Conclusions for Study K-odd:

The sponsor concluded *(Volume 192, page 156)* that rabeprazole at daily doses of either 10 or 20 mg was significantly more effective than placebo in reducing the relapse of erosive esophagitis in patients who had previously healed the erosions/ulcerations of that disease associated with GERD. The 20-mg/day dose was significantly better than the 10-mg/day dose of rabeprazole in preventing endoscopic relapse of erosive lesions (primary measures), as well as in reducing recurrence of heartburn symptoms (secondary measures) in this study. Both doses were well tolerated, and not significantly more risky than placebo.

Comment: These conclusions appear to be justified by the data of this study. There is no doubt that rabeprazole is far superior to placebo (no treatment) in reducing the relapse rate of erosive esophagitis in patients with GERD who have shown such lesions but have healed. The placebo-treated group showed once again how frequent and rapid the tendency to relapse actually is in this disease. The confirming secondary effects of reducing recurrence of heartburn symptoms, need for antacids, and maintenance of sense of well-being are additional benefits that may be especially important to the patients, who may not be as aware of the importance of endoscopic findings as are their physicians.

What this study did not show, but perhaps could do at least in part, was indicate how important the regimen used to heal the erosive esophagitis might be in affecting the tendency to relapse. The data were not provided by the sponsor as to what agent was used to heal the patients who came into the Study K-odd de novo, nor did it link the patients healed in Study J to their "rollover" into Study K-odd. The investigator numbers remained the same, but the patient numbers changed in one or several digits, as judged by the reports of the patients who had serious adverse events or were discontinued from study because of non-serious events. It would require some effort by the sponsor to provide this linkage, and to add the data on what agent was used to heal the patients entered de novo into Study K-odd who had not participated in Study J. It is suggested that this would be a potentially valuable analysis, useful in guiding treatment and possibly labeling, although perhaps not strictly required for an approval decision.

The dose of 20 mg/day for better maintenance seems to have been shown fairly well by this study, but it is noteworthy that 10 mg/day actually was somewhat better for healing lesions of erosive esophagitis than either 20 or 40 mg/day, as shown in the small pilot Study I. It would appear that selection of the 20-mg/day dose of rabeprazole was premature, and based not on data for healing, but on other considerations. Firm establishment of the best dose of rabeprazole remains to be established conclusively. Study I was simply not powered to determine the dose of rabeprazole, and was mis-named a dose-ranging study; it simply showed that rabeprazole was better than placebo for healing erosive esophagitis.

The sponsor did not make the observation that the severity of the original erosions/ulcerations affects significantly the time required for healing, which it does, and this too may affect the best dose to be used. This point should be confirmed and investigated further.

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

Study H4M-MC-NRRK, entitled "LY307640 Versus Placebo: Preventing Relapse in Erosive or Ulcerative Gastroesophageal Reflux Disease" was planned in September 1994 by Lilly Research Laboratories for conduct by Pharmaco LSR Inc. (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-even" in this section of the medical review of this NDA 20-973.)

The original protocol of 9 September 1994 *(Volume 201, pages 32-59)* had called for enrollment of 240 adults with erosive GERD that had healed. Amendment to the protocol on 31 December 1994 *(NRRK(b), Volume 201, page 89 and 94)* before initiation on 15 February 1996 doubled the number of patients to 480, and split the study into K-odd and K-even halves, based on whether the investigator number (as in Study J) were odd or even. This section deals with the "K-even" study, and resembles closely review of the "K-odd" study above. Investigators for Study K-even were those in Study J with even- investigator numbers (Volume 202, pages 6-8; 164-5):

Investigator, City	*rabeprazole 10*	*rabeprazole 20*	*placebo*	*total*
006/C. Birbara, Worcester MA	11	11	11	33
008/M. Brandon, San Diego CA	4	4	4	12
010/J. R. Breiter, Manchester CT	13	13	13	39
012/D. Campbell, Kansas City MO	7	7	7	21
016/D. Collins, Arvada CO	10	10	10	30
018/M. Drehobl, San Diego CA	1	1	2	4
020/M. Eisner, Zephyrhills FL	7	6	7	20
022/R. Fogel, Detroit MI	1	1	1	3
026/S. Ho, Minneapolis MN	2	2	2	6
028/D. Johnson, Norfolk VA	7	7	7	21
030/N. Kassman, Statesville NC	3	2	3	8
032/T. Kovacs, Los Angeles CA	6	7	7	20
034/F. L. Lanza, Houston TX	3	2	3	8
038/ A. McElroy, Johnson City TN	1	1	1	3
042/N. Nickl, Lexington KY	1	1	2	4
050/S. Sabesin, Chicago IL	2	2	2	6
052/M. Safdi, Cincinnati OH	2	2	3	7
054/B. Scott, Baton Rouge LA	3	2	2	7
056/N. Shah, Leonardtown MD	3	4	3	10
058/M. Sklar, Bingham Farms MI	1	1	1	3
060/L. Strong, Loveland CO	2	3	2	7
062/R. Soloway, Galveston TX	1	1	1	3
064/R. Willis, Harrogate TN	0	0	1	1
066/M. Shaukat, Phoenix AZ	4	4	4	12
total, 24 participating	*95*	*94*	*99*	*288*

Investigators 002 (A. Archambault, Montreal, Quebec), 004 (R. Bailey, Edmonton, Alberta), 014 (I. Cleator, Vancouver, British Columbia), 040 (G. May, Calgary, Alberta), 044 (M. Oravec, Oshawa, Ontario), and 048 (P. Rossos, Toronto, Ontario) of Canada, who has participated in Study J did not participate in the maintenance Study K-even, nor did two of the U.S. investigators, 024 (D. Gremillion, Nashville TN) or 046 (F. Ramirez, Phoenix AZ).

