Severity of Daytime Heartburn Pain
0 = none
1 = mild (present but causing little or no discomfort)
2 = moderate (annoying, but not interfering with daily activities)
3 = severe (causing marked discomfort and some interference with daily routine)
4 = terrible (disabling; interferes considerably with daily routine)

Severity of Nighttime Heartburn Pain
0 = none
1 = mild (disturbing, but the patient immediately goes back to sleep)
2 = moderate (annoying; the patient remains awake for a time before going back to sleep)
3 = severe (causing marked discomfort; the patient has difficulty returning to sleep)
4 = terrible (disabling; the patient is unable to get to sleep due to the discomfort)

Frequency of Symptoms
0 = none
1 = few (occurring <25% of the days since the preceding visit)
2 = several (occurring ≥25% but <50% of the days since the preceding visit)
3 = many (occurring ≥50% but <75% of the days since the preceding visit)
4 = continual (occurring >75% of the days since the preceding visit)

Classification of Patient's Well-Being
0 = very good
1 = good
2 = fair
3 = poor
4 = very poor

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." A third method to be used was a life-table technique that considers only patients "at risk" of healing at any given visit, from randomization to observed healing. An interim analysis of unblinded results provided by Pharmaco by a statistician of the data monitoring board was scheduled, for determination of the most appropriate dose only, for planning of subsequent studies, but not for interruption of this study nor were results to be communicated to Pharmaco or investigators. The protocol did not state what was to be done with patients healed at 4 weeks.

Comment: The stated analytical method explanation is confusing and contains a serious flaw in that healing is assumed at 8 weeks even if treatment was not given for 8 weeks. It is very well known that erosive esophagitis is extremely likely to recur after healing, and there cannot be any assurance that a patient healed at 4 weeks, then discontinued from treatment would still be healed at 8 weeks. The study was not powered to make significant distinctions between doses.

Study I was conducted from November 1993 to March 1994, by 20 investigators contracted by Pharmaco to participate; 2 others were recruited but enrolled no patients. In total, they randomized 103 patients (Volume 176, pages 347-55):

Investigator	*R 10*	*R 20*	*R 40*	*placebo*	*total*
001 S. R. Bazer, Durham NC	1	1	0	0	2
002 J. R. Breiter, Manchester CT	2	2	2	2	8
003 M. D. Brown, Berwyn IL	1	1	1	1	4
004 A. Coas, Ocoee FL	2	2	2	2	8
005 C. L. Colip, Portland OR	2	2	2	2	8
006 J. A. DiPalma, Mobile Al	1	0	0	0	1
007 E. R. Dorsch, Houston TX	1	1	1	1	4
008 N. Gitlin, Atlanta GA	2	2	2	2	8
009 D. Y. Graham, Houston TX	0	0	0	0	0
010 V. G. K. Hee, Vancouver WA	2	2	2	2	8
011 D. Johnson, Norfolk VA	2	2	2	2	8
012 D. Kruss, Oak Park IL	1	1	1	1	4
013 F. L. Lanza, Houston TX	2	2	2	2	8
014 A. Mangione, Jenkintown PA	1	0	1	0	2
015 L. Kirkegaard, Olympia Wa	0	0	1	1	2
016 C. M. Prather, Rochester MN	0	0	0	0	0
017 M. Robinson, Oklahoma City OK	1	1	1	1	4
018 W. M. Roufail, Winston-Salem NC	1	1	1	1	4
019 F. Ramirez, Phoenix AZ	1	1	1	1	4
020 K. Unnoppet, Birmingham AL	1	1	1	1	4
021 L. D. Wruble, Memphis TN	2	2	2	2	8
022 W. C. Wu, Winston-Salem NC	1	1	1	1	4
total	27	25	26	25	103

Note: R 10, rabeprazole 10 mg/day; R 20, rabeprazole 20 mg/day; R 40, rabeprazole 40 mg/day.

Of the 103 patients randomized by the 20 investigators), 77 (75%) were men and 26 were women (25%), ranging in age from 20 to 77 (mean 50) years and 18 were 65 or older. The four randomized groups were "comparable" in distributions of gender, age, race, weight, height, tobacco or alcohol use, caffeine consumption, number of doses of antacids used in the three days before starting study medication. Of the 103 randomized patients, 57 (55%) had grade 2 erosions, 37 (36%) grade 3, and 9 (9%) grade 4 deep or extensive ulcerations., and 52/103 (50%) had grade 4 frequency of heartburn (at 75% of the days before study). The severity of daytime heartburn was mild or moderate for 62% of the 103 patients and severe for 20%, and nighttime

heartburn severity was similar. Only 2 patients had disabling daytime heartburn and 6 had very severe, grade 4 nighttime heartburn, with no apparently significant differences between study groups *(Table 2.5, Volume 177, page 12)*. Most of the patients, 74/103 (72%) had been using antacids before the study, taking a mean of 2.8 doses per day.

