DISPOSITION OF PATIENTS IN STUDY NRRK-ODD

	total	R20	R10	PLA	---------	p-value	--------
Enrolled	209	69	70	70	*R20vR10*	*R10vPLA*	*R20vPLA*
- Relapse	-53	-5	-12	-36	*0.119*	*<0.001*	*<0.001*
- Lack of efficacy	-12	-0	-2	-10	*0.496*	*0.031*	*0.014*
- Lost/moved/quit	-14	-5	-4	-5	*N.S.*	*N.S.*	*N.S.*
- Violated protocol	-13	-4	-7	-2	*N.S.*	*N.S.*	*N.S.*
- Adverse event*	-9	-2	-5	-2	*N.S.*	*N.S.*	*N.S.*
Completed study	108	53	40	15	*0.013*	*<0.001*	*<0.001*
% completing	*51.7%*	*76.8%*	*57.1%*	*21.4%*			

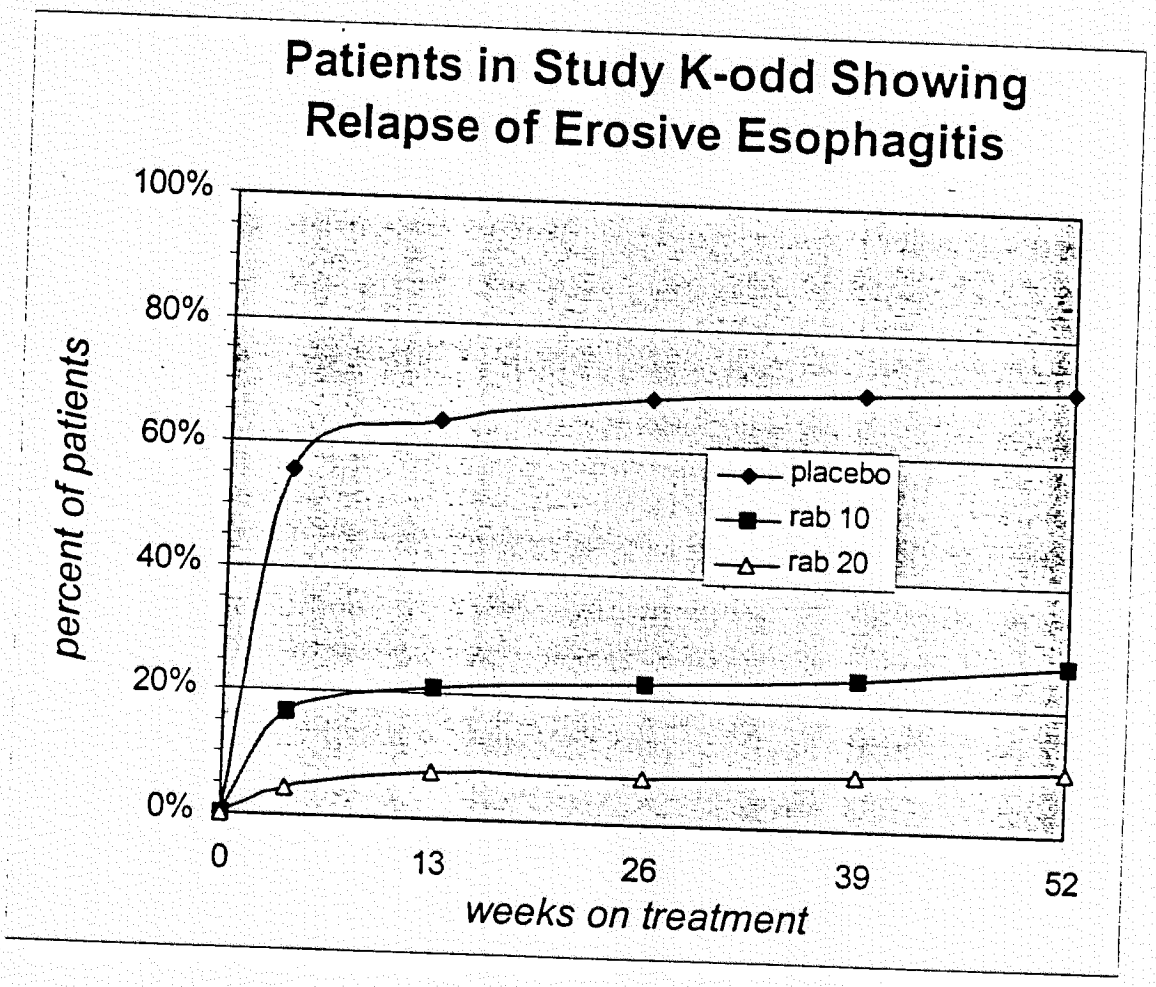
*Note: R20, rabeprazole 20 mg/day; R10, rabeprazole 10 mg/day; PLA, placebo; v, versus; * see below for details of adverse events.*

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%, as observed between placebo (36/70, 51.4%) and rabeprazole 10 mg/day (12/70, 17.1%, difference –34.3%), and rabeprazole 20 mg/day (5/69, 7.2%, difference – 44.2%). It was not powered to detect the difference between the two rabeprazole groups of <10%, and it did not (p = 0.1186, exact test). It would require a larger study to detect a significant difference between the rabeprazole treatment groups. If both perceived lack of efficacy and endoscopic relapse are combined, the treatment with rabeprazole 20 mg (5/69, 7.2%) just was significantly better (exact p = 0.046) than with rabeprazole 10 mg/day (14/70, 20.0%).

