Comment: Since this study was intended to show equivalence of rabeprazole to omeprazole, rather than superiority over it, statistical evidence that the two treatments were "similar" was based on a 95% confidence interval that contained the zero difference point and the lower limit greater than -15% difference. Proportions of patients healed on the two treatments p_r and p_o were to be used to construct the interval as $[(p_r \text{ and } p_o) \pm 1.96\{p_r(1-p_r)/n_r + p_o(1-p_o)/n_o\}^{1/2}]$, as shown in the protocol, page 16; Volume 187, page 283.

The protocol was amended on 2 February 1995 to provide for obtaining two additional biopsy specimens from the antral mucosa, one anterior and one posterior within 2 cm of the pylorus, and on 30 June 1995 to include thyroid function tests before and after treatment because of toxicology findings in dogs of slight thyroid follicular hypertrophy. Also, Sweden excluded patients on oral contraceptives or anti-epileptics because of possible interaction with rabeprazole. Study P was executed from 3 April 1995 to 15 Mar 1996 by 27 investigators who were under contract to Besselaar to recruit and study patients. Investigators were (*Volume 188, pages 4-6*):

Investigator, City	*rabeprazole*	*omeprazole*	*total*
001/ Pierre Hoang, Brussels, Belgium	2	2	4
021/ Jorgen Pederson, Solrod Strand, Denmark	1	0	1
023/ Bohumil Pluncar, Solrod Strand, Denmark	1	2	3
041/ Christiane Klein, Künzing,, Germany	7	7	14
044/ Dieter Raps, Schopfheim, Germany	1	0	1
048/ R. Burlefinger, Munchen, Germany	4	4	8
061/ B. Thjodliefsson, Reykjavik, Iceland	10	12	22
081/ John Patrick Crowe, Dublin, Ireland	6	6	12
082/ Paul William Napoleon Keeling, Dublin, Ireland	2	3	5
101/ Cornelius Dekkers, Breda, Netherlands	20	20	40
102/ Johannes Beker, Leischendam, Netherlands	20	20	40
121/ A. Gabrylewicz, Bialystok, Poland	2	2	4
122/ Eugeniusz Butruk, Warsaw, Poland	2	2	4
123/ Tadeusz Popiela, Krakow, Poland	2	2	4
124/ Krzysztof Marlicz, Szczecin, Poland	2	2	4
125/ Leslek Szczepanski, Lublin, Poland	0	1	1
142/ Manuel Diaz-Rubio, Madrid, Spain	1	1	2
144/ Juan Manuel Herrerias, Sevilla, Spain	1	0	1
161/ Irma Wright, Göteborg, Sweden	1	1	2
163/ Arnold Söderlind, Visby, Sweden	2	2	4
164/ Dan-Axel Hallbäck, Larlskoga, Sweden	0	1	1
166/ Hans Tanghöj, Eskilstuna, Sweden	3	3	6
181/ Graeme Kerr, Shrewsbury, England.	2	1	3
183/ Paul Swain, London, England	2	2	4
185/ P. J. Finch, Surrey, England	1	0	1
186/ John S. A. Collins, Northern Ireland	0	1	1
187/ K. D. Bardhan, Rotherham,England	5	5	10

They randomized 202 patients, 100 to rabeprazole, 102 to omeprazole. There were 126 men (62.4%) and 76 women, 197 (97.5%) of Caucasian descent, 1 of African descent (0.5%), and 4 (2.0%) of other racial heritage. They ranged in age from 20 to 86 years of age (mean 53.2), and 58 (28.7%) were 65 or older. Most of them (74%) did not use antacids for relief of GERD symptoms, but those who did took an average of 3.9 doses/day. At the screening endoscopy to determine eligibility, 87 (43.1%) had grade 2 erosive lesions, 106 (52.4%) grade 3, and 9 (4.5%) grade 4. Many (31%) of them complained of "continual" heartburn, grade 4 or >75% of the days, another 31% had heartburn more than half the days (grade 3), and only 2 (1%) had no heartburn (*Volume 187, pages 123*). No statistically significant differences between the randomized groups was noted for age, race, severity of lesions, frequency or severity of heartburn symptoms, use of antacids, alcohol, tobacco or caffeine, but a significantly (p=0.004) higher proportion of patients randomized to rabeprazole were female (47/100, 47.0%) than to omeprazole (29/102, 28.4%). No patients had duodenal or gastric ulcers, or grades 0,1, or 5 esophagitis, as was stated in and required by the protocol.

Comment: It was not stated how many patients were screened in order to find the 202 who were randomized, nor the reasons for excluding them. Also, it may be noted that more than half the patients were enrolled at only 3 (Drs. Beker and Dekkers in Holland, and Dr. Thjodliefsson in Iceland) of the 27 centers.