Comment: The report does not state how many other patients were screened but were not eligible for various reasons. No formal statistical calculations were presented in the report (Volume 176, pages 52-3) or Table 2.1 (Volume 177, pages 5-8) for comparisons of the randomized groups at baseline, before treatment.

Results of the planned ITT and ENDO analyses gave very similar findings, that significantly more ($p < 0.001$) patients were healed by any of the three rabeprazole doses than by placebo at both 4 and 8 weeks. In these analyses the number of patients healed at 8 weeks included also those who had been healed at 4 weeks but were not treated in the second 4 weeks thereafter. Among the three doses of rabeprazole, there were no significant differences ($p > 0.3$) in healing rates, although in all cases the rates for 10 mg rabeprazole were slightly better than for either 20 or 40 mg/day:

PROPORTIONS OF PATIENTS HEALED (TO GRADE 0 OR 1)

week	placebo	rabeprazole 10 mg	rabeprazole 20 mg	rabeprazole 40 mg
ITT	*25 patients*	*27 patients*	*25 patients*	*26 patients*
4	0 (0.0%)	17 (63.0%)	14 (56.0%)	14 (53.8%)
8	3 (12.0%)	25 (92.6%)	21 (84.0%)	22 (84.6%)
ENDO	*24 patients*	*27 patients*	*24 patients*	*25 patients*
4	0 (0.0%)	17 (63.0%)	14 (58.3%)	14 (56.0%)
8	3/20 (15.0%)	25 (92.6%)	21 (87.5%)	22 (88.0%)

Comment: The two types of analysis yield very similar results because only a few patients had missing values, and the differences between rabeprazole and placebo were quite large in all cases, giving highly significant ($p < 0.001$) results by stratified mantel-Haenszel chi-square statistics. However, for a dose ranging study in which the intent was to determine the best dose to use in further studies, the numbers of patients enrolled were far too small to detect any significant differences. What they found was that rabeprazole was far better than placebo, but they did not determine the best dose to use.

If the fact that patients who were healed at 4 weeks were no longer treated or observed, then a more correct analysis would be to examine separately those who were treated for 8 weeks, i.e., 25 patients on placebo, 10 on rabeprazole 10 mg/day, 11 on rabeprazole 20 mg/day, and 12 on rabeprazole 40 mg/day. The proportions healed after the second 4 weeks of treatment were still quite different: 3/25 (12.0%) on placebo, 8/10 (80.0%) on rabeprazole 10 mg, 7/11 (63.6%) on rabeprazole 20 mg, 8/12 (66.7%) on rabeprazole 40 mg. Even by a very conservative chi-square with Yates-correction and the relatively small numbers of patients treated with rabeprazole for more than 4 weeks, these results still show quite significantly better healing effect of rabeprazole for all three doses (10 mg, $p < 0.001$; 20 mg, , $p < 0.006$; and 40 mg, , $p < 0.004$). However, no

dose of rabeprazole was established by this alternative analysis, either. The reported secondary benefits of reducing frequency and severity of heartburn also appear to have been calculated using the same "last-observation-carried-forward" analyses for patients who were healed at 4 weeks and for whom no data were obtained for 8 weeks of treatment. Therefore, it may be more pertinent to consider only the 4-week ITT data for these secondary outcome measures.