Of the 288 patients who entered maintenance treatment in Study K-even, beginning on 15 February 1995, almost half (135/288, 46.9%) did not complete the full 52 weeks of study. The main reason for this *(Table 1.3, Volume 200, page 167)* was relapse or lack of perceived efficacy by 96 (33.3%) patients, significantly more ($p < 0.001$) in the placebo group (72/99, 72.7%). Other reasons provided to explain losses from the study failure to return by 18 (6.3%), protocol violations in 5 (1.7%), and adverse events in 16 (5.6%).

DISPOSITION OF PATIENTS IN STUDY NRRK-EVEN

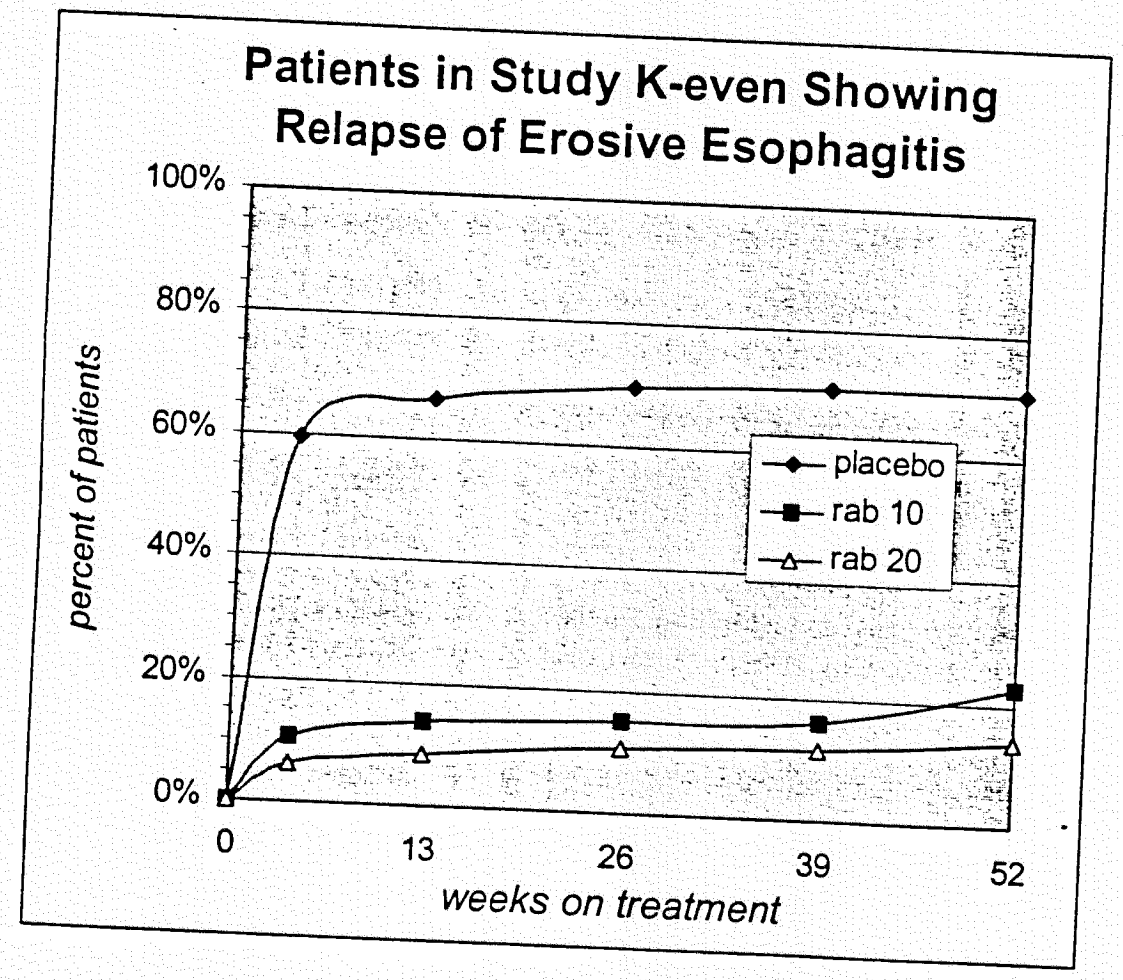
	total	R20	R10	PLA	---------	*p-value*	---------
Enrolled	288	94	95	99	*R20vR10*	*R10vPLA*	*R20vPLA*
- Relapse/no efficacy	-77	-6	-10	-61	*N.S.*	*<0.001*	*<0.001*
- Lack of efficacy	-19	-2	-6	-11	*N.S.*	*N.S.*	*0.019*
- Lost/moved	-6	-1	-4	-1	*N.S.*	*0.019*	*N.S.*
- Patient decision	-12	-7	-4	-1	*N.S.*	*0.005*	*0.001*
- Violated protocol	-5	-2	-0	-3	*N.S.*	*N.S.*	*N.S.*
- Adverse event*	-16	-7	-7	-2	*N.S.*	*0.001*	*< 0.001*
Completed study	153	69	64	20	*N.S.*	*<0.001*	*<0.001*
% completing	*53.1%*	*73.4%*	*67.3%*	*20.2%*			