Their endoscopic findings in the esophagus, stomach, and duodenum were not significantly differently distributed (*Table 2.2, Volume 187, page 121*). The severity of the esophageal erosive lesions before treatment was not significantly different (p = 0.784) in distribution in the two groups as randomized, but there were a few less grade 2 and slightly more grade 3 and grade 4 lesions in the rabeprazole group (*Table 2.3, Volume 187, page 122*):

SEVERITY OF EROSIVE ESOPHAGITIS BEFORE STUDY NRRP TREATMENT

	rabeprazole	omeprazole	total
	100 patients	*102 patients*	*202 patients*
Grade 2	41 (41.0%)	46 (45.1%)	87 (43.1%)
Grade 3	54 (54.0%)	52 (51.0%)	106 (52.5%)
Grade 4	5 (5.0%)	4 (3.9%)	9 (4.4%)

The distribution of heartburn frequency was similar in the two randomized groups (p = 0.182), however, and 125/202 (62%) reported heartburn on more than half the days, only 1% reporting none. Day and night heartburn severity was also comparable between the two groups, with about 70% the patients reporting moderate or severe heartburn in the daytime and 481% at night *(Tables 2.4 and 2.5, Volume 187, pages 123-4).*

Of the total 202 patients randomized to treatment by these 27 investigators in 9 European countries, 95 (95.0%) on rabeprazole and 97 (95.1%) on omeprazole completed the study as defined in the protocol. Although not stated in the protocol, the report states that patients healed at 4 weeks were not required to return for another endoscopy at week 8. They were counted as healed at 8 weeks for purposes of efficacy analyses (*Volume 187, pages 57-8*) .

Comment: As commented upon before, this approach to data analysis is disturbing, for it is well known that both symptoms and lesions of erosive esophagitis in patients with GERD 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 weeks and who were observed for 8 weeks should be reported separately and analyzed separately. It may be both misleading and wrong to assume data for a second 4 weeks when no data were collected. It is also questionable to "reclassify" randomization schemes because of medication errors later. It would seem to be preferable to report what was actually done, actually observed, rather than to make retrospective adjustments, particularly those that favor the study drug.

Disposition of the patients (*see Section 5.2 of the Report, page 58, and Tables 1.2 & 1.3, Volume 187, pages 64 and 114-5*) was reported for 202 patients accepted by the 27 investigators. There were 10 patients lost from study during its progress, 5 from each randomized treatment group, so 95% in each group completed the study:

	total	*rabeprazole*	*omeprazole*	*explanation/reason*
Patients randomized	202	100	102	
Protocol violation	**-4**	**-2**	**-2**	
187-3009 Fc48		*-1*		*Day 8-entry criteria not met*
041-3002 Mc24			*-1*	*Day 47-noncompliance*
061-3007 Fc62		*-1*		*Day 56-took excluded drug*
061-3001 Mc50			*-1*	*Day 57-noncompliance*
Adverse event	**-1**	**-1**	**-0**	
124-3001		*-1*		*Day 28- rash, pruritus*
Lack of perceived efficacy	**-3**	**-2**	**-1**	
041-3009 Fc38		*-1*		*Day 56- patient's opinion*
041-3013 Fc56		*-1*		*Day 28-patient's opinion*
041-3011 Fc43			*-1*	*Day 47-patient's opinion*
Lost or moved away*	**-2**	**-0**	**-2**	
186-3001 Mc41			*-1*	*Day 11 –*
142-3001 Mc28			*-1*	*Day 32 -*
Completed study	192	95	97	*not different: (p >0.95)*

*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. It is not clear why patients who completed 56 or more days of treatment under the study are listed as discontinued early, which applies to 061-3007 and 041-3009 on rabeprazole, and to 061-3001 on omeprazole, particularly for retrospective opinions.*

The sponsor analyzed and presented results of the study two ways: 1) by "ITT" that included 100 patients randomized to rabeprazole and 102 randomized to omeprazole; and 2) by "ENDO" for the 99 rabeprazole-treated patients and 100 omeprazole -treated patients who had endoscopy done at 4 weeks. Separately, ENDO analyzed the 97 rabeprazole-treated patients and 100 omeprazole-treated patients who had endoscopy done at 8 weeks. The time-to-event analysis described in the protocol was not presented.

By both types of analyses, rabeprazole 20 mg/day was equivalent to omeprazole 20 mg/day in producing healing of the erosions at both 4 weeks and for the combined healing at 8 weeks (p >0.5 for all comparisons of differences).