Not all of the patients in the study had heartburn before randomized treatment, so proportions of patients in whom heartburn frequency of severity were reduced could only be determined for those who had the symptoms before treatment. Such patients had erosive esophagitis discovered despite lack of symptoms at the time. Considering only the 4-week results from the study report *(Volume 176, pages 57-59)*:

IMPROVEMENT IN HEARTBURN SYMPTOMS AFTER 4 WEEKS OF TREATMENT

Heartburn	placebo	rabeprazole 10 mg	rabeprazole 20 mg	rabeprazole 40 mg
Improvement				
frequency	10/25 (40.0%)	23/26 (88.5%)	20/25 (80.0%)	23/26 (88.5%)
day severity	15/23 (65.2%)	23/23 (100%)	17/19 (89.5%)	22/2 (100%)
night severity	17/23 (73.9%)	24/25 (96.0%)	16/22 (72.7%)	22/23 (95.7%)
Resolution				
frequency	1/25 (4.0%)	13/26 (50.0%)	7/25 (28.0%)	14/26 (53.8%)
day severity	8/23 (34.8%)	20/23 (87.0%)	14/19 (73.7%)	18/22 (81.8%)
night severity	11/23 (47.8%)	21/25 (84.0%)	15/22 (68.2%)	21/23 (91.3%)

In these analyses, the ITT population was considered, and improvement was defined as any reduction in grade, while resolution was defined as improvement to none (grade 0). The observed differences between placebo and all of the rabeprazole treatments were again noted. When compared by chi-square analyses, the rabeprazole 10 and 40 mg doses were very significantly better ($p < 0.001$) than placebo for reduction and resolution of heartburn frequency, while the 20-mg dose was significantly better than placebo, the differences were less marked ($p = 0.005$; $p = 0.026$). Reduction in daytime heartburn was reported to be more impressive than for night time heartburn, but the effects of the 10 and 40-mg doses of rabeprazole were still significantly better than placebo. The 20-mg dose of rabeprazole failed to produce any improvement in nighttime heartburn ($p = 0.920$), did not show significantly better resolution of night heartburn ($p = 0.198$) or improvement in day heartburn ($p = 0.099$), although it did show significantly ($p = 0.022$) better resolution of day heartburn.

The patients' reports of general well being were less sensitive to change on these treatments, and although higher proportions said they felt better after 4 weeks of rabeprazole than placebo, the differences were significant only for the 10-mg rabeprazole dose. The number of doses of antacid used were less in all four study groups, but fell significantly more in the patients treated with rabeprazole. There were no significant differences between rabeprazole doses. Comparing the average numbers of antacid doses used per day (not the numbers of tablets) from the 3 days before admission to the average number used/day in the first 28 days on treatment:

AVERAGE ANTACID DOSES PER DAY, MEAN ± STANDARD DEVIATION

	placebo	rabeprazole 10 mg	rabeprazole 20 mg	rabeprazole 40 mg
	25 patients	*27 patients*	*25 patients*	*26 patients*
Pretreatment	3.28±3.47	3.15±4.79	2.64±3.26	2.23±1.48
On study, 28 days	1.69±1.69	0.80±1.30	0.55±0.97	0.33±0.81
difference	-1.59±2.10	-2.35±4.94	-2.09±3.00	-1.90±1.48
p value vs placebo		0.007	0.002	<0.001

Comment: Although the decrease in antacid doses was greatest in the group on 10 mg rabeprazole, the variance was larger, so the difference from placebo was less significant but still highly so. As reported (Volume 176, page 6), the results at 8 weeks did not take into consideration the reduced numbers of patients on study for the second 4 weeks, and are not summarized here.

Analyses of healing rates by retrospective subset analyses did not reveal any significant effects. The men showed slightly more (51/58, 87.9% healed) pronounced effect of rabeprazole than did the women (17/20, 85.0%), and less healing on placebo, although the relatively small number of women in the study, and in each treatment group, requires that these effects be interpreted with caution. As taken from Table 10.1 (Volume 177, pages 30-3):

HEALED PROPORTIONS BY 8 WEEKS, BY GENDER

	placebo	rabeprazole 10 mg	rabeprazole 20 mg	rabeprazole 40 mg
men	1/19 (5.3%)	19/20 (95.0%)	13/17 (76.5%)	19/21 (90.5%)
women	2/6 (33.3%)	6/7 (85.7%)	8/8 (100%)	3/5 (60.0%)

None of the analyses of age, race, tobacco/alcohol/caffeine consumption, antacid use, GERD symptoms pre-treatment, severity/extent of erosions, improvement in symptoms, treatment/time to healing, or compliance with study medication had effect on the primary outcome.

Safety problems were infrequent in this study, but three patients dropped out for adverse events, two from the placebo group and one from the rabeprazole 40-mg group. The reasons for these actions were: pneumonia after 42 days of placebo treatment in patient 008-4546, a 21-year-old white man; an arterial thrombosis after 31 days on placebo in patient 011-4662, a 67-year-old white man; and dizziness after 5 days of rabeprazole 40 mg/day in patient 005-4665, a 69-year-old white woman. In addition, patient 021-4624, a 67-year-old white man, was discovered to have a colon cancer after completion of the study. There were no deaths in the study.