*Note: R20, rabeprazole 20 mg/day; R10, rabeprazole 10 mg/day; PLA, placebo; v, versus; * see below for details of adverse events.*

Comment: The proportion of patients showing relapse on placebo was very significantly greater than in those on either dose of rabeprazole, and also statistically significant for perceived lack of efficacy on placebo compared to either dose of rabeprazole despite the relatively small numbers. The study was powered to detect a difference of at least 24% in relapse, as observed (Table 1.3, Volume 200, page 167) between placebo (61/99, 61.6%) and rabeprazole 10 mg/day (10/95, 10.5%, difference –51.1%), or rabeprazole 20 mg/day (6/94, 6.4%, difference – 55.2%). It was not powered to detect the difference between the two rabeprazole groups of <10%, and it did not ($p = 0.4342$, exact test). It would require a larger study to detect a significant difference between the rabeprazole treatment groups.

The 288 patients included 194 men, 94 women; 266 of Caucasian descent, 14 of African descent, and 8 of other descent; mean age 52 years (median 50.5, range 19 –85); 63 were 65 or older; none had duodenal or gastric ulcer at entry. Of 285 with baseline scores, 202 had been healed completely to grade 0, 83 to grade 1, and 223 had either no heartburn (152) or mild heartburn (71) at entry. The three study groups as randomized were not significantly different in distribution of gender, race, age, consumption of alcohol/tobacco/caffeine, grade 0/1 to which healed, or average antacid doses/day/user *(Table 2.1, Volume 200, pages 169-71)*.

Relapse rate of grade 2 or worse erosions/ulcerations by endoscopy was the primary outcome measure of this Study K-even, as it had been in K-odd. The results showed highly significant ($p < 0.001$) and clinically impressive reductions in the relapse rate on either dose of rabeprazole, especially on 20 mg/day. The difference was not significant for rabeprazole 20 mg/day, compared to rabeprazole 10 mg/day, all through the study, and at the end at 52 weeks. Calculation using the "ENDO" method, using only patients for whom endoscopic data were available, revealed the same results. Calculation by day-to-relapse event using Kaplan-Meier method showed both doses of rabeprazole very significantly superior to placebo ($p < 0.0001$) and the 20-mg dose to be no better ($p = 0.1432$) than the 10-mg dose of rabeprazole *(Volume 200, page 78)*. The results are obvious when displayed graphically:



Comment: Again it is not necessary to calculate the statistical significance of such a great superiority of rabeprazole, in either dose, over placebo (or no treatment) in reducing the relapse of esophageal erosions in these patients. It may be noted that the greatest benefit occurs in the first 4 weeks. After that there is a slow rise in the proportions of patients showing recurrence of disease in all the treatment groups. Long-term treatment, therefore, benefits the patients mainly by reducing the immediate relapse of GERD-associated erosive lesions. It cannot be concluded

that patients should be treated for only four weeks, however, because it is very likely that they would then show the rapid relapse effect, and their graphic data would show them "jumping" from one of the lower curves to the upper placebo curve at whatever time the rabeprazole treatment was stopped. Although this exact investigation was not done, and it does not seem ethical to do so, the implications are that patients with GERD who have a tendency to develop erosive and ulcerative lesions in their lower esophagi may need very long-term treatment to suppress the relapse of erosive esophagitis very likely to occur when they stop proton-pump inhibiting treatment.

It is notable that there was only a slight incremental benefit of the 20-mg daily dose of rabeprazole over the 10-mg daily dose in Study K-even, not statistically significant even in this somewhat larger study of 288 patients versus the 209 of Study K-odd. The study size was powered to show superiority over placebo, which both "halves" certainly did, assuming at least 24% reduction in proportions of patients showing relapse on rabeprazole compared to placebo. For that difference the study appears to have been "over-powered" since the actual differences in relapse rates were on the order of 50% rather than the assumed 24%. To show with any high degree of power differences in relapse rate between the two rabeprazole doses, a much larger study would be required. In this case, one study (K-odd) did show a significant advantage of the 20-mg dose, but the other (K-even) did not. Simply combining the studies after-the-fact does not fully satisfy the convincing establishment of the 20-mg daily dose of rabeprazole as superior to the 10-mg dose, although it does suggest it to be so. In the small healing Study I, the 10-mg dose was actually slightly, but not significantly superior to the 20-mg and 40-mg dose for healing erosive lesions of GERD.

Secondary measures of heartburn frequency, day and night heartburn severity, also showed very highly significant and clinically impressive reductions in grading *(Volume 200, pages 81-92)* on either dose of rabeprazole compared to placebo, but no significant difference between the two rabeprazole groups. For heartburn frequency *(pages 81-2)*:

RELAPSE RATES OF INCREASED HEARTBURN FREQUENCY IN STUDY NRRK-EVEN

	R20	**R10**	**PLA**	----------	*p-value*	----------
At Regular Visit	72 patients	72 patients	79 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
week 4	20 (28%)	19 (26%)	58 (73%)	*0.794*	*< 0.001*	*< 0.001*
week 13	16 (22%)	18 (25%)	57 (72%)	*0.539*	*< 0.001*	*< 0.001*
week 26	14 (19%)	22 (31%)	58 (73%)	*0.262*	*< 0.001*	*< 0.001*
week 39	18 (25%)	22 (31%)	57 (72%)	*0.506*	*< 0.001*	*< 0.001*
week 52	15 (21%)	22 (31%)	57 (72%)	*0.392*	*< 0.001*	*< 0.001*
Kaplan -Meier						
censored	44	36	18			
relapsed	28	36	61	*> 0.84*	*< 0.0001*	*< 0.0001*
mean days to relapse	252.8	240.2	74.3			
Day 364 probability	40%	53%	88%			

Note: R20, rabeprazole 20 mg/day; R10, rabeprazole 10 mg/day; PLA, placebo; v, versus.