PROPORTIONS OF PATIENTS HEALED IN STUDY NRRP

	rabeprazole	omeprazole	
"ITT"			p- value
4 weeks	81/100 (81.0%)	83/102 (81.4%)	0.957
8 weeks	92/100 (92.0%)	96/102 (94.1%)	0.557
"ENDO"			
4 weeks	81/99 (81.8%)	83/100 (83.0%)	0.884
8 weeks	92/97 (94.8%)	96/100 (96.0%)	0.701

*Comment: It was a flaw to reason 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 NRRP Appendix I-A, two patients on rabeprazole, 061-3007 and 082-3001, were treated with for a full 8 weeks although the latter showed healing to grade 1 at 4 weeks; both showed **worse** lesions at 8 weeks than at 4, despite continuation of rabeprazole.. 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.*

RANDOMIZED PATIENTS HEALED ON REGIMEN IN STUDY NRRP

	rabeprazole 20 mg/day	omeprazole 20 mg/day	p-value
First 4 weeks	81/100 (81.0%)	83/102 (81.4%)	> 0.9
Second 4 weeks	16/21 (76.2%)	19/23 (82.6%)	> 0.4
Over whole 8 weeks	92/100 (92.0%)	96/102 (94.1%)	> 0.5
-dropped	-5/100 (5.0%)	-5/102 (4.9%)	> 0.4
Left unhealed at end	8/100 (8.0%)	6/102 (5.9%)	> 0.4

Comment: There were no significant differences between healing rates of the two agents in this study. However, the rabeprazole healing of 81% of patients at 4 weeks is very much greater in these European studies ($p < 0.001$) than in the North American Study J (98/167, 58.7%). This could not be explained by any protocol differences or the severity of lesions entered. Why then?

Please see the NRRP Appendices to this section immediately below. It is remarkable that the two Dutch investigators, Drs. Beker and Dekker, had such consistent results as to strain credulity. For the 40 Beker (investigator 102) patients, 20 randomized to each drug, ALL had grade 3 esophageal erosions before treatment and ALL 40 healed completely to grade 0 at 4 weeks! None had adverse events, none dropped out, and all completed the study per protocol. Similarly, for the patients of Dekker (investigator 101), also exactly 20 randomized to each drug, ALL had grade 2 lesions before treatment and ALL 40 also healed completely to grade 0 at 4 weeks, with no cases of drop-out, adverse event, or protocol violation. Can such perfect results be credible?

Because of some doubt as to the data from centers 101 and 102, re-analysis of results without those 80 patients reduces the total number of patients to 122, 60 on rabeprazole and 62 on omeprazole 20 mg/day.

NON-DUTCH RANDOMIZED PATIENTS HEALED ON REGIMEN IN STUDY NRRP

	rabeprazole 20 mg/day	omeprazole 20 mg/day	p-value
First 4 weeks	41/60 (68.3%)	43/62 (69.4%)	> 0.45
Second 4 weeks	16/21 (76.2%)	19/23 (82.6%)	> 0.4
Over whole 8 weeks	53/60 (88.3%)	56/62 (85.5%)	> 0.43
-dropped	-5/60 (8.3%)	-5/62 (8.1%)	> 0.4
Left unhealed at end	8/60 (13.3%)	6/62 (9.7%)	> 0.35

Comment: Probably because of the high healing rates of the two proton-pump inhibitors the removal of as many as 40% of patients with healing rates of 100% did not affect much the overall healing at end of study, but did bring the 4-week healing rate into much closer correspondence with the North American rate for rabeprazole 20 mg/day of 59% in Study NRRJ. In the smaller dose-ranging Study NRRI, it may be recalled (see above) that the healing rate at 4 weeks was 56% for rabeprazole 20 mg/day and 63% for rabeprazole 10 mg/day. The reanalysis of the data excluding the Dutch patients does not challenge the validity of the conclusion that rabeprazole 20 mg/day is approximately equivalent to omeprazole 20 mg/day in healing the lesions, but the reported results do challenge the validity of the Dutch data.

The sponsor claims no statistically significant differences in the effects on heartburn of the two agents *(see Volume 187, pages 71-5)*. Most notable were the proportions of patients who showed complete resolution of symptoms frequency, daytime and nighttime severity to none, and also of normalization of their sense of well-being. Again, there was not a significant difference in the use of antacid doses, although both agents caused decreases. A few of the patients did not have heartburn symptoms, so the denominator figures vary somewhat.

Comment: Inspection of the heartburn symptoms section of the Patient Data Listing 5 (Volume 189, pages 343-418) does not show the same monotonous uniformity of results for the patients at sites 101 and 102 as had been seen for the endoscopy results. However, the confidence one may have in results from those centers, even for secondary measures, is compromised.