The 209 patients included 126 men, 83 women; 182 of Caucasian descent, 17 of African descent, and 10 of other descent; mean age 57 years (median 59, range 22 –83); 76 were 65 or older; none had duodenal or gastric ulcer at entry; and 151 were healed completely to grade 0, 52 to grade 1, and 152 had either no heartburn (116) or mild heartburn (36) 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, use of antacids (Volume 192, pages 72-3). The placebo group, however, included more patients with continual, grade 4 heartburn (20%) than either rabeprazole group (10 mg/day, 8%; 20 mg/day, 9%), and correspondingly fewer with no heartburn (46%) than either rabeprazole group (10 mg/day, 64%; 20 mg/day, 63%). The distribution difference in heartburn frequency was significant (p = 0.040).

Relapse rate of grade 2 or worse erosions/ulcerations by endoscopy was the primary outcome measure of this Study 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 also significant for rabeprazole 20 mg/day, compared to rabeprazole 10 mg/day, all through the study, and at the end at 52 weeks, by which time only 7 of the 67 (10.4%) patients who had received rabeprazole 20 mg/day had relapsed, compared to 18/66 (27.3%) on rabeprazole 10 mg/day (p = 0.027). 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 better ($p = 0.0159$) than the 10-mg dose of rabeprazole (Volume 192, page 80). The results are obvious when displayed graphically:



Comment: It is not necessary to resort to statistical analyses with results such as these, at least for the great superiority of rabeprazole treatment compared to no treatment (or placebo) in patients who have healed their erosive esophagitis previously. For comparison of the two rabeprazole doses, however, the statistical analyses support the superiority of the 20-mg dose for prevention of relapse, although the 10-mg dose is also very effective.

Secondary measures of heartburn frequency, day and night heartburn severity, also showed very highly significant and clinically impressive reductions in grading (as listed in Volume 192, pages 44-5) on either dose of rabeprazole compared to placebo, but no significant difference between the two rabeprazole groups. When patients who had no heartburn or only a few episodes (grades 0 or 1), relapse could be calculated if the frequency worsened to grade 2 (several episodes), grade 3 (many episodes), or grade 4 (continual heartburn, more than 75% of the days). Patients who had not experienced this degree of relief after healing to endoscopic grade 0 or 1, but had grade

2, 3, or 4 heartburn frequency were not counted as "relapsing" with respect to heartburn frequency. This approach was used also for counting relapses of daytime and nighttime heartburn, including only those who had been relieved to grade 0 (none) or 1 (mild) when their endoscopic lesion healed to grade 0 or 1. Since not all the patients had symptoms, the denominators change to reflect the group who had no symptoms after healing that were able to report relapses, as defined here. These could be analyzed at cross-sectional times at visits during the study, or analyzed by Kaplan-Meier methods on time-to-relapse. For heartburn frequency:

RELAPSE RATES OF INCREASED HEARTBURN FREQUENCY IN STUDY NRRK-ODD

	R20	R10	PLA	----------	p-value	----------
At Regular Visit	52 patients	55 patients	45 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
week 4	6 (12%)	9 (16%)	26 (58%)	*0.373*	*< 0.001*	*< 0.001*
week 13	6 (12%)	12 (22%)	28 (62%)	*0.307*	*< 0.001*	*< 0.001*
week 26	4 (8%)	13 (24%)	29 (64%)	*0.061*	*< 0.001*	*< 0.001*
week 39	8 (15%)	12 (22%)	28 (62%)	*0.329*	*< 0.001*	*< 0.001*
week 52	4 (8%)	9 (16%)	28 (62%)	*0.256*	*< 0.001*	*< 0.001*
Kaplan -Meier						
censored	39	39	14			
relapsed	13	16	31	*> 0.38*	*< 0.0001*	*< 0.0001*
mean days to relapse	232.8	274.9	63.8			
Day 362 probability	28%	36%	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:

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

	R20	R10	PLA	---------	p-value	----------
At Regular Visit	62 patients	64 patients	61 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
Week 4	2 (3%)	2 (3%)	17 (28%)	*0.878*	*< 0.001*	*< 0.001*
Week 13	1 (2%)	4 (6%)	18 (30%)	*0.151*	*< 0.001*	*0.002*
Week 26	3 (5%)	4 (6%)	20 (33%)	*0.326*	*< 0.001*	*0.001*
Week 39	3 (5%)	5 (8%)	18 (30%)	*0.186*	*< 0.001*	*0.006*
Week 52	2 (3%)	3 (5%)	19 (31%)	*0.324*	*< 0.001*	*< 0.001*
Kaplan –Meier						
Censored	57	59	39			
Relapsed	5	5	22	*> 0.26*	*< 0.0001*	*< 0.0001*
mean days to relapse	272.2	262.2	120.4		*< 0.0001*	*< 0.0001*
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 these analyses were taken from Volume 192 of the submission, pages 83-6 for heartburn frequency, pages 86-9 for daytime heartburn, and pages 89-92 for nighttime heartburn relapse).*