Patient 005-4665 was a 69-year-old white female who was found to have grade 4 erosive esophagitis on 13 January 1994 and was randomized to rabeprazole 40 mg/day. She had a history of post-menopausal osteoarthritis, intermittent diarrhea and constipation, hiatal hernia, and anemia. She complained of **dizziness** beginning on the day after starting study medication, and withdrew from the study after 4 doses. Examination showed no decreases in blood pressure or blood hemoglobin/hematocrit, compared to the baseline levels, and no other explanation for her symptoms.

Patient 008-4546 was an obese (BMI 30.5) 21-year-old white male who developed **pneumonia** diagnosed 25 days after he had been randomized to placebo for treatment of grade 2 erosions on 8 December 1993, and he quit the study 16 days later after 42 doses of the study medication. He was treated with antibiotics and recovered; no further studies were done.

Patient 011-4662 was a 67-year-old white male who had a history of coronary angioplasty, aorto-bifemoral bypass, groin bypass, left and right femoral bypass and previous thrombectomy. He was hypertensive, hypercholesterolemic, had histories of kidney infection and prostatic hyperplasia. He was found to have grade 4 erosive esophagitis on 12 January 1994 and was randomized to placebo. **Arterial occlusion** in the right lower leg was diagnosed 11 February, and he had a femoral-femoral and femoral-popliteal bypass done 3 days later, which failed to prevent recurrent occlusion on the 7th post-operative day and necessitated a second right femoral-popliteal bypass on 22 February. He was treated with heparin and later with warfarin after discharge. His follow-up endoscopy showed no improvement in the esophageal ulceration.

Patient 021-4624 was a 67-year-old white male who entered the study after discovery of grade 2 esophageal erosions on 8 December 1993 and was successfully treated to healing on 27 days of rabeprazole 20 mg/day. About a week later he called on 12 January 1994 to report rectal bleeding with bowel movements, and was found to have **adenocarcinoma of the sigmoid colon**, considered to have predated the study and unrelated to study medication.

Comment: The serious adverse events observed – pneumonia, arterial thrombosis, and colon cancer – were not likely to have been caused by study medication, especially since the first two were seen in patients randomized to placebo. It is possible that the rabeprazole caused dizziness in the patient (005-4665) on rabeprazole 40 mg, but highly unlikely that sigmoid adenocarcinoma could have been caused by 27 days of rabeprazole 20 mg.

Other adverse effects that did not cause serious effects or discontinuation from the study were seen in all four study groups. Most of the patients (60/103, 58%) had at least one symptom during the study, but there was no significant increase in any of them over what was seen in the placebo group. The most frequent symptoms reported were diarrhea (16%), headache (16%), rhinitis (15%), flu syndrome (10%), pharyngitis (10%), nausea (9%), vomiting (7%), asthenia (5%), and cough (5%). It may be noted that most of the patients entered the study in November-December-January of 1993-4, so that upper respiratory viral infections were prevalent at the time the study was being done. There were no clear dose-relationship to adverse events in the rabeprazole-treated groups, with the possible exception of dizziness, seen in 3/26 (11.5%) of the patients on 40 mg/day, compared to none on the lower doses or placebo; perhaps because of the small numbers involved, this result was not statistically significant. The 10-mg rabeprazole group had significantly ($p = 0.004$) fewer patients (11/27, 41%) reporting at least one complaint than were reported by patients taking 20 mg of rabeprazole (20/25, 80%); the difference was in fewer reports of flu syndrome, diarrhea, vomiting, and dizziness in those on the lower dose.

Laboratory tests showed no clinically significant changes indicating an excess incidence of abnormalities in rabeprazole-treated patients compared to those on placebo, nor any rabeprazole-

dose-related patterns of abnormalities (see Section 7.3, Volume 176, pages 86-94). Serum gastrin levels were clearly increased by rabeprazole, and in a dose-related manner, which became significant for the 20 and 40-mg rabeprazole doses. The mean change (± standard error) in serum gastrin levels from before the study to the endpoint (or last observation) was:

