT

	rabeprazole	ranitidine	total
	167 patients	*169 patients*	*336 patients*
Grade 2	92 (55.1%)	81 (47.9%)	173 (51.5%)
Grade 3	60 (35.9%)	69 (40.8%)	129 (38.4%)
Grade 4	15 (9.0%)	19 (11.2%)	34 (10.1%)

The distribution of heartburn frequency was almost identical between the two randomized groups, however, and 248/336 (73.8%) reported heartburn on more than half the days, only 4% reporting none. Day and night heartburn severity was also comparable between the two groups, with about half the patients reporting moderate or severe heartburn in the daytime and 61% at night *(Tables 2.4 and 2.5, Volume 164, pages 137-8)*.

Of the total 338 patients randomized to treatment by these 63 investigators, 9 in Canada and 54 in the United States, 154 on rabeprazole and 157 on ranitidine completed the study as defined in the protocol. It was stated (*Protocol section 3.9.2.3, page 10; Volume 164, page 290*) that patients shown endoscopically to be healed after 4 weeks therapy did not have to return for another endoscopy at 8 weeks. They were counted as healed at 8 weeks for purposes of efficacy analyses (*Report, Section 4.2, Analysis of Efficacy, pages 47-51; found in Volume 164, pages 54-8*) and missing data for secondary analyses were assumed.

Comment: This approach to data analysis is disturbing, for it is very well known that both symptoms and lesions of erosive esophagitis in patients with GERD tend to recur very promptly on discontinuation of treatment. If the patients were treated only for 4 weeks, then all that can be said about them is what was observed at 4 weeks. Patients who were treated for 8 should be reported separately and analyzed separately .It is also questionable to "reclassify" randomization schemes because of medication errors later. Then 170 patients were randomized to ranitidine and 168 to rabeprazole. Both of the Katz patients showed non-healing by rabeprazole at 4 weeks, although both patients improved from grade 3 to grade 2, and became asymptomatic for heartburn frequency.

Disposition of the patients (*Section 5.2 of the Report, pages 56-8; found in Volume 164, pages 63-5*) was reported for 338 patients accepted by the 63 investigators, without any report of how many patients were screened and excluded for failing to meet entry criteria for what reason. There were no patients entered who had duodenal or gastric ulcers at screening endoscopy, and none with grades 0 or 1 or 5 esophageal findings (*Tables 2.2 and 2.3, Volume 164, pages 135 and 136*). Taking as a basis the original randomization to 168 patients on rabeprazole and 170 on ranitidine, patients who dropped out (*described on page 63, and on pages 195-6, Volume 164*):

	total	*rabeprazole*	*ranitidine*	*explanation/reason*
Patients randomized	338	168	170	
Protocol violation	**-8**	**-5**	**-3**	
019-8129 Mc67		*-1*		*Day 1-did not take medication*
064-8447 Fc24		*-1*		*Day 1-pregnant by HCG test*
060-8416 Fc66		*-1*		*Day 19-taking imipramine*
007-8043 Fc32			*-1*	*Day 21-taking imipramine, etc*
016-8106 Fc51			*-1*	*Day 21-using excluded drugs*
003-8021 Mc85		*-1*		*Day 22-taking allopurinol*
031-8213 Mc59			*-1*	*Day 27- took **rabeprazole***
031-8211 Mc74		*-1*		*Day 50-took **ranitidine***
Adverse event	**-8**	**-4**	**-4**	
003-8015 Fc37			*-1*	*Day 5-mild nausea*
010-8066 Fc30		*-1*		*Day 6- severe abdominal pain*
035-8240 Mc38			*-1*	*Day 10-severeimpotence*
015-8103 Fc66		*-1*		*Day 19-moderate headache*
034-8234 Mc63			*-1*	*Day 23-severe abdominal pain*
058-8400 Mc83		*-1*		*Day 28: **study drug q.i.d.1-9***
010-8462 Fc45			*-1*	*Day 49-severe chest pain*
028-8191 Fc66		*-1*		*Day 53-moderate bronchitis*
Lack of perceived efficacy	**-3**	**-2**	**-1**	
009-8060 Mc39			*-1*	*Day 9- investigator's opinion*
056-8509 Mc48		*-1*		*Day 15-patient's opinion*
021-8457 Mo44		*-1*		*Day 28-patient's opinion*
Patient decision to quit*	**-5**	**-2**	**-3**	
004-8024 Fc71		*-1*		*Day 3 - last dose*
005-8030 Mc62			*-1*	*Day 16 - last dose*
004-8589 Fc45			*-1*	*Day 21 – last dose*
051-8353 Mc44			*-1*	*Day 29 – last dose*
024-8165 Mc54		*-1*		*Day 32 – last dose*
Lost or moved away*	**-3**	**-1**	**-2**	
004-8028 Mo45		*-1*		*Day 0 – never took drug*
050-8347 Mc57			*-1*	*Day 0 – never took drug*
021-8143 Mc37			*-1*	*Day 31 -*
Completed study	311	154	157	*not different: (p >0.75)*