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

	R20	R10	PLA	---------	p-value	----------
At Regular Visit	61 patients	61 patients	56 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
Week 4	1 (2%)	5 (8%)	18 (32%)	*0.150*	*< 0.001*	*0.005*
Week 13	0 (0%)	4 (7%)	16 (29%)	*0.047*	*< 0.001*	*0.002*
Week 26	1 (2%)	7 (11%)	20 (36%)	*0.036*	*< 0.001*	*0.006*
Week 39	4 (7%)	5 (8%)	18 (32%)	*0.826*	*< 0.001*	*0.003*
Week 52	1 (2%)	4 (7%)	19 (34%)	*0.187*	*< 0.001*	*< 0.001*
Kaplan –Meier						
Censored	56	52	33			
Relapsed	5	9	23	*> 0.15*	*< 0.0001*	*< 0.0001*
mean days to relapse	277.8	249.0	152.6			
Day 285 probability	9%	18%	61%			

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

Other secondary measures of efficacy included the patients' rating of their overall well being and use of antacids for relief of symptoms. 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-ODD

	R20	R10	PLA	---------	p-value	----------
At Regular Visit	58 patients	59 patients	56 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
Week 4	3 (5%)	4 (7%)	12 (21%)	*0.431*	*0.020*	*0.033*
Week 13	2 (3%)	7 (12%)	13 (23%)	*0.048*	*0.004*	*0.126*
Week 26	4 (7%)	7 (12%)	15 (27%)	*0.199*	*0.009*	*0.055*
Week 39	6 (10%)	8 (814)	14 (25%)	*0.446*	*0.037*	*0.103*
Week 52	5 (9%)	7 (123)	15 (27%)	*0.359*	*0.024*	*0.048*
Kaplan –Meier						
Censored	51	47	38			
Relapsed	7	12	18	*> 0.10*	*0.0001*	*0.0049*
mean days to relapse	309.0	256.7	174.7			
Day 366 probability	13%	28%	55%			

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, compared to the time of healed lesions:

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	56: -0.51	56: -0.10	59: +0.74	*0.385*	*< 0.001*	*< 0.001*
Week 13	49: -0.47	45: -0.24	25: +0.64	*0.742*	*< 0.001*	*< 0.001*
Week 26	49: -0.65	42: -0.24	17: +0.66	*0.741*	*< 0.001*	*< 0.001*
Week 39	45: -0.47	35: -0.39	15: +0.15	*0.938*	*< 0.001*	*< 0.001*
Week 52	43: -0.24	34: -0.46	14: -0.59	*0.414*	*< 0.001*	*< 0.001*

Compliance in taking study medication was 90.2% for patients taking rabeprazole 20 mg/day, 89.3% for rabeprazole 10 mg/day, and 94.0% for those taking placebo. This was calculated as 100 x (tablets dispensed-tablets returned)/(2 x number of days since last visit).

Per-protocol analyses were available for 64 patients from each of the rabeprazole groups and from 68 patients on placebo (196/209, 93.8%). The results showed no difference from those summarized above in the ITT analyses, and the conclusions were the same.

Some safety problems were reported in this 12-month maintenance study, but it may be noted that patients in the placebo group were under observation for significantly ($p < 0.001$) shorter times than either rabeprazole group. There was also a significantly ($p = 0.009$) shorter period of observation for the rabeprazole 10-mg/day group compared to the 20-mg/day group, because of more dropouts for relapses.

DAYS OF OBSERVATION ON STUDY NRRK-ODD

	R20	R10	PLA	--------	*p-value*	--------
	69 patients	70 patients	70 patients	*R20vR10*	*R20vPLA*	*R10vPLA*
mean±S.D.	309 ± 118	249 ± 149	120 ± 140	*0.009*	*<0.001*	*<0.001*
median	364	360	30			
range	(1 – 388)	(1 – 403)	(1 – 378)			

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. A total of 16 patients with serious adverse events (SAEs) were reported, all of whom were hospitalized. Of these, 7 were in 7 patients from the rabeprazole 10-mg/day group, 6 in 4 patients from the rabeprazole 20-mg/day group, and 3 in 2 patients from the placebo group.

Comment: As noted above, patients on rabeprazole, especially on 20 mg/day, were in the study and under observation for longer than those on placebo by factors of 2.6 times as long for rabeprazole 20 mg/day and about 2.0 times as long for rabeprazole 10 mg/day. On a basis of SAEs/year of exposure in the placebo group, it might have been expected that there would have been 9 SAEs in the placebo group, so the 7 and 10 so adjusted to a per-year basis in the groups on rabeprazole 20 mg/day and rabeprazole 10 mg/day are quite close, if the SAEs were random events and the groups were of equal size.