For daytime heartburn severity, relapsing from none or mild (grade 0 or 1) to grade 2, 3, or 4 (moderate, severe, terrible), similar tabulations show *(Volume 200, pages 84-8)*:

RELAPSE RATES OF INCREASED DAYTIME HEARTBURN SEVERITY IN STUDY NRRK-EVEN

	R20	R10	PLA	---	p-value	---
At Regular Visit	87 patients	84 patients	90 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
Week 4	5 (6%)	9 (11%)	24 (27%)	*0.228*	***0.002***	***0.008***
Week 13	5 (6%)	10 (12%)	22 (24%)	*0.159*	***0.001***	***0.021***
Week 26	3 (3%)	9 (11%)	24 (27%)	*0.095*	***< 0.001***	***0.008***
Week 39	5 (6%)	10 (12%)	24 (27%)	*0.168*	***< 0.001***	***0.013***
Week 52	5 (6%)	11 (13%)	23 (26%)	*0.102*	***< 0.001***	***0.040***
Kaplan –Meier						
Censored	57	59	39			
Relapsed	5	5	22	***0.032***	***< 0.0001***	***0.0085***
mean days to relapse	272.2	262.2	120.4			
Day 285 probability	9%	10%	54%			

Note: R20, rabeprazole 20 mg/day; R10, rabeprazole 10 mg/day; PLA, placebo; v, versus.

For nighttime heartburn severity, relapsing from none or mild (grade 0 or 1) to grade 2, 3, or 4 (moderate, severe, terrible), similar tabulations showed results that were highly significant with respect to placebo, but of slight or no significant difference between rabeprazole doses. *(Results for this analysis were taken from Volume 200 of the submission, pages 88-92).*

RELAPSE RATES OF INCREASED NIGHTTIME HEARTBURN SEVERITY IN STUDY NRRK-EVEN

	R20	R10	PLA	---	p-value	---
At Regular Visit	87 patients	80 patients	87 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
Week 4	7 (8%)	11 (14%)	23 (26%)	*0.247*	***0.004***	*0.086*
Week 13	3 (3%)	11 (14%)	24 (28%)	***0.020***	***< 0.001***	***0.022***
Week 26	6 (7%)	14 (18%)	24 (28%)	***0.010***	***< 0.001***	*0.205*
Week 39	8 (9%)	14 (18%)	23 (26%)	*0.125*	***0.003***	*0.138*
Week 52	8 (9%)	13 (16%)	23 (26%)	*0.078*	***0.003***	*0.132*
Kaplan –Meier						
Censored	73	57	59			
Relapsed	14	23	28	*0.035*	***0.0005***	***0.0312***
mean days to relapse	324.7	293.2	178.9			
Day 365 probability	19%	31%	47%			

Note: R20, rabeprazole 20 mg/day; R10, rabeprazole 10 mg/day; PLA, placebo; v, versus.

Comment: It may be noted that the results of Study K-even were a little different than for Study K-odd. Considerably higher relapse rates for heartburn frequency were seen overall in all of the treatment groups in Study K-even, in the range of 10-15% higher, although the differences between rabeprazole and placebo were preserved. For daytime and nighttime heartburn severity, the relapse rates on rabeprazole were about twice as great. Why should this vary so much? The two protocols were identical, the distribution of investigators and locations appeared to show no bias, and it is difficult to understand these differences. If the measures are simply extremely variable, the their value may be diminished.

Other secondary measures of efficacy included the patients' rating of their overall well being *(Volume 200, pages 92-7)*. Relapses from very good or good states (grade 0 or 1) at the time of healed lesions to fair, poor, or very poor (grade 2, 3, or 4):

RELAPSE RATES FROM STATE OF WELL-BEING IN STUDY NRRK-EVEN

	R20	R10	PLA	---	*p-value*	---
At Regular Visit	84 patients	80 patients	86 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
Week 4	7 (8%)	15 (19%)	25 (29%)	***0.042***	***0.020***	*0.142*
Week 13	7 (8%)	13 (16%)	22 (26%)	*0.068*	***0.004***	*0.234*
Week 26	8 (10%)	13 (16%)	25 (29%)	*0.135*	***0.009***	***0.049***
Week 39	8 (10%)	15 (19%)	24 (28%)	*0.101*	***0.037***	*0.176*
Week 52	7 (8%)	15 (19%)	25 (29%)	***0.037***	***0.024***	*0.133*
Kaplan –Meier						
Censored	68	52	55			
Relapsed	28	16	31	*0.059*	*<0.0001*	***0.0058***
mean days to relapse	243.6	250.3	207.5			
Day 364 probability	21%	38%	56%			

Note: R20, rabeprazole 20 mg/day; R10, rabeprazole 10 mg/day; PLA, placebo; v, versus.