Serum Gastrin	placebo	rabeprazole 10 mg	rabeprazole 20 mg	rabeprazole 40 mg
pg/mL	*23 patients*	*27 patients*	*24 patients*	*26 patients*
mean change	- 14.7	+ 18.0	+ 31.8	+ 36.2
standard error	19.8	7.3	14.6	18.8
p vs placebo		0.210	0.007	< 0.001

Gastric biopsies taken from the gastric corpus mucosa (4 or more full thickness specimens taken about 10 cm below the cardia, oriented on filter paper with mucosa up, and fixed in neutral buffered formalin) were taken at the first and last endoscopic examinations. The fixed specimens were shipped to and reviewed by Dr. Y. Dayal in Boston MA (*Volume 176, page 135*). Stains by hematoxylin and eosin were evaluated for chronic gastritis (grade 0, normal; grade 1, chronic superficial gastritis, grade 2, chronic interstitial gastritis, or grade 3, chronic atrophic gastritis). Silver impregnation techniques were used to evaluate argyrophilic enterchromaffinlike (ECL) cell growth (grade 0, normal; grade 1, diffuse; grade 2, linear; grade 3, micronodular; grade 4, adenomatoid; grade 5, dysplastic; grade 6, carcinoid). No significant differences were seen between treatment groups with respect to either gastritis or ECL growth, although 3 patients on 40 mg rabeprazole/day showed diffuse ECL growth at endpoint, compared to none in the other groups or before treatment (*Table NRRI.17.7, Volume 176, page 97*). Vital signs, including blood pressure, pulse and respiratory rates, electrocardiograms, and body weight showed no significant changes or differences between groups in this study.

It was concluded by the sponsor (*Volume 176, pages 103-6*) that rabeprazole, in all three doses of 10, 20, and 40 mg/day, was significantly more effective than placebo in healing erosive esophageal lesions, and in reducing heartburn frequency and need for antacid doses for relief. There were no significant differences between the three rabeprazole doses seen in this study. No notable safety problems were observed that could be attributed clearly to rabeprazole or that showed a rabeprazole dose-relationship.

Comment: Rabeprazole, in this "dose-ranging" study, proved to be clearly superior to placebo in healing erosions of esophagitis associated with GERD, but the study did not establish the best dose to be used. If the principle of lowest effective dose were invoked, the dose indicated for the healing of erosive esophagitis supported by this study would be 10 mg/day for 4 or 8 weeks, with interim endoscopic inspection at 4 weeks to determine if healing had occurred, as it had by then in 17/27 (63%). In fact, the 10-mg dose was slightly better than either the 20 or 40-mg daily doses, although this study was not powered to prove differences between rabeprazole doses, and the differences observed were not statistically significant. It was of interest that the larger and more extensive esophageal lesions took significantly longer to heal on rabeprazole; none of the 5 grade 4 ulcerations were healed at 4 weeks, whereas 46% of the 28 grade 3 and 71% of the 45 grade 2 lesions were healed then, with no significant differences between rabeprazole doses.

Study NRRI, Appendix I-A
Accounting for all patients randomized

ESOPHAGEAL EROSIONS IN PATIENTS RANDOMIZED TO **PLACEBO**

inv-pt no	*s-r-a*	*screened*
002-4507	Mc40	23-Nov-93
002-4633	Fc42	07-Dec-93
003-4514	Mc43	20-Nov-93
004-4519	Mc56	24-Nov-93
004-4524	Fc41	23-Dec-93
005-4525	Mc66	24-Nov-93
005-4666	Mc49	19-Jan-94
007-4588	Mc35	14-Dec-93
008-4546	Mc21	08-Dec-93
008-4650	Mc46	15-Dec-93
010-4558	Fc62	26-Nov-93
010-4660	Mc47	07-Jan-94
011-4563	Mc54	09-Dec-93
011-4662	Mc67	12-Jan-94
012-4571	Mc57	26-Jan-94
013-4573	Mc55	18-Nov-93
013-4578	Fc42	09-Dec-93
015-4585	Mc36	14-Jan-94
017-4599	Mc45	16-Dec-93
018-4606	Mc75	12-Jan-94
019-4610	Mc46	07-Dec-93
020-4615	Fc61	15-Dec-93
021-4623	Mc51	07-Dec-93
012-4626	Fc44	14-Dec-93
022-4628	Mc56	13-Dec-93
total	*19m/6f*	

Note: inv-pt no, investigator and patient identification numbers; s-r-a, sex, race, age of patient; score 0, baseline erosion score; Rx days 1, treatment days until first endoscopy on study; score 1, erosion score after 4 weeks; RX days 2, treatment days until second endoscopy, score 2 erosion score after 8 weeks treatment; M/m, male; F/f, female; c, Caucasian, b, Black, h, Hispanic.