It may be expected that some intercurrent, random medical events are likely to occur over period of up to a year and be reported in a closely watched study group with a mean age of 57 years and 36% of them 65 or older (Table 2.1, Volume 192, page 165). Many of these people had prior medical problems, not sufficiently severe to cause them to be excluded perhaps, but tending to predispose them to medical events in their futures. For such problems they may have been taking other medications not specifically excluded under the protocol but which had the potential for possible drug-drug interactions. In this context the importance of a placebo group becomes paramount, and the standard against which events in the rabeprazole group are measured.

SERIOUS ADVERSE EVENTS OCCURRING DURING STUDY NRRK-ODD

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

Rabeprazole 20 mg/day (69 patients):

043-9295	Mc80	Malignant melanoma, left knee	Day 69
061-9423	Ma36	Convulsion, seizure disorder	Day 73
001-9002	Mc68	Costochondritis	Day 76
		Hernia repair	Day 231
041-9287	Fc79	Hypertension worsening; tachycardia	Day 104;
		Nephrolithiasis; nephrolithotripsy	Day 154; 199
067-9751	Fc51	Left ovarian cyst, oophorectomy	Day 235

Rabeprazole 10 mg/day (70 patients):

029-9197	Mc32	Myocardial infarction; bypass procedure	Day 77-8
063-9436	Fc81	Pneumonia, bilateral	Day 79
041-9756	Fc37	Viral gastroenteritis	Day 114
033-9231	Fc80	Cerebral hemorrhage	Day 166
001-9006	Fa48	Diarrhea, hyperventilation, syncope	Day 205
041-9285	Mc76	Acute cholecystitis, cholangitis	Day 274
005-9029	Fc34	Depression, suicidal ideation	Day 294

Placebo (70 patients)

045-9314	Mc45	Anemia, chest pain, congestive heart failure	Day 10
041-9754	Fc69	Chest pain and hypertension	Day 24
001-9001	Mc38	Basal cell carcinoma, shoulder skin	Day 111

Serious events occurred in 12/139 patients on rabeprazole 10 or 20 mg, and in 3/70 on placebo:

Rabeprazole 20 mg/day (69 patients):

Patient 043-9295, an 80-year-old man with a history of hearing loss, obesity, prostatic hyperplasia and transurethral resection, hemorrhoids, inguinal hernia repair, in addition to hiatal hernia and GERD, healed his grade 2 erosions to grade 0 after 29 days on rabeprazole 20 mg/day in Study J (043-8295). He was re-randomized to rabeprazole for maintenance study K-odd on 12 April 1995. On 20 June 1995 it was discovered that an apparent sebaceous cyst that had been removed from his left knee was in fact a **malignant melanoma**. He had been on rabeprazole 20 mg for 29 days in Study J and 70 more in Study K-odd. He stopped study medication 2 July.

(Volume 196, page 10). His endoscopy on 10 May had shown no recurrence, but another on 5 July after stopping the rabeprazole showed grade 2 erosions *(Volume 197, pages 201-2)*.

Patient 061-9423, a 36-year-old man of African descent, had a history of seizure disorder since 1978 diagnosed as cerebellar atrophy in 1992. He also had a history of "substance" (?alcohol) abuse, pancreatic pseudocyst, pancreatitis with pleural effusion, pancreatic abscess and gram-negative sepsis in 1993, left shoulder dislocation and tendonitis. He had been treated with ranitidine in Study J (061-8425) for 55 days, and healed his grade 3 esophagitis to grade 1, and was re-randomized as #061-9423 on rabeprazole 20 mg/day on 22 May 1995. After 74 days on study K-odd, he was admitted to hospital for **evaluation of his seizure disorder** and adjustment of his regimen for seizure control, but he had no seizures immediately before or during the hospitalization of 7 days *(Volume 196, page 56)*. He completed the Study K-odd and remained healed completely (grade 0) for 52 weeks *(Volume 197, pages 254-6)*.

Patient 001-9002, a 68-year-old Caucasian man, had a history of penicillin allergy, hypertension, seborrheic dermatitis, cholelithiasis and cholecystitis, shoulder tendonitis, pneumonia, and duodenal ulcer, in addition to GERD. He had healed his grade 3 esophageal erosions (20 February 1995) to grade 0 on rabeprazole 20 mg/day over 57 days in Study J (001-8001), and was immediately on 18 April 1995 entered into Study NRRK-odd, and re-randomized to rabeprazole 20 mg/day. On 3 July, after a total of 134 days (57 in Study J and 77 in Study K-odd) on the 20-mg daily dose of rabeprazole he developed chest pain while golfing, diagnosed in hospital as non-cardiac, probably **costochondritis**. Chest x-ray showed a small pleural effusion and left lobe infiltrate, and he was discharged the next day. He recovered fully after treatment with erythromycin for 10 days as an out-patient. A second hospitalization on 5 December 1995, on Day 231 of Study K-odd, occurred for elective repair of a **right inguinal hernia** that he had noted about two weeks before. He completed the Study K-odd without endoscopic relapse over 52 weeks of observation (volume 197, pages 84-6).