*Comment: *Patients do not always give adequate or even true reasons for quitting a study, and may simply withdraw consent or fail to return, sometimes when there may be an adverse effect of perceived lack of benefit.*

The sponsor analyzed and presented results of the study two ways: 1) by "ITT" that included 167 patients randomized to rabeprazole and 169 randomized to ranitidine; and 2) by "ENDO" for the 163 rabeprazole-treated patients and 162 ranitidine-treated patients who had endoscopy done at 4 weeks. Separately, ENDO analyzed the 158 rabeprazole-treated patients and 158 ranitidine-treated patients who had endoscopy done at 8 weeks. The time-to-event analysis described in the protocol was not presented.

Comment: The two patients mixed up at Dr. Katz' site in Great Neck NY were both treated for 4 weeks on rabeprazole, and both showed partial healing from grade 3 to grade 2 erosions. One of them, patient 031-8213, had been randomized to ranitidine originally, and was "reclassified" as having been randomized to rabeprazole. The other, patient 031-8211, by error received ranitidine for the second 4 weeks, between endoscopies done on 10 April and 1 May (21 days) and was found to have healed completely to grade 0 (see Volume 167, pages 130-2). Both patients were excluded from efficacy analyses.

By both types of analyses, rabeprazole 20 mg/day was significantly superior to ranitidine 150 mg q.i.d. in producing healing of the erosions at both 4 weeks and for the combined healing at 8 weeks ($p < 0.001$ for all comparisons).

PROPORTIONS OF PATIENTS HEALED

	rabeprazole	ranitidine	
"ITT"			p- value
4 weeks	98/167 (59%)	60/169 (36%)	<0.001
8 weeks	146/167 (87%)	112/169 (66%)	<0.001
"ENDO"			
4 weeks	98/163 (60%)	60/162 (37%)	<0.001
8 weeks	146/158 (92%)	112/158 (71%)	<0.001

Comment: These results were very compelling in favor of the superiority of rabeprazole 20 mg each morning for 4 or 8 weeks over the standard, approved regimen of ranitidine 150 four times a day, for healing the endoscopic lesions of erosive esophagitis associated with GERD. The inclusion of the two excluded patients of Dr. Katz would slightly decrease the differences between the study groups but would not change the conclusion that rabeprazole was superior to rantidine in healing the lesions. At 4 weeks, adding in the two excluded patients who were actually treated with rabeprazole and failed to heal, 98/169 (58%) on rabeprazole is still very significantly ($p < 0.001$) better than 60/169 (36%) on ranitidine. Another flaw was the reasoning that it could be assumed that, if the patient were healed at 4 weeks, he/she would still be healed at 8 weeks. This was not the case in some patients who were treated for an additional 4 weeks despite having shown healing at the 4-week-endoscopy. Examples of such patients may be seen in the Appendices following in which all the patients are accounted for. As may be seen in Appendix I-A, two patients on rabeprazole, 009-8057 and 058-8402, were treated with for a full 8 weeks to complete healing (grade 0) despite healing to grade 0 and grade 1, respectively, at week 4. In the rantidine group (Appendix I-B), four patients were so treated, three of whom