Patient 002-4507 dropped out after 24 days of treatment; he had complained of terrible daytime and severe nighttime heartburn, despite endoscopic improvement from esophageal ulcerations to erosions of grade 2 extent. Patient 010-4660 quit the study after endoscopy showed no improvement at 28 days, and continual moderate daytime heartburn continued. Patient 011-4662 also showed no endoscopic response at 28 days, although heartburn severity had improved but remained continual. (*See Patient Listings 4 and 5, Volume 177, pages 201-14 and Volume 178, pages 1-4*).

Study NRRI, Appendix I-B
Accounting for all patients randomized

ESOPHAGEAL EROSIONS IN PATIENTS RANDOMIZED TO RABEPRAZOLE 10 MG/DAY

inv-pt no	*s-r-a*	*screened*
001-4503	Fc77	02-Feb-94
002-4508	Mc47	23-Nov-93
002-4634	Mc47	09-Dec-93
003-4516	Mc35	13-Dec-93
004-4521	Mc75	13-Dec-93
004-4646	Fc58	27-Jan-94
005-4528	Fc69	30-Nov-93
005-4664	Mc46	27-Dec-93
006-4531	Mc46	24-Jan-94
007-4540	Fc30	25-Jan-94
008-4543	Mc59	10-Dec-93
008-4651	Mc50	17-Dec-93
010-4556	Mc51	22-Nov-93
010-4659	Mc55	03-Jan-94
011-4561	Fc64	03-Dec-93
011-4647	Mc29	06-Jan-94
012-4569	Fc62	29-Dec-93
013-4576	Mc63	06-Dec-93
013-4643	Mc45	14-Dec-93
014-4582	Mc54	04-Feb-94
017-4600	Mc59	20-Dec-93
018-4604	Mc71	28-Dec-93
019-4611	Mc71	17-Dec-93
020-4616	Mc24	20-Dec-93
021-4622	Mc29	07-Dec-93
021-4668	Fc29	06-Jan-94
022-4629	Mc67	04-Jan-94
total	*20m/7f*	

Note: inv-pt no, investigator and patient identification numbers; s-r-a, sex, race, age of patient; score 0, baseline erosion score; Rx days 1, treatment days until first endoscopy on study; score 1, erosion score after 4 weeks; RX days 2, treatment days until second endoscopy, score 2 erosion score after 8 weeks treatment; M/m, male; F/f, female; c, Caucasian, b, Black, h, Hispanic.

Study NRRI, Appendix I-C
Accounting for all patients randomized

ESOPHAGEAL EROSIONS IN PATIENTS RANDOMIZED TO RABEPRAZOLE 20 MG/DAY

inv-pt no	*s-r-a*	*screened*
001-4501	Mc35	07-Jan-94
002-4511	Fc43	06-Dec-93
002-4512	Mc29	15-Nov-93
003-4515	Mc32	30-Nov-93
004-4520	Fc63	29-Nov-93
004-4523	Fc71	22-Dec-93
005-4526	Mc66	29-Nov-93
005-4667	Mc68	31-Jan-94
007-4537	Fc46	30-Nov-93
008-4544	Mc28	09-Dec-93
008-4649	Mc39	15-Dec-93
010-4555	Mc43	18-Nov-93
010-4640	Mc44	31-Dec-93
011-4565	Mc48	30-Dec-93
011-4566	Mb47	29-Dec-93
012-4567	Mc49	09-Dec-93
013-4574	Fc58	23-Nov-93
013-4644	Fc47	16-Dec-93
017-4597	Mc51	01-Dec-93
018-4605	Fc33	31-Dec-93
019-4612	Mc38	28-Jan-94
020-4617	Fc44	21-Dec-93
021-4624	Mc67	08-Dec-93
021-4653	Mc29	17-Dec-93
022-4630	Mc59	06-Jan-94
total	*17m/8f*	

Note: inv-pt no, investigator and patient identification numbers; s-r-a, sex, race, age of patient; score 0, baseline erosion score; Rx days 1, treatment days until first endoscopy on study; score 1, erosion score after 4 weeks; RX days 2, treatment days until second endoscopy, score 2 erosion score after 8 weeks treatment; M/m, male; F/f, female; c, Caucasian, b, Black, h, Hispanic.