Patient 041-9287, a 79-year-old Caucasian woman, had a history of chronic constipation, menopause in 1962, chronic bronchitis, hypercholesterolemia, degenerative arthritis, bilateral hearing loss, kidney stone, hypertension, gallstones, gastric and esophageal polyps, herpes zoster, skin basal cell carcinoma, posterior frontal calcified meningioma, hypokalemia, abdominal cramps, elevated liver injury tests, in addition to her GERD. She was taking regularly or upon occasions over 25 drugs other than study medication *(Volume 196, pages 43-6)*. She entered Study K-odd *de novo* on 11 July 1995 (endoscopy done 5 days before had shown grade 0 esophagus), and was randomized to receive rabeprazole 20 mg/day. Repeat endoscopies on 7 August and 5 October continued to show grade 0 esophagus *(Volume 197, pages 195-7)*, but on 23 October her family physician found her to have **blood pressure 190/90** and an electrocardiogram showed **multifocal atrial tachycardia**, for which she was admitted to hospital for evaluation and adjustment of her regimen. A second hospital admission occurred on 11 December for extracorporeal shock-wave **lithotripsy of kidney stones** the next day (Day 155 of Study K-odd). Following this a third hospitalization on 24 January 1996 (Day 198 of Study K-odd) was arranged for **percutaneous nephrostomy** stent placement, and nephrolithotripsy. She was discharged in 1 February and completed Study K-odd, showing no recurrence of esophageal erosions.

Patient 067-9751, a 51-year-old Caucasian woman, had a history of hysterectomy in 1972, chronic arthritis since age 7, in addition to her GERD. She entered Study K-odd *de novo* on 23 October 1995, and was randomized to receive rabeprazole 20 mg/day. Her grade 1 esophagitis found at endoscopy on 19 October 1995 remained healed a grade 0 on her subsequent endoscopic examinations at 4, 13 and 26 weeks (16 Nov 1995; 18 January and 25 April 1996). A **left ovarian cyst** was discovered on 14 June 1996, and she was immediately hospitalized for left salpingectomy and bilateral oophorectomy. The specimen of the enlarged ovary showed mucinous cystadenoma, but no carcinoma. She was discharged and completed the study at 52 weeks (18 October 1996) with no relapse of esophagitis.

Rabeprazole 10 mg/day (70 patients):

Patient 029-9197, a 32-year-old Caucasian man, had a history of appendectomy in 1973 and depression in 1989, in addition to his GERD. He had been in Study J (029-8198) for 26 days on rabeprazole 20 mg/day, healing the grade 2 erosions seen on 11 March 1995 to a grade of 1 on 6 April. He was re-randomized to rabeprazole 10 mg/day on 13 April, and showed grade 0 esophagus on 11 May at his 4-week visit *(Volume 196, page 334)*. On 3 July he called to report that he had had a **myocardial infarction** on the night of 29 June, for which he was hospitalized and the next day had bypass surgery. His study medication was discontinued at admission (Day 78 of Study K-odd), and was not resumed.

Patient 063-9436, an 81-year-old Caucasian woman, had a history of allergy to seasonal pollens, as well as to penicillin and erythromycin, hysterectomy, malignant breast nodule resected, surgery on the foot and hand, leg cramps, in addition to her GERD. She had been treated with rabeprazole 20 mg/day for 28 days in Study J (063-8438), and had healed grade 2 erosions found on 2 May 1995 to grade 0 after 28 days. She entered Study K-odd on 7 June, and was randomized to 10 mg of rabeprazole/day. She was found to have "double" **pneumonia** on 25 August (Day 80 of Study K-odd), and was hospitalized two days later. She responded to antibiotics and was discharged after 6 days, having interrupted study medication from 30 August to 8 September. Her endoscopy on 19 September showed grade 2 esophagitis, and she was deemed to have relapsed. Because of an error in communication, she continued rabeprazole 10 mg/day until 20 October, but no endoscopy was done to see if she may have re-healed.

Patient 041-9756, a 37-year-old Caucasian woman, had a history of peptic ulcer disease in 1973, tubal ligation in 1983, hiatal hernia and GERD. She entered Study K-odd *de novo* on 5 September 1995, and continued healing at grade 1 of the esophageal edema/erythema she had shown on 31 August. Repeat endoscopies at 4 and 13 weeks (6 October and 8 December) showed grade 1 esophageal status. On 30 December (Day 117), she presented at an emergency room with acute right-sided abdominal pain of two-days' duration, with fever, nausea, chills, and some diarrhea *(Volume 196, pages 50-1)*. She was hospitalized overnight and discharged with a diagnosis of "**viral GI syndrome.**" She completed the study, showing continued grade 1 esophagitis (healing) at the 26- and 52-week visits on 6 March and 11 September 1996 *(Volume 197, pages 12-4)*.

Patient 033-9231, an 80-year-old Caucasian woman, had a history hysterectomy in 1975, hypothyroidism, cataracts, cerebral amyloidosis, and homonymous hemianopsia, as well as GERD. She entered Study K-odd *de novo* on 31 July 1995, was randomized to rabeprazole 10 mg/day *(Volume 196, pages 37-8)*. Her initial grade 0 esophagus remained healed (grade 0) at 4 and 13-week visits on 28 August and 30 October 1995, but on 13 January 1996 (Day 164) she complained of impaired vision and was hospitalized for treatment of right **intracerebral hemorrhagic stroke**. She made a reasonable recovery, and completed the study, showing continued grade 0 healing at the 26- and 52-week visits on 13 February and 19 August 1996 *(Volume 196, pages 336-8)*.