Antacid use decreased in both groups taking rabeprazole, with no significant difference between them, but increased significantly in the placebo group in the early periods at 4 and 13 weeks, compared to usage at the time of healed lesions *(Volume 200, pages 97-8)*:

Antacid Doses/day	**R20**	**R10**	**PLA**	---	*p-value*	---
Change from baseline	pts: doses/d	pts: doses/d	pts: doses/d	*R20vR10*	*R20vPLA*	*R10vPLA*
Week 4	86: -0.18	86: -0.44	96: +0.86	*0.394*	***< 0.001***	***< 0.001***
Week 13	78: -0.23	73: -0.55	36: +0.38	*0.626*	***< 0.001***	***< 0.001***
Week 26	71: -0.20	72: -0.65	28: -0.03	*0.455*	***0.010***	***0.002***
Week 39	66: -0.22	67: -0.79	20: -0.06	*0.378*	*0.447*	*0.175*
Week 52	62: -0.31	59: -0.78	18: -0.11	*0.559*	***0.014***	***0.042***

Comment: The dose-response relationship seen in Study K-odd for reduction in antacid doses was not seen in this Study K-even, although the differences again were not significant.

Compliance in taking study medication was 81.9% for patients taking rabeprazole 20 mg/day, 80.7% for rabeprazole 10 mg/day, and 74.7% for those taking placebo. This was calculated as 100 x (tablets dispensed-tablets returned)/(2 x number of days since last visit).

Comment: Again, little differences that are difficult to understand. Compliance in taking study medications was consistently lower in the Study K-even than had been reported in Study K-odd by about 8 to 19%. (See page 67 of this report for comparison)

Per-protocol analyses were available for 87 patients from each of the rabeprazole groups and from 95 patients on placebo (269/288, 93.4%). The results showed no difference from those summarized above in the ITT analyses, and the conclusions were the same.

Safety problems reported were more frequent in patients on rabeprazole, but it may be noted again that patients in the placebo group were observed for significantly ($p < 0.001$) shorter times (less then half) than either rabeprazole group *(Table 12, Volume 200, page 257)*. There was no significant difference in time of observation between the rabeprazole groups.

DAYS OF OBSERVATION ON STUDY NRRK-EVEN

	R20	R10	PLA	---------	*p-value*	---------
	94 patients	95 patients	99 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
mean±S.D.	301 ± 119	288 ± 134	113 ± 139	*0.474*	*<0.001*	*<0.001*
median	363	364	30			
range	(2 – 381)	(1 – 400)	(1 – 382)			

Note: R20, rabeprazole 20 mg/day; R10, rabeprazole 10 mg/day; PLA, placebo; v, versus; S.D., standard deviation.

There were **no deaths** reported **during** this study among the participating patients. However, 3 patients died *after* the study, 2 (#034-9237 and 010-9486) who had been on rabeprazole 20 mg/day until 26 and 63 days before, and 1 (012-9081) who had been on placebo until 70 days before. The patients who had been on rabeprazole died of liver cancer (010-9486, a 73-year-old man) and metastatic lung cancer (034-9237, a 57-year-old man). The patient who had been on placebo (012-9081) was a 31-year-old man who died in his sleep of presumed cardiac arrhythmia after an unknown dose of amitriptyline. None of these deaths appeared related to study medication. *(Narratives are summarized in Attachment 13, Volume 204, pages 10-6).*

Deaths After Study NRRK-even

Patient 034-9237, a 57-year-old Caucasian man, had a history of lumbar laminectomy on 1960, left knee cartilage repair in 1970, chronic back and leg pain since 1980, sinusitis, hiatal hernia since 1995 with erosive esophagitis. He entered the study *de novo* on 24 August 1995, with grade 1 esophageal findings (Volume 206: 116-7) and was randomized to **rabeprazole 20** mg/day. Chest x-ray done on 17 January 1996 (Day 147) because of pain revealed a right upper lobe mass. The patient had had vomiting for 12 days before, which did not resolve, and he withdrew from study on 19 January. Brain and liver metastases of his non-small-cell **lung carcinoma** were found, and he died in hospice on 14 February, 26 days after quitting the study *(Volume 204:15-6)*.

Patient 010-9486, a 73-year-old Caucasian man, had a medical history of cholecystectomy in 1957, hypertension since 1973, bilateral cataracts in 1980, hearing loss, diverticulosis since 1983 and seven colonic polypectomies between 1985 and 1994, hemorrhoids in 1986, type II diabetes since 1990, hiatal hernia since 1994, duodenal ulcer 1995, esophageal ring dilatation in 1994 and erosive esophagitis since 1995. He entered the study *de novo* on 12 April with grade 0 esophagus *(Volume 205:312-3)*, and was randomized to **rabeprazole 20** mg/day. Serum liver-related enzymes were elevated throughout the study, and portal hypertension was found on 12 July 1995. Scans showed hepatosplenomegaly, and a possible hepatoma, but liver biopsy showed mildly active micronodular cirrhosis but no malignancy 6 days after the last dose of study medication had been taken on 2 August (Day 103) because of

erosion relapse to grade 2. A month later he developed nausea, vomiting, lethargy, and ascites; he was discharged after fluids and electrolytes were given, but **liver cancer** was diagnosed on 4 October (63 days after the last dose of rabeprazole) from which he died 8 days later *(Volume 204: 10-2).*

Patient 012-9081, a 31-year-old Caucasian man, had a history of knee and back pain since 1976, knee and heel surgical procedures, abdominal pain with bloating and diarrhea sine 1980, Osgood-Schlatter disease 1981, gunshot injury of the left index finger 1994. He had duodenal and gastric ulcers in 1995, and erosive esophagitis treated before entry into study. He was found to have healed the esophagus to grade 0 on 6 March 1995, and was randomized to **placebo**. The erosions recurred (grade 2) on 13 April and he was withdrawn from study (Day 38). About 10 weeks later, he was found dead in bed on 21 June 1995, and it was discovered he had taken an unknown amount of amitriptyline prescribed for his father. It was speculated that the amitriptyline may have induced a fatal ***cardiac arrhythmia***.