Patients 003-4515 and 005-4667 dropped out of the study after only 15 and 4 days of treatment, respectively, because they felt lack of efficacy of treatment; both complained of "terrible" nighttime heartburn (see Patient Listing 5, Volume 178, pages 18-9).

Study NRRI, Appendix I-D
Accounting for all patients randomized

ESOPHAGEAL EROSIONS IN PATIENTS RANDOMIZED TO RABEPRAZOLE 40 MG/DAY

inv-pt no	*s-r-a*	*screened*
002-4509	Mc35	02-Dec-93
002-4510	Mc46	03-Dec-93
003-4513	Fc63	20-Nov-93
004-4522	Mc68	15-Dec-93
004-4645	Fc64	18-Jan-94
005-4527	Mc44	30-Nov-93
005-4665	Fc69	13-Jan-94
007-4539	Mc36	05-Jan-94
008-4547	Mc20	09-Dec-93
008-4548	Mc62	11-Dec-93
010-4559	Mc31	29-Nov-93
010-4639	Mc25	17-Dec-93
011-4562	Fc61	03-Dec-93
011-4648	Mc70	07-Jan-94
012-4570	Mc69	06-Jan-94
013-4575	Mc29	06-Dec-93
013-4577	Mc48	07-Dec-93
014-4583	Mc63	04-Feb-94
015-4587	Mc71	26-Jan-94
017-4598	Mc35	13-Dec-93
018-4603	Mc49	30-Nov-93
019-4609	Mc42	22-Nov-93
020-4618	Mc34	21-Dec-93
021-4621	Mc63	23-Nov-93
021-4654	Mc45	30-Dec-93
022-4627	Fb44	30-Nov-93
total	*21m/5f*	

Note: inv-pt no, investigator and patient identification numbers; s-r-a, sex, race, age of patient; score 0, baseline erosion score; Rx days 1, treatment days until first endoscopy on study; score 1, erosion score after 4 weeks; RX days 2, treatment days until second endoscopy. score 2 erosion score after 8 weeks treatment; M/m, male; F/f, female; c, Caucasian, b, Black, h, Hispanic.

Comment: It was decided to identify each patient randomized into this healing study, mainly in order to be able to follow into maintenance treatment those who entered the subsequent Study NRRK-odd/even. It was also done to evaluate the healing responses in terms of the initial lesion severity, and to assess the effects of the second 4 weeks of treatment separately for those who had it. This will be done also for the other healing Studies NRRJ and NRRP.

B. Study NRRJ (February-September 1995): rabeprazole vs ranitidine

Study H4M-MC-NRRJ, entitled "[redacted]307640 Versus Ranitidine in the Treatment of Erosive or Ulcerative Gastroesophageal Reflux Disease" was planned in September 1994 by [redacted] for conduct by [redacted] (It is also referred to in this application as Study E3810-A001-303 by Eisai Inc. For brevity it will be referred to as "Study J" in this section of the medical review of this NDA 20-973.)

The protocol *(Volume 164, pages 278-99)* called for enrollment of approximately 310 adults with erosive GERD of at least 3 months' duration and of severity/extent of grade 2 to 4 on the same modified Hetzel-Dent scale, as evaluated at endoscopy done by a gastroenterologist, as had been specified also for Study NRRI.

The number of patients was based on estimated healing of 70% of patients on rabeprazole 20 mg/day and 54% of those on ranitidine 150 mg q.i.d., with 80% power to detect this difference at $\alpha = 0.05$ two tailed, by the Casagrande (1978) formula. It was stated in the protocol (Volume 164, page 285) that the healing rates expected for ranitidine were based on an unpublished meta-analysis of clinical trials comparing omeprazole and ranitidine. By those estimates 155 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 rantidine was as approved in its labeling (Glaxo, 1993), 150 mg four times a day for healing of endoscopically diagnosed erosive esophagitis. It may be noted that the labeling stated that 142 of 200 (71%) patients with erosive esophagitis had been healed by 8 weeks on ranitidine 150 mg q.i.d., compared to 63 of 176 (36%) on placebo. At 4 weeks, 96 of 206 (47%) had healed, and by 12 weeks 162/192 (84%) had healed on ranitidine. It is unclear why the study size estimates were based on assuming only 54% of patients on that dose of ranitidine would be healed by 8 weeks. In fact, as has been noted in the comments on Study NRRI the healing rates might very well depend heavily on the relative proportion of patients with grade 4 and grade 3 esophageal lesions, which heal more slowly than grade 2 erosions.