Patient 001-9006, a 48-year-old woman of African descent, had a history of tubal ligation in 1978, hysterectomy in 1987, hypothyroidism, irritable colon, atypical chest pain, myalgia and arthralgia of the limbs, vaginal dryness, and GERD. She was treated in Study J for 58 days on rabeprazole 20 mg/day (001-8006), healing the grade 3 esophagitis seen on 5 April to grade 0 on 30 May 1995. She entered Study K-odd on 2 June, and was randomized to rabeprazole 10 mg/day. She showed continued healing a grade 0 at her 4, 13, and 26-week visits (28 June, 30 August, and 29 November), but developed severe abdominal pain, diarrhea, and fainted on 24 December (Day 206 of Study K-odd). She was hospitalized, where it was discovered she had had several similar episodes, without any objective findings. She was discharged with diagnoses of **hyperventilation, irritable bowel, and syncope**, on Lomotil p.r.n for cramps and diarrhea. She completed the study, showing grade 1 mild esophagitis on 28 March and grade 0 complete healing on 7 June 1996.

Patient 005-9029, a 34-year-old Caucasian woman, had a history of ,alcoholism, drug addiction, tubal ligation in 1992, obesity, anxiety and depression, left wrist fracture, and allergies to penicillin, aspirin, codeine, Darvocet, Percodan, Percocet, in addition to GERD. She had been treated in Study J (005-8029), which slowly healed her grade 2 esophagitis seen on 7 March 1995 to grade 1 after 56 days (2 May) on rabeprazole 20 mg/day. She was randomized to rabeprazole 10 mg/day in Study K-odd, beginning on 9 May, showing maintenance of healing at grade 1 on 9 June, grade 0 on 1 August and 10 November 1995. On 27 February 1996 (Day 295 of Study k-odd) she was hospitalized for **depression, suicidal attempt** with Tegretol overdose. She was discharged after 6 days, completed the study, with relapse to grade 2 on 1 May 1996.

Patient 041-9285, a 76-year-old Caucasian man, had a history of hypertension, fatigue, marginal blepharitis, cataract, and peripheral retinal pigment epithelial alteration, in addition to GERD. He had been in Study J (041-8284), on rabeprazole 20 mg/day for 28 days to heal his grade 2 erosions seen on 14 March 1995 to grade 0 on 11 April. He was re-randomized in Study K-odd to rabeprazole 10 mg/day starting 44 days later on 26 May after re-endoscopy the day before showed grade 1 mild but still healed esophagitis. Repeat endoscopies on 22 June, and 24 August continued to show grade 1 , and he was completely healed to grade 0 at the 26-week visit on 22 November 1995. On 15 March 1996 (Day 295 of Study K-odd) he became febrile and weak, fainted and was hospitalized. He was jaundiced, due acute **cholecystitis with cholangitis and *E. coli* bacteremia**. Cholecystectomy was done later on rehospitalization 8-16 April. He missed several days of study drug and was found to have relapsed to grade 2 on 22 May 1996.

Placebo (70 patients)

Patient 045-9314, a 45-year-old Caucasian man, had a history of hypertension, hyperlipidemia, coronary artery disease since age 36, type-2 diabetes mellitus, coronary artery bypass in 1986 and repair of aortic coarctation in 1987, mitral regurgitation, cardiomyopathy and congestive heart failure since 1994, molluscum contagiosum, and arthritis, in addition to his GERD. He entered Study K-odd *de novo* on 6 September 1995 and was randomized to placebo. On 16 September (Study Day 11) he developed **chest pain and dyspnea**, and was found to be anemic (hematocrit 0.32-0.34). His serum total cholesterol was marked elevated at 795 mg/dL and triglycerides 3995 mg/mL. An electrocardiogram showed premature atrial and ventricular contraction, old inferior infarction, and non-specific ST and T-wave changes. He was discharged on 20 September, although study medication had been stopped the day before. Endoscopy on 21 September showed relapse of grade 3 esophagitis just 15 days after a pre-study finding of grade 0 had been seen on 6 September.

Patient 041-9754, 69-year-old Caucasian woman, had a history of appendectomy in 1942, back pain, penicillin allergy, hysterectomy in 1959, cholecystectomy in 1971, hypertension, arthritis, menopause, iodine allergy, hypercholesterolemia, diverticulosis and diverticulitis in 1988, colostomy in 1990 and reversal of colostomy in 1991, insomnia, ventral hernia repair in 1992, bilateral cataracts and vitreous retinal detachment, hiatal hernia and GERD. She entered Study K-odd *de novo* on 9 August with grade 0 esophagus and was randomized to receive placebo. On 25 August (Study Day 17) she developed **severe chest pain and hypertension** of 210/102 mm Hg and was hospitalized. She was discharged after 4 days, with no additional diagnostic findings and withdrew from the Study at Visit 2 on 7 September because the investigator thought her chest pain due to recurrent GERD symptoms (lack of efficacy), although endoscopy showed no relapse of erosive esophagitis (grade 0).