A total of 26 patients with non-fatal serious adverse events (SAEs) were reported. Of these, 19 were in 15 patients on rabeprazole 10-mg/day (1 patient, *006-9639,* had been randomized to that dose but never received any study medication), 12 in 10 patients on rabeprazole 20-mg/day, and 1 in 1 patient on placebo *(Volume 200, pages 105-7; Volume 204, pages 134-51).*

Serious Adverse Events Occurring During Study NRRK-even

inv-pt no.	*G-r-A*	*serious adverse event*	*study day of onset*

*Note: inv=investigator, pt=patient, no.-number, G=gender, r=race, and A=age in years: * discontinued*

Rabeprazole 20 mg/day (94 patients):

012-9548*	Ma53	Myalgia, musculosketetal pain	Day 25
012-9551	Mc62	Skin carcinoma, squamous, back	Day 57
016-9110*	Mc59	Ulcerative colitis, pain bloody diarrhea	Day 137
006-9560	Fc53	Fractured ankle, femur	Day 154
012-9469*	Mc66	Right deep leg vein thrombosis	Day 159
028-9795*	Fc66	Right lower lobe pneumonia	Day 161
006-9805	Mc45	Herniated L4 disc, back pain	Day168
		Laminectomy, two separate times	Day 202; 347
028-9794	Mc64	Subendocardial infarction	Day 188
032-9224	Mc42	Convulsive seizure	Day 192
066-9826	Mc66	Surgical procedure, oximetry	Day 298

Rabeprazole 10 mg/day (95 patients):

(006-9639	*Fc64*	*Transient ischemic attack, cerebrovascular accident*	*Day 0)*
060-9417	Fc81*	Melena	Day 28

006-9822	Fc55	Herniated lumbar disc, back pain	Day 30
		Surgical decompression of herniated disc	Day 51
032-9544	Mc64*	Gastrointestinal bleeding	Day 30
066-9689	Mc48*	Basal cell carcinoma, skin; rheumatoid arthritis*	Day 39
052-9363	Mc61	Chest pain, dyspnea, coronary angioplasty	Day 46
020-9635	Mc48	Post-operative flare of rheumatoid arthritis	Day 47
018-9125	Mc72	Basal cell carcinoma, skin	Day 75
006-9640	Fc46	Depression, suicide attempt	Day 96
006-9710	Mc60	Ethanol addiction	Day 112
		Myocardial infarction	Day 155
012-9079	Mc64*	Drug overdose, diltiazem, accidental	Day 156
010-9770	Fc66*	Colon carcinoma	Day 144
		Deep vein thrombosis	Day 160
006-9473	Mc40	Acute pancreatitis	Day 206
		Surgical procedure right knee	Day 257
030-9210	Mc55	Myocardial infarction, coronary artery disease	Day 273
066-9827	Mc63	Benign keratoacanthoma, left neck	Day 320

Placebo (99 patients)

010-9771	Fc30	Hysterectomy, bilateral oophorectomy	Day 267

Serious events occurred in 1 of 99 patients (1.0%) on placebo, in 14 of 95 (14.7%) on rabeprazole 10 mg/day and in another who had been randomized to that dose but never took any, and in 10 of 94 (10.6%) on rabeprazole 20 mg/day.

Rabeprazole 20 mg/day (94 patients):

Patient 012-9548, a 53-year-old man of African descent, had a history of hypertension since 1960, headaches, inguinal herniorrhaphy in 1966, diverticulosis, gastric ulcer in 1970, colon resection in 1976, lumber diskectomies in 1976 and 1987, suicidal overdose in 1987, wound dehiscence in 1989, diabetes with peripheral neuropathy and retinopathy, insomnia, depression, and chest pain. He entered the study de novo on 5 April 1995 with grade 0 esophagus, and was randomized to **rabeprazole 20 mg**/day. On 30 April (Day 26) he complained of heavy, pressing chest pain, and was evaluated in hospital without finding any evidence of heart injury. He was discharged after 2 days with diagnosis of **myalgia, musculosketetal pain.** He quit the study, although endoscopy on 5 May showed no relapse.

Patient 012-9551, a 62-year-old Caucasian man, had a history of actinic keratoses since 1963; duodenal ulcer with bleeding in 1973, 1982, 1994; squamous cell skin carcinoma of right neck 1983, left preauricular 1988 and right temporal 1992 basal cell carcinoma, and erosive esophagitis. He entered study *de novo* on 1 May 1995, was randomized to **rabeprazole 20 mg**,

after endoscopy 2 days before showed grade 0. He remained healed at endoscopy on 30 May, 25 July, 24 October 1995 and 23 April 1996 *(Volume 206:11-3)*. Another **squamous cell carcinoma** of the skin of his back was diagnosed on 27 June and excised 24 July.