showed further improvement from grade 1 at 4 weeks to grade 0 at 8 weeks (022-8150, 029-8200, 058-8401), but one (patient 022-8149) actually ***worsened*** *back to grade 2. If no treatment were given, then it certainly could not be assumed that healing at week 4 could be assumed to be true at week 8. The only way to resolve this question, since the study design flaw does not permit any other solution, is to look at* ***only those patients who were treated and observed over the second two weeks*** *of the study, and to compare healing rates on the two regimens. Since the group on rabeprazole had shown significantly more healing at 4 weeks, there were fewer to carry over to a second 4 weeks of treatment than in the rantidine-treated group. Of the 63 patients on rabeprazole who went on to continue treatment for the second two weeks, 48 (76.2%) healed, compared to 55 of 91 (60.4%) on ranitidine; the difference was still statistically significant in favor of rabeprazole (p = 0.041, by chi-squared test).*

RANDOMIZED PATIENTS HEALED ON REGIMEN

	rabeprazole 20 mg/day	ranitidine 150 mg qid	p-value
First 4 weeks	98†/169 (58.0%)	60/169 (35.5%)	< 0.001
Second 4 weeks	48/63 (76.2%)	55*/91 (60.4%)	0.041
Over whole 8 weeks	146/168 (86.9%)	113/170 (66.5%)	< 0.001
-dropped	-8/168 (4.8%)	-11/170 (6.5%)	N.S.
Left unhealed at end	14/168 (8.3%)	46/170 (27.1%)	< 0.001

Note: Includes patient 031-8213 who was randomized to ranitidine but treated with rabeprazole, and patient 031-8211 who healed on ranitidine after failing on rabeprazole.

It may be noted that significantly fewer patients were left unhealed after the entire regimen of treatment had been carried out, and that, even considering the smaller numbers who were actually treated in the second 4 weeks, the rabeprazole superiority was still present. These analyses include all patients randomized, and the patient 031-8211 who healed on ranitidine was counted in the second 4-week period. A point that again was missed in the sponsor's analysis was the marked effect of the extent of the original esophageal lesions on the healing rates, particularly noted at 4 weeks, but still present at 8 weeks. Grade 4 lesions healed significantly slower; grade 3 lesions intermediately; and grade 2 lesions were most rapidly healed.

EFFECT OF ESOPHAGEAL LESION SIZE ON ITT HEALING RATES

	rabeprazole	*ranitidine*	*both*
At 4 weeks	***p< 0.001***	***p>0.4***	***p< 0.001***
Grade 4	4/15 (26.7%)	5/19 (26.3%)	9/34 (26.5%)
Grade3	27/62 (43.5%)	22/70 (31.4%)	49/132 (37.1%)
Grade2	67/92 (72.1%)	32/80 (40.0%)	99/172 (57.6%)
At end of study	***p>0.5***	***p>0.47***	***p> 0.18***
Grade 4	11/15 (73.3%)	11/19 (57.9%)	22/34 (64.7%)
Grade 3	49/61 (80.3%)	46/71 (64.8%)	95/132 (72.0%)
Grade2	78/92 (84.8%)	57/80 (71.3%)	135/172 (78.5%)

By chi-squared testing, 2 degrees of freedom, the results were highly significant for rabeprazole at 4 weeks, and although not for ranitidine, still highly significant if both were combined. A clear

trend is evident for results at study end, although the convergence of healing rates as more time was allowed made the differences not statistically significant. It is evident that the severity/extent of the original lesion, before treatment, was a very important factor in affecting healing rates. This would suggest that further trials on healing of erosive esophagitis perhaps should be stratified for lesion severity by endoscopic Hetzel-Dent grade, in order to obtain a more valid comparison between treatment regimens, and possibly to guide the dose and duration of treatment for therapy. This was noted by this reviewer for Study NRRI, but the sponsor did not report analysis based on this factor, and did not stratify Study NRRJ on that basis.

It was of interest that the healing rates for the two agents used in estimating the study size were both far less than actually observed. The protocol section (3.4.3, page 5; see Volume 164, page 285) on study size requirements, for power of 80% to detect at significant, two-sided error of 0.05, was based on assuming an 8-week healing rate of 70% for rabeprazole 20 mg/day and only 54% for ranitidine 150 mg q.i.d. It was stated that the ranitidine healing rate was based on the sponsor's unpublished meta-analysis of results from clinical trials comparing ranitidine and omeprazole. However, the approved labeling for ranitidine 150 mg q.i.d. for healing erosive esophagitis states a healing rate of 71% (142/200) after 8 weeks, which was much closer to what was observed in this study. Fortunately, the rabeprazole healing rate was even greater, significantly greater than predicted at 87%, so its superiority was demonstrated.