CHANGES IN HEARTBURN SYMPTOMS ON TREATMENT IN STUDY NRRP

	rabeprazole 20 mg/day	*omeprazole 20 mg/day*	*p-value*
FREQUENCY			
Improvement			
4 weeks	67/98 (68%)	76/102 (75%)	0.359
8 weeks	72/98 (73%)	78/102 (76%)	0.661
Resolution			
4 weeks	29/98 (30%)	27/102 (26%)	0.583
8 weeks	37/98 (38%)	32/102 (31%)	0.276
DAYTIME SEVERITY			
Improvement			
4 weeks	78/97 (80%)	74/97 (76%)	0.523
8 weeks	84/97 (87%)	80/97 (82%)	0.446
Resolution			
4 weeks	60/97 (62%)	59/97 (61%)	0.894
8 weeks	66/97 (68%)	64/97 (66%)	0.751
NIGHTTIME SEVERITY			
Improvement			
4 weeks	55/73 (75%)	55/75 (73%)	0.830
8 weeks	57/73 (78%)	63/75 (84%)	0.435
Resolution			
4 weeks	45/73 (62%)	43/75 (57%)	0.706
8 weeks	47/73 (64%)	50/75 (67%)	0.709
OVERALL WELL-BEING			
Improvement			
4 weeks	60/94 (64%)	53/93 (57%)	0.306
8 weeks	64/94 (68%)	62/93 (67%)	0.828
Normalization			
4 weeks	38/94 (40%)	31/93 (33%)	0.331
8 weeks	41/94 (44%)	38/93 (41%)	0.736

By all of these subjective, secondary measures there were no significant differences between the rabeprazole and omeprazole treatments. The improvements and resolutions were most impressive at 4 weeks, with relatively little further gain at 8 weeks.

Safety problems were not prominent in this study, despite the fact that many (29%) 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. In general, there were relatively fewer adverse events reported in this study of Europeans and in the North American Study NRRJ. Only about 30% of the patients reported any adverse event during the study (rabeprazole 32%; omeprazole 28%), much less than the 103/168 (61%) in patients on rabeprazole 20 mg/day in Study NRRJ.

Serious events occurred in 1 patient on rabeprazole

Rabeprazole group:

Patient 166-3004, a 70-year-old white Swedish man, with a history of hypertension, received rabeprazole for 28 days and healed his grade 3 esophagitis completely. Although he had no chest pain, his electrocardiogram showed abnormal T-waves, first-degree block, sinus bradycardia, and he was diagnosed as having a **myocardial infarction**. He did not require treatment, but was discontinued from the study.

Only 1 patient **discontinued** from the study because of non-serious adverse events,

Rabeprazole group:

Patient 124-3001, a 40-year-old white Polish man, reported a skin rash on Day 2 that was treated with antazoline hydrochloride and calcium. His esophagitis had improved slightly from grade 3 to grade 2, but he was withdrawn from the study on Day 29.

Other Minor Abnormalities

Minor complaints were reported by about 30% of the patients, 32/100 (32%) of those on rabeprazole and 29/102 (28%) of those on omprazole (p N.S., 0.581), most commonly headache, hernia, diarrhea. Flatulence was more frequent (4%) in omeprazole-treated patients, compared to 0% in rabeprazole-treated patients.

Transient serum alanine aminotransferase (ALT) elevations were seen in 2/83 patients during rabeprazole administration and in 9/84 on omeprazole ($p = 0.031$), none to as much as twice the upper limit of normal. No jaundice or other indicators of liver effects were seen. Thyroid tests, including serum thyroxine, thyroid-stimulating hormone, triiodothyronine uptake and free thryroxine index were in the normal range after treatment with both agents, and no significant differences were seen between them. Serum gastrin rose after treatments with both PPIs, somewhat but not significantly ($p = 0.25$) more on rabeprazole (increase of 36.3 ± 99.3) than omeprazole (23.0 ± 59.8 pg/mL). No differences were noted between patients on the two agents with respect to effects on gastric mucosal argyrophil enterchomaffinlike histologic findings.

Conclusions

The sponsor concluded that healing rates were comparable in the two groups, and resolution of symptoms was also approximately equivalent. *(Comment: Despite exclusion of the Dutch patients with the incredible endoscopic findings, the conclusions were sustained by the others Please see the following section D for recommendations on the conclusion of equivalence.)*