Patient 016-9110, a 59-year-old Caucasian man, had a history of allergic rhinitis since 1956, back surgery 1969, colitis since 1990, hypertension since 1993 and myocardial infarction that year with angioplasty, arthritis of the hand since 1994, allergy to peanuts, and erosive esophagitis *(Volume 204:31-3)*. He entered the study *de novo* on 21 February 1995, randomized to **rabeprazole 20 mg**/day, and remained healed (grade 0) on 24 March, 26 May, and 10 July *(Volume 206:19-20)*, but had discontinued study medication on 6 July (Day 136) because of 4 weeks of increasingly intense abdominal cramps, bloody diarrheal stools, vomiting and weakness, with fever and dehydration. Colonoscopy on 10 July showed severe ulcerating right and transverse colitis with rectosigmoid sparing, probably **Crohn's colitis**.

Patient 006-9560, a 53-year-old Caucasian woman, had a history of cholecystectomy 1960, obesity, thalassemia minor since 1961, herniated lumbar disk and laminectomy in 1967, ovarian cyst and hysterectomy in 1973, diabetes mellitus since 1989, hyperlipidemia, cataracts, chronic obstructive lung disease and sleep apnea since 1990, internal hemorrhoids, osteomyelitis of left toe and knee 1992, and erosive esophagitis *(Volume 204:59-60)*. She entered study *de novo* on 2 May 1995 after endoscopy the day before showed grade 1 healing. On **rabeprazole 20** mg/day she continued healed on 31 May, 27 July, 25 October and at completion on 6 May 1996 *(Volume 205:264-6)*. However, on 3 October (Day 155) she slipped, fell, and **fractured her left femur and ankle**, with operative reduction and internal fixation in hospital. She missed 3 days of study medication, but did not relapse.

Patient 012-9469, a 66 year-old man, had a history of appendectomy 1941, chronic obstructive lung disease since 1984, leg cramps 1988, diverticulosis, colon polypectomy 1991 and 1994, gastric and duodenal ulcers and *H. pylori* infection 1994, left lower lung lobectomy for bronchiolitis obliterans and viral sialadenitis 1994 *(Volume 204:26-7)*. He entered the study de novo on 20 March 1995, 6 days after endoscopy showed healing to grade 1, and was randomized to **rabeprazole 20** mg/day. He remained healed *(Volume 206:7-8)* at grade 0 on 18 April and grade 1 on 20 June, but developed right **deep leg vein thrombosis** on 24 August and was treated in hospital with heparin and warfarin, and discontinued study medication on 29 August. He also was found to have prostatic enlargement but refused further workup.

Patient 028-9795, a 66 year-old Caucasian woman, had a history of chronic obstructive lung disease, lung carcinoma and left upper lobectomy 1992, and bronchitis. She was post menopausal since 1979, allergic to penicillin and Augmentin, hypertensive, and had arthritis of the right hip, hiatal and paraesophageal hernia, and erosive esophagitis *(Volume 204:34-6)*. She entered the study after withdrawing from Study J (028-8191) because of need for prednisone for her bronchitis, although she had healed from grade 3 to grade 1 on rabeprazole 20 mg/day for 53 days. She was healed to grade 0 on 19 July 1995, again randomized to **rabeprazole 20** mg/day, and remained healed at grade 0 on 18 August and 25 October. *(Volume 206:82-3)*. On 27 December (Day 171) she developed **right lower lobe pneumonia**, treated in hospital, but

complicated by pleural effusion and poor response. Endoscopy showed grade 1 esophagitis with incarcerated hiatal hernia on 16 January 1996, and study medication was stopped 2 days later.

Patient 006-9805, a 45-year-old Caucasian man, had a history of cerebral aneurysm 1992, ruptured colon 1993, osteoarthritis, and erosive esophagitis *(Volume 204:65-7)*. He entered the study *de novo* on 13 September 1995, when endoscopy showed grade 1 healing, randomized to **rabeprazole 20** mg/day. He remained healed at grade 1 on subsequent endoscopic examinations on 16 October and 18 December 1995 and 18 March 1996 *(Volume 205:288-90)*. He was hospitalized on 1 March 1996 for severe low back pain, attributed to **herniated L4 disk**, treated for pain, discharged, and then had a laminectomy on 4 April and another surgical procedure on 26 August 1996. He completed the study without relapse, and showed grade 1 healing on 16 September 1996.

Patient 028-9794, a 64-year-old Caucasian man, had a history of penicillin allergy, diabetes mellitus with retinopathy since 1980, hypertension and stroke 1985, herniated lumber disk L5 and back surgery 1988 and 1989, right and left carotid stenosis 1991, rotator cuff tear and bilateral carpal tunnel syndrome 1992, pleural thickening related to asbestosis and small right lung granuloma 1993, hiatal hernia with Schatzki ring and erosive esophagitis *(Volume 204:83-5)*. He entered the study *de novo* on 1 August 1995 with grade 0 esophagus, was randomized to **rabeprazole 20** mg/day and remained healed on 1 September, 27 October 1995, and 25 January 1996. However, on 5 February 1996 (Day 189) he experienced severe, crushing chest pain and was hospitalized for treatment of **subendocardial infarction** with diffuse coronary artery disease. Despite this, he completed study 26 July 1996 *(Volume 206:78-80)*, showing no relapse.