The healing rate for rabeprazole 20 mg each morning in Study NRRJ was comparable to that seen for the same dose in Study NRRI:

PROPORTIONS OF PATIENTS HEALED ON RABEPRAZOLE 20 MG/DAY

	Study J	Study I
4 weeks	98/169 (58%)	14/25 (56%)
8 weeks	146/169 (86%)	21/25 (84%)

When the extent of healing, to normal-appearing esophageal mucosa (grade 0), compared to some residual erythema/edema/friability (grade 1) was compared for rabeprazole 20 mg/day and ranitidine 150 mg q.i.d., a definite difference ($p < 0.01$) was seen in favor of rabeprazole:

COMPARISON OF DEGREE OF HEALING ON THE TWO TREATMENTS

	rabeprazole		**Initial**		ranitidine	
0	***1***	***either***	**severity**	***0***	***1***	***either***
7	4	11	**Grade 4**	7	4	11
40	10	50	**Grade 3**	33	12	45
71	14	85	**Grade 2**	35	22	57
118	28	146	**All grades**	75	38	113
(80.8%)				(66.4%)		

The secondary analyses for heartburn reduction were carried out for overall frequency of symptom occurrence and by severity of daytime and nighttime symptoms, and were analyzed for improvement in grade by any amount, compared to the pre-study grading, and by resolution to grade 0 (none) from any initial grade. A few of the patients did not have heartburn symptoms, so the denominator figures vary somewhat:

IMPROVEMENT OR RESOLUTION OF SYMPTOMS ON TREATMENT

	rabeprazole 20 mg/day	*ranitidine 150 mg q.i.d*	*p-value*
FREQUENCY			
Improvement			
4 weeks	121/161 (75.2%)	91/158 (57.6%)	< 0.001
8 weeks	127/161 (78.9%)	108/158 (68.4%)	0.032
Resolution			
4 weeks	72/161 (44.7%)	42/158 (26.6%)	< 0.001
8 weeks	81/161 (50.3%)	45/158 (28.5%)	< 0.001
DAYTIME SEVERITY			
Improvement			
4 weeks	95/135 (70.4%)	84/124 (67.7%)	N.S.
8 weeks	102/135 (75.6%)	99/124 (79.8%)	N.S.
Resolution			
4 weeks	79/135 (58.5%)	53/124 (42.7%)	0.017
8 weeks	92/135 (68.1%)	67/124 (54.0%)	0.025
NIGHTTIME SEVERITY			
Improvement			
4 weeks	101/127 (79.5%)	107/131 (81.7%)	N.S.
8 weeks	110/127 (86.6%)	113/131 (86.3%)	N.S.
Resolution			
4 weeks	84/127 (66.1%)	67/131 (51.1%)	0.012
8 weeks	94/127 (74.0%)	74/131 (56.5%)	0.002
OVERALL WELL-BEING			
Improvement			
4 weeks	80/135 (59.3%)	63/138 (45.7%)	0.020
8 weeks	86/135 (63.7%)	73/138 (52.9%)	0.056
Normalization			
4 weeks	57/135 (42.2%)	40/138 (29.0%)	0.021
8 weeks	62/135 (45.9%)	42/138 (30.4%)	0.007

By all of these subjective, secondary measures there were significant differences in favor of the rabeprazole treatment over ranitidine, especially if complete resolution or normalization to grade 0 was the point of comparison. The improvements and resolutions were most impressive at 4 weeks, with relatively little further gain at 8 weeks.

Antacid use in both groups decreased on treatment, but the differences from pre-study numbers of doses were about equal, and not statistically different between groups.

Comment: Patients obviously would like to have as swift and complete disappearance of their symptoms as possible, perhaps even more than they might like their lesions to be healed by endoscopy. It may be noted that ranitidine did produce improvements in grades of heartburn severity in proportions of patients that were comparable to those treated with rabeprazole, but definitely fewer patients improved to complete disappearance of heartburn (to grade 0, none.).