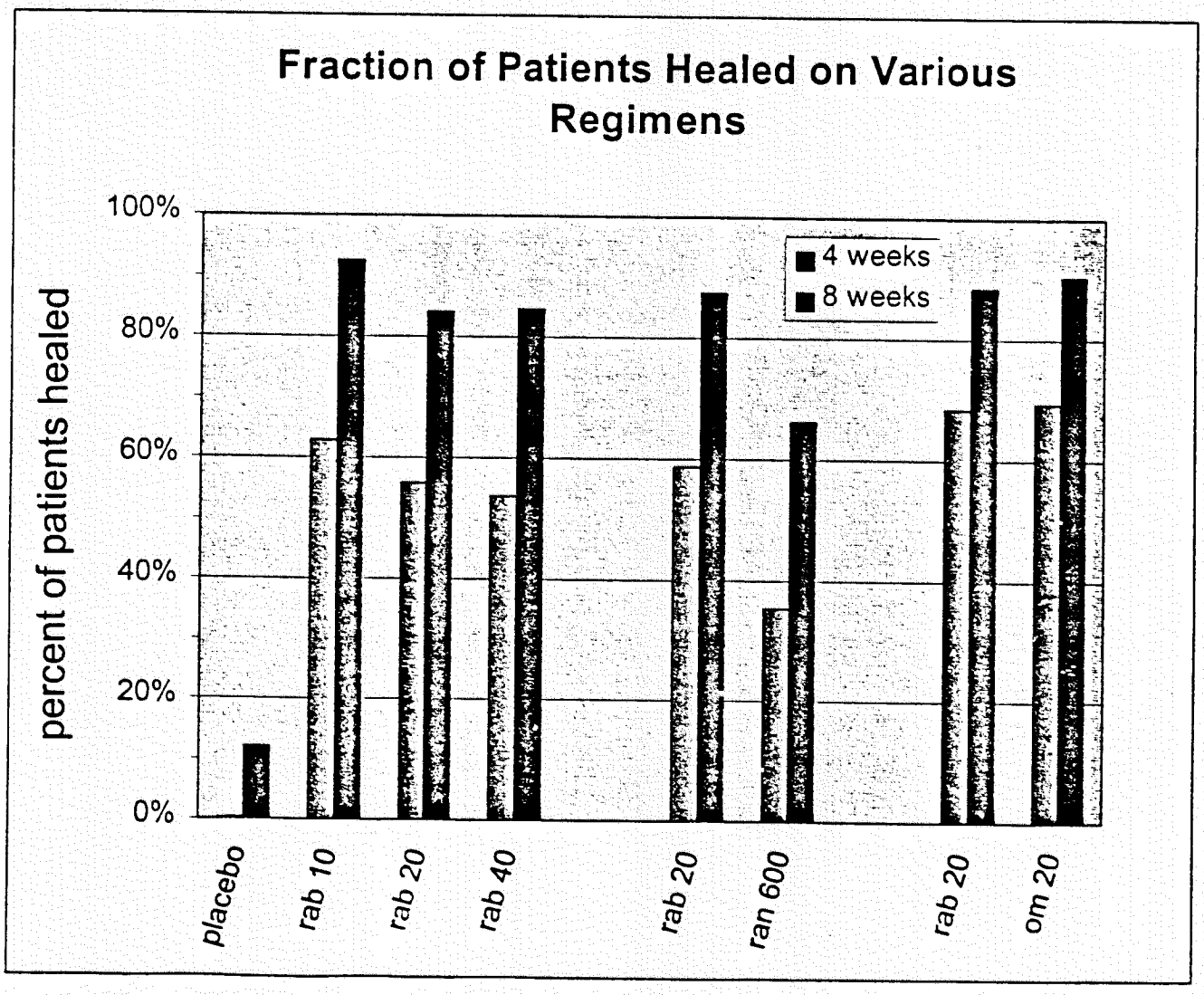
5 Page(s) Redacted

Raw DATA

C. Overview of healing studies

The three studies done compared rabeprazole 20 mg/day with placebo, ranitidine 150 mg q.i.d., and omeprazole 20 mg/day, as well as to rabeprazole 10 and 40 mg/day. It was found that rabeprazole 20 mg/day was significantly superior to both placebo and ranitidine (in its approved dose and regimen) in healing the erosive lesions of esophagitis associated with GERD, and equivalent to omeprazole (in its approved dose and regimen).

Comment: It was not well established, however, that the healing dose of rabeprazole should be 20 mg/day, since the dose of 10 mg/day was fully as effective, if not slightly (but not significantly) more so. The "dose-ranging" study was designed to show superiority of rabeprazole over placebo, and was not powered to show distinctions between the three rabeprazole doses. Since only 27 patients were studied on the rabeprazole 10 mg/day dose in one underpowered study (compared to 293 on rabeprazole 20 mg/day in the three studies), the optimal dose was never adequately established.



Comment: It may be seen that rabeprazole 20 mg/day (rab 20) fairly consistently healed about 60% of the patients by 4 weeks and by 8 weeks about 85% were healed. These results were far superior to placebo ($p < 0.001$) in Study I, and significantly better than ranitidine 150 mg q.i.d. (or 600 mg/day, ran 600) in Study J, but omeprazole 20 mg/day (on 20, for the non-Dutch European data from Study P) and the other doses of rabeprazole of 10 and 40 mg/day (rab 10 and rab 40, in Study I) were not significantly different.

Not noted by the sponsor but apparent in all three studies, especially at 4 weeks and in North America, was the slower healing of more severe and extensive esophageal lesions.