Patient 032-9224, a 42-year-old Caucasian man, had a history of schizophrenoid depression since 1979, resection of a lung cyst, abdominal pain and vomiting 1994, diabetes mellitus since 1995, and erosive esophagitis *(Volume 204:86-8)*. He entered the study *de novo* on 10 April 1995 with grade 0 esophagus *(Volume 206:95-7)*, was randomized to **rabeprazole 20** mg/day and remained healed on 2 May and 11 July at grade 0, and grade 1 on 2 October. On 19 October (Day 193) he had two **convulsive seizures**, attributed to his antipsychotic medications paroxetine and respiridone. Hospitalization for study disclosed no epileptogenic foci, and he was discharged after 2 days. He completed the study without relapse, showing grade 1 findings on 16 April 1996.

Patient 066-9826, a 66-year-old Caucasian man, had a history of obesity since 1945, sinusitis since 1955, hypersomnolence since 1966, arteriosclerotic heart disease since 1970, myocardial infarction 1970, penicillin allergy, acne rosacea and rhinophyma since 1985, actinic keratoses, aortic aneurysm repair 1989, transurethral resection 1989, diabetes mellitus since 1994, tinnitus and hearing loss, left calcaneal spur, hyperlipidemia 1994, and erosive esophagitis *(Volume 204:92-4)*. He entered the study *de novo* on 13 September 1995 with grade 0 esophagus, was randomized to **rabeprazole 20** mg/day, and remained healed on 11 October and 13 December 1995, 19 March 1996. He was hospitalized electively on 8 July 1996 **for nocturnal ear oximetry study for his chronic somnolence**, found to improve on nasal oxygen, and was discharged on 11 July. He completed study without relapse on 9 September 1996 *(Volume 206:165-7)*.

Rabeprazole 10 mg/day (95 patients):

***Patient 006-9639**, a 64-year-old Caucasian woman, never took study medication but had been randomized to receive rabeprazole 10 mg/day. She had been screened on 30 May 1995, but before endoscopy was done she reported symptoms of dizziness, showed loss of memory and slurred speech. She did not participate in the study, and took **no study medication**. She was hospitalized and treated for **cerebrovascular accident**.*

Patient 060-9417, an 81-year-old Caucasian woman, had a history of ovarian cyst and appendectomy 1937, tonsillectomy 1946, vaginal hernia repair and tubal ligation 1946, right ankle fracture 1972, menopause 1975, right ankle fusion 1982, hypertension, cataracts, sinusitis, kidney stone 1985, hand paresthesia, shingles 1993, angina pectoris since 1993, carpal tunnel syndrome, antral gastritis and duodenitis, hiatal hernia, Schatzki ring and erosive esophagitis 1995 *(Volume 204:43-5)*. She entered the study *de novo* on 14 April 1995, and was randomized to **rabeprazole 10** mg/day. She was endoscoped again on 11 May 1995, showed a minor erosion at the lip of the hiatal hernia, and was biopsied. She reported **melena** on 15 May, following 2 days of nausea and dizziness, and repeat endoscopy showed two erosions at the biopsy sites, which seemed to account for her bleeding. She was withdrawn from the study (Day 32). Her hematocrit recovered from 0.26 to 0.45 in August 1995.

Patient 006-9822, a 55-year-old Caucasian woman, had a history of hysterectomy 1976, hot flashes 1985, migraines 1987, irritable bowel since 1991, bladder suspension 1991, cholecystectomy 1992, asthma and leg cramps since 1993, osteoarthritis, constipation, back pain, and erosive esophagitis *(Volume 204:68-70)*. She entered the study *de novo* on 16 October with grade 1 esophagus, and was randomized to **rabeprazole 10** mg/day. She remained healed on 13 November, On 15 November she was hospitalized for increasing back pain and was found by magnetic resonance imaging to have a **herniated lumbar disk**. She was readmitted for diskectomy on 7 December, but she continued on study, showing no relapse on 10 January, 10 April, or 10 October 1996 *(Volume 205:28-30)*.

Patient 032-9544, a 64-year-old Caucasian man, had a history of inguinal hernia in 1947 and 1962, coronary artery disease and myocardial infarction in 1981 and 1983, hearing loss right ear since 1989, glaucoma of the left eye 1992, pharyngeal polyp 1992, pulmonary emboli 1992, gastroduodenitis with bleeding 1993, osteoarthritis since 1993, transient ischemic attack 1994 and 1995, erosive esophagitis *(Volume 204:41-2)*. He entered the study *de novo* on 2 May 1995 with grade 0 esophagus *(Volume 205:190)* and was randomized to **rabeprazole 10** mg/day. Endoscopy on 30 May showed no relapse (grade 1), but on 1 June (Day 31) he noted black stools, was hospitalized for **gastrointestinal bleeding,** and study drug was stopped. He was discharged the next day on prescription medication.

Patient 066-9689, a 48-year-old Caucasian man, had a history of pneumonia in 1965,m kidney stones 1988, hypertension, rheumatoid arthritis, hiatal hernia, duodenal ulcer and erosive esophagitis in 1995 *(Volume 204:46-7)*. He entered the study *de novo* on 23 June 1995, after endoscopy 2 days before showed grade 0 findings, and was randomized to **rabeprazole 10** mg/day. He remained healed on 21 July *(Volume 205:245)*, but elected to withdraw because of