Patient 001-9001, a 38-year-old Caucasian man, had a history of lipoma of the back, esophagitis dating back to 1991, right rotator cuff injury in 1992, prostatitis, excision of basal cell skin carcinoma in 1993, and active GERD *(Volume 196, pages 27-8)*. He had been treated in Study J (001-8003) during which he showed healing of grade 3 esophagitis (22 February 1995) on 55 days of ranitidine 150 mg q.i.d. to grade 0 on 18 April. He was entered into Study K-odd the same day and was randomized to receive placebo. Follow-up endoscopies at 4 and 13 weeks showed grade 1 change on 18 May and 18 July *(Volume 197, pages 276-8)*. On 7 August (Study Day 111) he was found to have another **basal cell carcinoma** of the skin on his shoulder, excised three weeks later. He completed the Study and did not relapse, showing grade 1 findings at 26 weeks (17 October) and grade 0 at 52 weeks (19 April 1996).

Comment: Of the serious events reported, and summarized briefly above, most appeared to arise from previous medical problems pre-dating entry of the patients into the study, or were simply intercurrent events that would be expected in such a population sample, with no apparent relation to study drug. The chest pain in the two patients on placebo might have been due to recurring GERD symptoms, as was suspected by the investigator for patient 041-9754, but more likely due to the extreme hyperlipidemia and coronary artery disease of patient 045-9314, although he did show very rapid relapse of esophageal erosions.

Discontinuations for adverse events from Study K-odd:

Despite the serious events, most (13/15) of the patients described above continued in Study K-odd and completed (9/15), or reached a Study endpoint (4/15) of relapse or lack of efficacy, except for patients 043-9295 and 029-9197 who had serious adverse events that caused discontinuation. Only 7 patients discontinued from the study because of non-serious adverse events. They are described briefly below:

Rabeprazole 20-mg/day group (69):

Patient 003-9015, a 51-year-old white man, had a history of hypertension, headaches, macular microaneurysm, [inguinal?] hernia, and GERD. He entered Study K-odd *de novo* on 20 March 1995 with grade 0 endoscopic findings *(Volume 196, page 93)*, but developed symptoms of constipation after only 7 days on study drug, with intermittent diarrhea, abdominal pain and **blurred vision** occurring on 30 March (Study Day 11). He was withdrawn from study, still healed (grade 0) by endoscopy on 19 April (Day 31). His diarrhea had subsided but abdominal pain persisted. He had been hypertensive (162/92) at screening, and his right eye showed parafocal retinal telangiectasia with possible macular microaneurysm 2 days after entry into the study. The blurred vision cleared after study medication was stopped.

Rabeprazole 10-mg/day group (70):

Patient 019-9129, a 45-year-old Caucasian man, had an unremarkable medical history except for his GERD. He entered Study K-odd de novo on 21 April 1995, after endoscopy had shown grade 1 findings on 6 April *(Volume 196, page 334)*, and was randomized to rabeprazole 10 mg/day. Study medication was not immediately available, and could not be dispensed until 22 April, but before taking any he noted **tingling in the left side of his face** and withdrew from the study without taking study medication (Day 0). Unopened study medication was returned, and final endoscopy showed him still healed at Grade 0 on 11 May.

Patient 041-9614, a 78-year-old Caucasian woman, had a history of penicillin allergy, glaucoma, ovarian tumor excision in 1985, colon polypectomy 1985, hypertension, left leg artery bypass 1989, hyperlipidemia, cerebrovascular accident, sigmoid diverticula, cataract removal 1993, hiatal hernia, esophageal ulcer and stricture dilated in 1995 (7 March). She was taken into Study K-odd on 26 April 1995 when endoscopy showed grade 0 findings and no stricture *(Volume 197, page 10)*, and she was randomized to receive rabeprazole 10 mg/day. After about 11 days on study, she began noticing **nausea, vomiting, diarrhea, blurred vision**, itching and rash of the left arm, edema of the right arm, and tachycardia. She was withdrawn from study on 10 May (Day 15), after which all of the symptoms stopped, and she was found to have Grade 4 ulceration on 24 May.

Patient 003-9017, a 45-year-old Caucasian man, had a history only of asthma since age 6 and a left knee surgical procedure in 1994, in addition to GERD *(Volume 196, page 13-4)*. He had been treated in Study J (003-8018) in which grade 2 esophagitis found on 14 March 1995

healed to grade 1 at endoscopy 27 days later (10 April) on rabeprazole 20 mg/day. He entered Study K-odd on 12 April, and was re-randomized to rabeprazole 10 mg/day. At the Visit 2 endoscopy he was found to have a **duodenal ulcer**, although the esophagitis had not relapsed (Grade 1) on 10 May *(Volume 196, page 243)*. He was withdrawn from the study.