EFFECT OF INITIAL LESION EXTENT ON HEALING OF ESOPHAGEAL EROSIONS AT 4 WEEKS

	Grade 4	Grade 3	Grade 2	All Lesions
Study NRRI				
placebo	0/1 (0.0%)	0/9 (0.0%)	0/12 (0.0%)	0/25 (0.0%)
rabeprazole 10/d	0/1 (0.0%)	6/12 (50.0%)	11/14 (78.6%)	17/27 (63.0%)
rabeprazole 20/d	0/2 (0.0%)	3/6 (50.0%)	11/17 (64.7%)	14/25 (56.0%)
rabeprazole 40/d	0/2 (0.0%)	4/10 (40.0%)	10/14 (71.4%)	14/26 (53.9%)
Study NRRJ				
rabeprazole 20/d	4/15 (26.7%)	27/61(44.3%)	67/92 (72.8%)	98/168 (58.3%)
ranitidine 150 qid	5/19 (26.3%)	23/71 (32.4%)	32/80 (40.0%)	60/170 (35.3%)
Study P*				
rabeprazole 20/d	1/5 (20%)	28/34 (82.4%)	12/21 (57.1%)	41/60 (68.3%)
omeprazole 20/d	4/4 (100%)	22/32 (68.8%)	17/26 (65.4%)	43/62 (69.4%)
All rabeprazole 20/d	5/22(22.7%)	58/101 (57.4%)	90/130 (69.2%)	153/253 (60.5%)
All rabeprazole doses	5/25 (20.0%)	68/123 (55.3%)	111/158 (70.3%)	184/306 (60.1%)
All drugs	14/48 (29.2%)	113/226 (50.0%)	160/264 (60.6%)	287/538 (53.4%)
All studied	14/52(26.9%)	113/235 (48.1%)	160/276 (58.0%)	287/563 (51.0%)

* *Note: These figures exclude data from the 80 patients at the two Dutch sites.*

The effect was highly significant ($p < 0.001$) for rabeprazole on Study NRRJ, for all rabeprazole 20 mg/day in the three studies combined, for all rabeprazole-treated patients, as well as for the combined effect in all patients studied and for all drugs combined. However, the results were not statistically significant for ranitidine when it was considered alone, and there was no effect whatsoever in the European study of omeprazole. It is not surprising that larger, deeper, more extensive lesions may not be healed as quickly as smaller and more superficial, less extensive lesions, but it is apparently an important factor that should be taken into consideration when planning or evaluating treatment.

By 8 weeks, equal proportions of patients showed healing of grade 2 and 3 lesions. Healing of the grade 4 lesions had "caught up" and was no longer significantly slower, although the same trend still was noticeable, and consistently fewer of the patients with initial grade 4 lesions were healed.

EFFECT OF INITIAL LESION EXTENT ON HEALING OF ESOPHAGEAL EROSIONS AT 8 WEEKS

	Grade 4	Grade 3	Grade 2	All Lesions
Study NRRI				
placebo	0/4 (0.0%)	2/9 (22.2%)	1/12 (8.3%)	3/25 (12.0%)
rabeprazole 10/d	0/1 (0.0%)	6/12 (50.0%)	11/14 (78.6%)	17/27 (63.0%)
rabeprazole 20/d	2/2 (0.0%)	4/6 (50.0%)	11/17 (64.7%)	17/25 (68.0%)
rabeprazole 40/d	0/2 (0.0%)	9/10 (90.0%)	10/14 (71.4%)	19/26 (7319%)
Study NRRJ				
rabeprazole 20/d	11/15 (73.3%)	49/61(80.3%)	78/92 (84.8%)	138/168 (82.1%)
ranitidine 150 qid	11/19 (57.9%)	46/71 (64.8%)	57/80 (71.3%)	114/170 (67.1%)
Study P*				
rabeprazole 20/d	3/5 (60%)	32/34 (94.1%)	18/21 (85.7%)	53/60 (88.3%)
omeprazole 20/d	4/4 (100%)	30/32 (93.8%)	22/26 (84.6%)	56/62 (90.3%)
All rabeprazole 20/d	16/22 (72.7%)	85/101 (84.2%)	107/130 (82.3%)	208/253 (82.2%)
All rabeprazole doses	16/25 (64.0%)	100/123 (81.3%)	128/158 (81.0%)	244/306 (79.71%)
All drugs	31/48 (64.6%)	176/226 (72.9.0%)	207/264 (78.4%)	414/538 (77.0%)
All studied	31/52 (59.6%)	178/235 (75.7%)	208/276 (75.4%)	417/563 (74.1%)

* Note: These figures exclude data from the 80 patients at the two Dutch sites.

The European equivalence study between rabeprazole and omeprazole was planned for 200 patients, 100 on each drug, and 202 patients were enrolled. Because of questions about the Dutch centers, subtracting 80 patients leaves only 122. Although the residual 60 patients on rabeprazole and 62 on omeprazole showed very similar healing rates, the power of the study to detect a true difference if there were one was diminished to about 60% to detect a 15% difference. It was somewhat reassuring that the observed healing rate for the residual group on omeprazole, after taking away the dubious 100% rate in the 40 Dutch patients, was reasonably close to the literature, and the residual 60 patients on rabeprazole showed healing rates close to those observed in the North American patients.