Safety problems were not prominent in this study, despite the fact that many of the patients were elderly, had many other medical problems before entering the study, and were susceptible to new problems that might emerge during the up to 8-10 weeks of observation. There were no deaths during the study.

Serious events occurred in 3 patients on rabeprazole and 2 on ranitidine.

Rabeprazole group:

Patient 058-8400, an 83-year-old white man, by mistake **overdosed** for the first 4 days of the study, taking 20 mg four times/day (80 mg/day for 4 days). He had history of mild hypertension, colon diverticulosis, ulcerative colitis, hiatal hernia, osteoporosis, and degenerative lumbar disc disease, in addition to his GERD and grade 4 esophagitis with ulceration. His error was discovered and he was withdrawn from study drug on the 9th Day. He took no more, but it was found at the 4-week visit by endoscopy 32 days after the screening endoscopy that his ulceration had improved to superficial and the esophagitis grade decreased to 2. His rabeprazole overdose caused no symptoms or apparent adverse effects.

Patient 063-8441, a 44-year-old white woman, was in an **automobile accident** on Day 30 of her study, in which she suffered a moderate concussion and abrasions of the left arm. She was hospitalized for 3 days of observation, took no more rabeprazole after the 29th dose. She returned to Dr. White's clinic where repeat endoscopy showed that her previous grade 2 erosive esophagitis had completely healed to grade 0; she still had an hiatal hernia and Schatski ring.

Patient 059-8409, a 59-year-old Afro-American man, had a history of hypertension, chronic obstructive lung disease, hiatal hernia, chronic sinusitis and allergic rhinitis, and degenerative joint disease. At his initial endoscopy he had grade 3 erosions but was not seen to have Barrett's changes then or at follow-up endoscopies 25 and 53 days later which showed improvement to grade 2 but not healing. It was then discovered that the biopsy showed Barrett's mucosa with high-grade dysplasia **suspicious for intramucosal carcinoma**. No details of follow-up treatment were obtained *(see Narrative, Volume 169, pages 412-3).*

Comment: None of these problems were evaluated by the sponsor as having been likely to have been caused by rabeprazole, with which I concur. The details of the cases, even in the narrative reports in Volume 169, were scanty. Case reports are listed in the index as being provided by CD-ROM, Volume 282.

Ranitidine group:

Patient 010-8462, a 45-year-old white woman, had a history of hypertension, diabetes mellitus, obesity, cigarette smoking, partial thyroidectomy and hypothyroidism, foot pain following two surgical procedures in 1992, anxiety, diverticulosis since 1989, hiatal hernia, previous gastric ulcer with intermittent duodenitis and gastritis. She did not heal her grade 3 erosions after 28 days on ranitidine, and on Day 44 she developed **severe chest pain**, sweating, and heaviness of the left arm. She was admitted for observation and study. Stress testing showed anteroseptal ischemia, and she was discharged on medication after two days. She stopped study drug on the 49th day, and endoscopy showed healing to grade 1 on the 58th day after the original finding of erosive esophagitis. Two weeks later, off study, she was found by catheterization to have 60% right coronary artery and 50% posterolateral branch stenosis.

Patient 034-8233, a 52-year-old white man, had a history of tension headaches, alcoholism and abrasions of the arms and hands. He was treated for a full 56 days on ranitidine, but his grade 4 erosive esophagitis failed to heal beyond a slight decrease to grade 3. After completing the study, he then presented to an emergency room 9 days later with abdominal pain, diagnosed as **acute diverticulitis** for which he was hospitalized for 3 days *(see Narrative: Volume 169, page 411 – does not agree with brief summary in safety section 7.3.1.2, Volume 164, page 85, which states he was hospitalized for 19 days)*. He was then discharged on omeprazole and metronidazole, but no further follow-up was reported.

Comment: Neither of these serious events appears to have been caused by ranitidine, but were simply intercurrent events that might be expected to occur sporadically in such a study population sample.