Criteria for patients selection into Study J were as used for Study I. 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 advised 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 [redacted]307640/E3810/rabeprazole 20 mg or matching placebo, plus tablets four times each day that could be either ranitidine 150 mg or its matching placebo. In addition to 4-week supplies of these study medications, patients were given 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.

Measures of efficacy were the same as had been used in Study I. 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. Patients healed at 4 weeks were not required to return for visit 3 at 8 weeks, but their results were to be interpreted as showing healing at 8 weeks also.

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. in the protocol *(Volume 164, pages 288-9)*. Scales used for rating secondary measures were the same as used in Study I for frequency of heartburn, severity of day and night heartburn, well-being. 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 (see sample Case Report From, Volume 164, page 323-30), 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 164, pages 288-9).

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." A third method to be used was a life-table technique that considers only patients "at risk" of healing at any given visit, actually the time from randomization to observed healing, a method that "tends to produce results that lie between the previous two methods . . . does not allow comparison at each endoscopy, so it is not the primary method of analysis." No interim analyses were planned for this study.

Study J was executed from 9 February to 1 September 1995 by 63 investigators who were under contract to Pharmaco to recruit and study patients; 3 others were recruited but enrolled no patients. They randomized 338 patients, 169 to each study arm. There were 231 men (68.3%) and 107 women, 302 (89.4%) of whom were Caucasian, 23 (6.8%), African descent (6.8%), and 13 of other racial heritage (3.8%). They ranged in age from 19 to 86 years of age (mean 50.9). Most

of them (66%) used antacids for relief of GERD symptoms, taking an average of 5.3 doses/day. At the screening endoscopy to determine eligibility, 173 (51%) had grade 2 erosive lesions, 129 (38%) grade 3, and 34 (10%) grade 4. Most (54%) of them complained of "continual" heartburn, grade 4 or >75% of the days, and only 14/338 (4%) had no heartburn (*Volume 164, pages 67-8*). The investigators included (*see Volume 164, pages 342-8*):

Investigator, City	*rabeprazole*	*ranitidine*	*total*
001/R. Aaronson, Chicago Heights IL	4	4	8
002/A. Archambault, Montreal, Quebec	1	2	3
003/R. Baerg, Tacoma WA	2	2	4
004/R. Bailey, Edmonton, Alberta	4	4	8
005/D. Ballard, Cincinnati OH	2	2	4
006/C. Birbara, Worcester MA	2	2	4
007/P. Bird, Norman OK	4	4	8
008/M. Brandon, San Diego CA	4	4	8
009/W. Bray, Charlotte NC	2	2	4
010/J. R. Breiter, Manchester CT	8	8	16
011/J. Caldwell, Daytona Beach FL	3	3	6
012/D. Campbell, Kansas City MO	4	4	8
013/A. Coas, Ocoee FL	4	4	8
014/I. Cleator, Vancouver, British Columbia	2	1	3
015/C. L. Colip, Portland OR	4	4	8
016/D. Collins, Arvada CO	4	4	8
017/D. Daly, Montreal, Quebec	2	1	3
018/M. Drehobl, San Diego CA	2	2	4
019/T. Durbin, Long Beach CA	2	2	4
020/M. Eisner, Zephyrhills FL	4	4	8
021/A. Farley, Montreal, Quebec	5	5	10
022/R. Fogel, Detroit MI	2	2	4
023/N. Gitlin, Atlanta GA	2	1	3
024/D. Gremillion, Nashville TN	2	2	4
025/G. K. Hee, Vancouver WA	2	2	4
026/S. Ho, Minneapolis MN	2	2	4
027/R. Hunt, Hamilton, Ontario	0	0	0
028/D. Johnson, Norfolk VA	5	5	10
029/J. Kaine, Sarasota FL	2	2	4
030/N. Kassman, Statesville NC	2	2	4
031/S. Katz, Great Neck NY	*3*	*4**	7
032/T. Kovacs, Los Angeles CA	2	2	4
033/D. Kruss, Oak Park IL	2	2	4
034/F. L. Lanza, Houston TX	4	4	8
035/D. Leddin, Halifax, Nova Scotia	4	4	8
036/*none			
037/ A. McCullough, Cleveland OH	2	2	4
038/ A. McElroy, Johnson City TN	2	2	4