To be sure of the equivalence for rabeprazole 20 mg/day to omeprazole 20 mg/day, and to explore more convincingly the optimum dose of rabeprazole for healing, it is suggested that approval of the claim for equivalence to omeprazole be deferred, in light of the irregularities of the European study. A confirming and extending study of equivalence, and of the best dose of rabeprazole for healing, properly designed and powered to detect differences of 10% in healing rates between any of the three regimens (rabeprazole 20 mg/day, omeprazole 20 mg/day, rabeprazole 10 mg/day), would be very desirable. There does not appear to be any need for placebo of H2-blocking agent control groups, since rabeprazole has been shown to be very persuasively superior to them, and proton-pump inhibitors have become the standard of practice for management of this disease.

III. Controlled Clinical Studies for Maintenance of Healing

Three studies have been done and reports submitted for the maintenance-of-healing indication. They included both placebo (NRRK-odd and NRRK-even) and active drugs (NRRQ) as the control groups

Study	*Where Done*	*Start*	*Finish*	*Treatments*	*Weeks*	*Pts*	*Invs*
Maintenance							
NRR**K-odd**	North America	Feb '95	Oct '96	P; R 10, 20	52	209	27
NRR**K-even**	North America	Feb '95	Oct '96	P; R 10, 20	52	288	24
NRR**Q**	Europe	May '95	May '97	R 20; O 20	52	243	21

Note: Treatments: P, placebo; R 10, rabeprazole 10 mg/day; R 20, rabeprazole 20 mg/day; O 20, omeprazole 20 mg/day. Pts, number of patients randomized; Invs, number of investigators participating

The North American studies were intended to demonstrate significant superiority of rabeprazole 10 or 20 mg/day over placebo in maintaining the healing of endoscopically proved healing of erosive esophagitis, assuming the rabeprazole would reduce the relapse rate within a year by at least 24%. The European Study Q was intended to show the equivalence of rabeprazole 20 mg/day to omeprazole 20 mg/day in maintaining healing of the erosive esophagitis associated with GERD, assuming a relapse rate of 20% for both agents.

A. Study NRRK-odd (February 1995-October 1996): rabeprazole 10, 20 vs placebo

Study H4M-MC-NRRK, entitled "[ ]307640 Versus Placebo: Preventing Relapse in Erosive or Ulcerative Gastroesophageal Reflux Disease" was planned in September 1994 by [ ] for conduct by [ ] (It is also referred to in this application as Study E3810-A001-304 by Eisai Inc. For brevity it will be referred to as "Study K" in this section of the medical review of this NDA 20-973.)

The original protocol of 9 September 1994 *(Volume 164, pages 153-80)* called for enrollment of approximately 240 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 that had been proved endoscopically to have healed. Healing may have occurred either in Study NRRJ (no repeat endoscopy needed if within 7 days), or under standard clinical care within 90 days but with endoscopic confirmation, before enrollment. The severity/extent of lesions was stated in the protocol to be evaluated at endoscopy done by a gastroenterologist, as had been specified also for Study NRRJ. Healing was defined as decrease in grade of lesions from 2, 3, or 4 to grade 0 or 1. Patients healed in Study J were to be re-randomized , along with other patients not formally studied but similarly healed, into Study K. Patients were to be assigned to receive rabeprazole 10 mg, rabeprazole 20 mg, or placebo daily for up to 52 weeks. The study size was based on assuming an 80% power to detect at least 24% absolute difference between rabeprazole and placebo treatment within a year, which by the Casagrande (1978) formula required 80 patients per group.

Comment: As the protocol (Volume 193, page 160) indicates, each patient was to take two tablets each morning, a pink (10-mg) and a light yellow (20-mg) tablet, if the study drug was as to be marketed if approved (Volume 1, page 13). The pink tablets (A2) could be either ACIPHEX® 10 (imprinted E241) or an identical placebo (P1), and the light yellow tablets (A1) could be either ACIPHEX® 20 (imprinted E243) or an identical placebo (P2). Kits with 52 study medication cards each containing a week-and-a day's supply were made up for each randomized patient, providing (A1+P2) for those assigned to rabeprazole 20 mg/day, (A2+P1) for those assigned to rabeprazole 10 mg/day, (P1+P2) for those assigned to placebo. It would have been possible for patients and staff to distinguish between the pink and yellow tablets, but not whether or not they may have been active drug or placebo.