Discontinued from Study J Because of Adverse Events

Rabeprazole group:

Patient 010-8066, a 30-year-old white woman, had a history of irritable bowel syndrome, anxiety, endometriosis, and otitis media in addition to her GERD, erosive esophagitis and Barrett's changes. After taking study medication for 2 days, she reported that the first dose had caused **nausea and stomach pains**. Study medication was interrupted for 2 days, resumed for 2 more with recurrence of the same symptoms, and finally stopped on Day 6 *(see Volume 169, page 401)*. Her grade 3 esophageal ulcerations were unchanged at endoscopic re-examination done 18 days after the first endoscopy *(Volume 167, page 42)*.

Patient 015-8103, a 66-year-old white woman, had a history of hypertension, diverticulosis, irritable bowel syndrome, and several surgical procedures including appendectomy, hysterectomy, right ovary resection, polypectomy, right leg vein stripping, and right breast lumpectomy. After 3 days on study medication, she complained of **headache**, and study drug was stopped after 17 days. No increase in blood pressure was observed *(Volume 169, page 403)*. There was no improvement in her grade 2 esophagitis at endoscopy on Day 22.

Patient 028-8191, a 66-year-old white woman, had chronic obstructive lung disease, hypertension, penicillin allergy, and a paraesophageal hernia. She had undergone left upper lung lobectomy in 1992 for squamous cell carcinoma, and had subsequent anemia in 1995. After 52 days on study medication she developed cough diagnosed as **bronchitis** and study drug was stopped the next day, but she was continued on omeprazole. She was treated with ciprofloxacin and prednisone, and recovered but serum ALT and AST were transiently elevated slightly a week after study drug was stopped. Her grade 3 esophagitis improved to grade 2 at Day 28, and healed to grade 1 on Day 59, a week after study drug had been stopped.

Ranitidine group:

Patient 003-8015, a 37-year-old white woman, had a history of tubal ligation, insomnia, hypercholesterolemia, and anemia. Even before taking her first dose of study medication, she noted mild stomach discomfort, nausea, decreased appetite, and pain under the right breast. The **nausea** persisted, and she stopped study medication on Day 5, and the symptoms resolved the next day. Her grade 2 esophagitis was unchanged at repeat endoscopy on Day 12.

Patient 035-8240, a 38-year-old white man with no history of medical problems, noted diarrhea on the first day of taking study medication, developed a flu-like syndrome and impotence over the next 2 days. The flu symptoms subsided but the **impotence** persisted and a second episode of diarrhea occurred on Day 10, and study drug was stopped on Day 12. His grade 3 esophagitis was not re-examined. The impotence did not resolve after quitting the study.

Patient **034-8234**, a 63-year-old white man, had a history of lumber vertebral-2 fracture in 1979, right inguinal herniorrhaphy 1988. He developed **lower abdominal crampy pain** after 8 days on study medication, quit on Day 22, and recovered by Day 27. He also complained of temporal headache and of some diminished vision and "floaters" in his visual fields; ophthalmologic examination revealed sclerotic cataracts in both eyes, posterior vitreous detachments and condensations, for which corrective lenses and annual follow-up were advised. His grade 2 esophageal superficial ulceration was unchanged at re-endoscopy on Day 32.

Minor complaints were reported by over 60% of the patients, 103/168 (61%) of those on rabeprazole and 112/170 (66%) of those on ranitidine (p N.S., 0.309), most commonly headache, diarrhea, nausea, abdominal pain, and rhinitis, none of which were more frequent in the rabeprazole group than then ranitidine group. Only flatulence was more frequent (9%) in rabeprazole-treated patients, compared to 4% in ranitidine-treated patients. Dyspepsia was less frequent in the rabeprazole-treated patients (none) compared to 4% of the ranitidine-treated patients; patients on ranitidine had significantly more nausea, vomiting, and rhinitis. Amblyopia was reported in 1 patient on rabeprazole (0.6%) and in 3 on ranitidine (1.8%).

Transient serum alanine aminotransferase (ALT) elevations were seen in 7 patients during rabeprazole administration , none to as much as twice the upper limit of normal, and in 1 on ranitidine. No jaundice or other indicators of liver effects were seen.

Serum gastrin rose insignificantly in patients on ranitidine (mean of 58.2 ± 59.0 standard deviation, to 64.5 ± 44.2 pg/mL), compared to becoming significantly ($p < 0.001$) higher among patients on rabeprazole (from 63.3 ± 83.6 to 100.7 ± 79.6 pg/mL).

Examination of the gastric mucosal biopsies taken at initial and final endoscopic examinations revealed no significant differences in the distribution of ECL hyperplasia, either before or after treatment with either agent. About 85% of the patients whose biopsies were adequate for reading were normal at baseline and after treatment.

Inspection of the gastric corpus mucosal biopsies for Helicobacter pylori (Hp) showed similar proportions of patients with mild-to-moderate numbers of visible bacteria before treatment, but significantly fewer in the group treated with rabeprazole than ranitidine. There were no patients with severe or heavy infiltrates, and there was no decrease by ranitidine treatment, of the biopsy specimens that could be evaluated *(data from Table 16.2.1, Volume 164, page 231).*

MILD-MODERATE H. PYLORI INFILTRATES IN GASTRIC CORPUS MUCOSA

	rabeprazole 20 mg/d	*ranitidine 150 mg qid*	*p-value*
Before treatment	42/160 (26.3%)	48/159 (30.2%)	N.S.
After treatment	24/144 (16.7%)	44/141 (31.2%)	< 0.005
Effect of treatment	*p < 0.05*	*p = N.S.*	

Comment: Overall, rabeprazole 20 mg/day appeared at least as safe as the already approved and very widely used regimen of ranitidine 150 mg q.i.d. There were no clear-cut indicators from this study of problems to look for with special attention, but the ALT elevations will require further attention, particularly in the longer-term maintenance studies. The significantly greater rise in serum gastrin was as expected for a PPI. The disappearance of visible Hp organisms after treatment with PPIs has been observed previously for lansoprazole and omeprazole, and does not indicate eradication of the organism but some type of suppression that causes loss of ability to grow on culture, to produce active urease, and perhaps a change in morphology or numbers.

Conclusions

The sponsor concluded that this study showed rabeprazole 20 mg/day to be significantly superior to the approved dose of ranitidine 150 mg four times/day in healing erosive esophagitis and resolving heartburn symptoms, with no increase in safety risk compared to ranitidine.

Comment: The data support the sponsor's conclusions, and I agree that rabeprazole was significantly superior to the approved dose and regimen of ranitidine in healing the lesions of erosive esophagitis associated with GERD.

8 Page(s) Redacted

RAW DATA

C. Study NRRP (April 1995-March 1996): rabeprazole 20 vs omeprazole 20 mg/day

Study P was carried out in Europe by 27 investigators who enrolled 202 patients between 3 April 1995 and 15 March 1996, to compare the healing rates, in patients with erosive esophagitis, of rabeprazole 20 mg and omeprazole 20 mg each morning for 4 or 8 weeks.

Study H4M-MC-NRRP(b), entitled "[redacted]307640 Versus Omeprazole in the Treatment of Erosive or Ulcerative Gastroesophageal Reflux Disease" was planned in August 1994 by [redacted] for conduct by [redacted] (It is also referred to by Eisai Inc. in this application as Study E3810-E044-307. For brevity it will be referred to as "Study P" in this section of the medical review of this NDA 20-973.)

The protocol (see Volume 187, pages 265-95) called for enrollment of approximately 200 adults with erosive GERD of at least 3 months' duration and of severity/extent of grade 2 to 4 on a modified Hetzel-Dent scale, as evaluated at endoscopy done by a gastroenterologist, as had been specified also for Studies NRRI and NRRJ.

The number of patients was based on estimated healing of 84% of patients on rabeprazole 20 mg/day and the same for those on omeprazole 20 mg/day, with 80% power to detect a 15% difference (if omeprazole showed only 65% of patients healed, for example) at $\alpha = 0.05$ (two-tailed), by the Casagrande (1978) formula. It was stated in the protocol (Volume 187, page 272) that the healing rates expected for omeprazole were based on an unpublished meta-analysis of trials comparing omeprazole and ranitidine. Therefore, 100 patients per arm would be needed.