The interval between entry endoscopy showing healing and the initiation of study medication was not to exceed 7 days. Follow-up visits with endoscopy were scheduled for 4, 13, 26, and 52 weeks, and a visit without endoscopy at 39 weeks (± 3 days at week 4, and ± 7 days for the other visits). Finding of grade 2 or worse esophagitis was to be taken as showing relapse of disease. No interim analyses were planned. The endoscopic criteria were as before:

Grade 0 =	normal mucosa, no abnormalities noted
Grade 1 =	no macroscopic erosions, but presence of erythema, hyperemia, and/or friability of the esophageal mucosa
Grade 2 =	superficial ulceration or erosions involving less than 10% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Grade 3 =	superficial ulceration or erosions involving of greater than or equal to 10% but less than 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Grade 4 =	deep ulceration anywhere in the esophagus or confluent erosion of more than 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Grade 5 =	stricture, as defined by a narrowing of the esophagus that does not allow easy passage of the endoscope without dilatation (patient must be discontinued).

Protocol amendments were made 31 October, 31 December 1994 and 14 February and 30 June 1995. Patients were being studied between 13 February 1995 and 18 October 1996. The IND [redacted] had been transferred from Eisai [redacted] in April 1993, and the during the study designed and carried out by [redacted] back to Eisai Corporation of North America on 21 December 1995, then to Eisai Incorporated on 31 March 1997 for preparation and submission of the report. Amendment B (NRRKb) on 21 December 1994 broke the study into two investigator sets, with odd and even investigator numbers and doubled the study population, Section 3.4, to 480 patients *(Volume 193, page 98)*. Amendment C (NRRKc) on 14 February 1995 corrected the sample size section 3.4.3 *(Volume 193, page 71)* to 480 patients. Minor changes on 31 October 1994 (NRRKa) corrected an error in the weeks for study medication and antacid distribution, and on 30 June 1995 (NRRKd) added thyroid function testing *(Volume 192, page 53)* Other details of the amended protocol were very similar to those specified for Study J, with respect to inclusion/exclusion criteria, diet, concomitant therapy, symptom scores, antacid use, etc.

The investigators for this Study K-odd were the same as in Study J who had odd-numbers for their investigator numbers (see also page 23 of this review for list of Study J investigators), and listed in Volume 194, pages 1-4:

Investigator, City	*rabeprazole 10*	*rabeprazole 20*	*placebo*	*total*
001/R. Aaronson, Chicago Heights IL2	2	3	3	8
003/R. Baerg, Tacoma WA	1	2	2	5
005/D. Ballard, Cincinnati OH	1	0	1	2
007/P. Bird, Norman OK	0	0	1	1
009/W. Bray, Charlotte NC	2	1	1	4
011/J. Caldwell, Daytona Beach FL	2	2	2	6
013/A. Coas, Ocoee FL	10	11	11	32
015/C. L. Colip, Portland OR	6	6	6	18
019/T. Durbin, Long Beach CA	2	2	1	5
023/N. Gitlin, Atlanta GA	1	1	1	3
025/G. K. Hee, Vancouver WA	4	3	4	11
029/J. Kaine, Sarasota FL	1	0	1	2
033/D. Kruss, Oak Park IL	2	2	2	6
037/ A. McCullough, Cleveland OH	1	1	1	3
041/M. Moskowitz, Beaver PA	5	4	5	14
043/H. Offenburg, Gainesville FL	1	1	1	3
045/D. Pambianco, Charlottesville VA	2	2	2	6
047/D. Riff, Anaheim CA	5	5	5	15
049/W. M. Roufail, Winston-Salem NC	1	1	0	2
051/S. Safevi, Irving TX	2	3	3	8
053/H. Schwartz, Miami FL	4	4	4	12
055/D. Scott, Shereveport LA	2	2	0	4
059/S. Sontag, Hines IL	3	2	2	7
061/Z. Vlahcevic, Richmond VA	1	2	2	5
063/R. White, Sacramento CA	4	4	3	11
065/L. D. Wruble, Memphis TN	2	2	3	7
067/T. Bianchi, Tallassee AL	3	3	3	9
total, 27 participating	*70*	*69*	*70*	*209*

Investigators 017 (D. Daly, Montreal, Quebec), 021 (A. Farley, Montreal, Quebec), 027 (R. Hunt, Hamilton, Ontario), 035 (D. Leddin, Halifax, Nova Scotia), 039 (J. McHattie, Regina, Saskatchewan) of Canada did not participate in the maintenance Study K-odd, nor did two of the U.S. investigators, 031 (S. Katz, Great Neck NY) or 057 (B. Shivakumar, Davenport IA).

Of the 209 patients who entered maintenance treatment, almost half (101/209, 48.3%) did not complete the full 52 weeks of study, mostly because of relapse in 53 (25.4%) or lack of perceived efficacy by 12 (5.7%) patients, significantly more ($p < 0.001$) in the placebo group. Other reasons provided to explain losses from the study failure to return by 14 (6.7%), protocol violations in 13 (6.2%), and adverse events in 9 (4.3%).