Comment: At the time this protocol was written, the dose of rabeprazole had been chosen as 20 mg/day from the interim analysis of Study NRRI by the independent data monitoring board. The dose and regimen for omeprazole was as approved in its labeling (Merck, 1994), 20 mg daily for 4 to 8 weeks for healing of endoscopically diagnosed erosive esophagitis of grade 2 or higher. It may be noted that the labeling stated that 61 of 83 (74%) patients with erosive esophagitis had been healed by 8 weeks on omeprazole 20 mg/day, compared to 6 of 43 (14%) on placebo. At 4 weeks, 32 of 83 (39%) had healed. A higher dose of 40 mg/day of omeprazole was no better.

Criteria for patients selection into Study P were the same as used for Studies I and J. Patients with Barrett's changes but not strictures were acceptable, but patients with primary esophageal motility disorder, previous gastric/esophageal surgical procedures, varices or pyloric stenosis were excluded. Patients were not allowed to have been treated with any PPI or H2-blocker, prostaglandin, sucralfate, within 2 weeks, or with corticosteroids, NSAIDs, anticoagulants, motility agents (metoclopramide, cisapride), anticholinergics, antidepressants, anti neoplastic agents concurrently. Patients were excluded also if they had active peptic ulcers or gastrointestinal bleeding, Zollinger-Ellison syndrome, or clinically significant renal, hepatic, cardiopulmonary, neoplastic, or other disease or drug abuse. They were to avoid foods that they knew exacerbated their symptoms, and to limit consumption of caffeine, alcohol, and tobacco.

If eligible and consenting, patients were to take one tablet with water each morning, which could be either LY307640/E3810/rabeprazole 20 mg tablets or omeprazole 20 mg capsules. In addition to 4-week supplies of these study medications, patients were given Maalox® or Mylanta® tablets for relief if needed. Patients were instructed that they could use acetaminophen for pain during the study, but not salicylates other than low-dose aspirin for cardiovascular disease prophylaxis.

Comment: It was not clear from the protocol whether the medications were blinded at all, but it was stated in the report that the study used matching placebos (Report, Volume 187, page 34).. Many of the patients and all of the investigators were familiar with the appearance of omeprazole 20 mg capsules of PRILOSEC®, even if not with the new rabeprazole tablets. The protocol does not mention the provision of placebo tablets of rabeprazole for those randomized to omeprazole, nor of omeprazole placebo capsules for those randomized to rabeprazole. Although the protocol has a standard section on blinding (Section 3.7, page 6 of the protocol, see Volume 187, page 273), it would not appear that blinding was well planned in the protocol.

Measures of efficacy were the same as had been used in Studies I and J. After the screening endoscopy the patients were scheduled to return at 4 weeks (28±3 days) and, if not healed to grade 0 or 1, at 8 weeks (56±3 days) after starting blinded medication regimen. The primary measure of treatment success was to be healing of the esophagitis to grade 0 or 1 by endoscopy. The protocol does not specify what should be done if the patient shows healing at 4 weeks, in which respect it is more like the protocol for Study I than for Study J

Secondary measures of effectiveness of treatment were the frequency, daytime and nighttime severity of heartburn, and overall well-being, as listed in paragraph 3.9.1.2. of the protocol *(Volume 187, pages 275-9)*. Scales used for rating secondary measures were the same as for Studies NRRI and NRRJ.

Secondary measures of effectiveness of treatment were to be graded by the patients on daily diaries for the first week of blinded treatment and by the investigators at each visit for the previous day *(Case Report Form, Volume 187, page 306-320)*, of the frequency, daytime and nighttime severity of heartburn, and overall well-being, as listed in paragraph 3.9.1.2. of the protocol *(Volume 187, pages 275-6)*.

It was planned in the protocol to compare proportions of patients healed using Mantel-Haenszel statistics, stratified by investigative site. The primary intent-to-treat (ITT) analysis was to consider a missing endoscopy report as the same as the most recent non-missing result, that would "allows all randomized patients to be analyzed, and treats missing values as treatment failures unless the patient has already healed at a previous visit." A second method based on only endoscopies performed (ENDO) would consider endoscopies missing after healing was observed would be counted as healing. It was stated that "While the ITT method tends to underestimate and the ENDO method tends to overestimate the true healing rates, these estimations are not problematic since treatment effects are the parameters of interest, not individual group healing rates." *(Volume 187, page 283)*. No interim analyses were planned for this study.