Patient 067-9249, a 64-year-old Caucasian man, had a history of inguinal herniorrhaphy in 1972, hypertension, arthritis, hiatal hernia, diverticulosis, esophageal stricture and dilatation in 1990, sinus surgery in 1990, pterygium, colitis, prostatitis, amblyopia, urinary tract infection, bronchitis, cholecystitis and colon polypectomy in 1995 *(Volume 196, pages 24-5)*. He entered Study K-odd *de novo* on 24 March 1995 on placebo after endoscopy the day before had shown grade 0 findings of the esophagus. Subsequent endoscopic examinations showed continued normal esophagus (grade 0) at 4, 13, 26, and 39 weeks (23 June, 18 August, 17 November 1995, and 30 January 1996). On 25 January 1996, after two weeks on metronidazole and ciprofloxacin for treatment of diverticulitis, he was found to have **atrial and ventricular premature beats**. Holter monitoring confirmed this, showed premature atrial contractions, multiple premature ventricular contractions, episode of supraventricular tachycardia, and a 3-beat run of ventricular tachycardia. He was hypertensive, with blood pressure 170/100, and he was withdrawn from study drug on 26 January at Visit 5 (Study Day 246). No arrhythmias were detected on 27 February, after 32 days off rabeprazole.

Placebo group (70):

Patient 061-9425, a 72-year-old Caucasian man, had a history of chronic obstructive lung disease since age 20, appendectomy, actinic keratoses and fungal dermatitis since 1974, left upper lobe lung nodule since 1982, degenerative joint disease, colonic polyps, peripheral edema, hypertension, in addition to GERD *(Volume 196, pages 22-3)*. He entered Study K-odd de novo on 20 June 1995, when endoscopy showed healed esophagus (Grade 0), and was randomized to placebo. After the first dose (Day 1) of study medication he complained of **headache, generalized itching and burning stomach pain**, and he was advised to take no more study drug. All symptoms subsided on 23 June. No further endoscopy was done *(Volume 197, pages 390-2)*.

Patient 053-9366, a 46-year-old Asian man, had a history of tonsillectomy at age 10, penicillin allergy, hepatitis B, Helicobacter pylori positivity in 1995, in addition to GERD *(Volume 196, page 20-1)*. He was treated in Study J (053-8366) with rabeprazole 20 mg/day for 27 days, healing his grade 2 erosions to grade 0 at the 4-week visit on 22 March 1995. He was re-randomized to placebo in Study K-odd, starting 27 March without further endoscopy. After the first dose of placebo, he complained of blurred vision, and at the 4-week visit on 26 April he was found to have two 5-mm **duodenal ulcers** but the esophagus was still grade 0 *(Volume 197, page 379)*. He was withdrawn from the study that day, by which the blurred vision symptom had resolved. The duodenal ulcer was treated off-study and was reported healed.

Comment: These adverse events that led to discontinuations included symptoms that might possibly be of concern as rabeprazole-induced, such as the blurred vision in Patient 003-9015, but the symptom also occurred in Patient 053-9366 after one dose of placebo. Duodenal ulcer

without relapse of esophageal erosion occurred in Patient 003-9017 after 4 weeks on rabeprazole 10 mg/day, but also in Patient 053-9366 after a month on placebo.

Treatment-emergent symptoms that occurred in significantly higher frequency in rabeprazole-treated patients than in placebo-treated patients included unspecified pain, diarrhea, and unspecified infections *(Table 13.1, Volume 192, pages 255-60)*. It was also noted *(Volume 192, pages 108-15)* that there was a highly significant ($p = 0.008$) excess in proportions of patients on rabeprazole 20 mg/day (57/69, 83%) and rabeprazole 10 mg/day (58/70, 83%) who had at least one symptom or event occurring on treatment, than in the placebo group (43/70, 61%). The excess frequency in rabeprazole-treated patients was also seen for rhinitis, flu syndrome, fever, sinusitis, dizziness, abdominal pain, and accidental injuries. It was also pointed out by the sponsor that the patients on rabeprazole were under observation in the study for longer periods of time, more than twice as long *(Table 12, Volume 192, page 254)*. As a result, random or intercurrent events not caused by study medication would be expected at least twice as often as in patients observed for shorter periods on placebo. Life table analyses indicated that there were no differences in these events between rabeprazole and placebo treatment when adjusted for exposure by Kaplan-Meier analyses *(Tables 13.5.1-14, Volume 192, pages 286-338)*.

Comment: It certainly does not make sense that rabeprazole should cause an increased incidence of accidents or upper respiratory infections or back pain. The argument that these events were seen more often in rabeprazole-treated patients than in placebo-treated patients because they were at risk for longer of having those event happen does seem plausible. However, the point could be proved conclusively only by continuing to observe patients treated by placebo after they had either failed to respond (lack of efficacy) or relapsed with esophageal erosions could there be very convincing evidence to support this explanation. The design of the study did not allow for this, so that some question remains.

There were no notable differences between rabeprazole and placebo treatment with respect to blood counts or chemistries, thyroid function tests, urinalyses, ophthalmologic examinations, vital signs, electrocardiograms, or gastric mucosal hyperplasia scores. The serum gastrin levels were not significantly different in the three study drug groups at the beginning of the maintenance study, but showed an inversely dose-related decrease on maintenance study drug: most (-31.2 pg/mL) in the placebo group, less (-20.6 pg/mL) in the rabeprazole 10-mg/day group, and nil (+1.8 pg/mL) in the rabeprazole 20-mg/day group.

Comment: It should be borne in mind that all of the patients who entered this study had been healed of their erosive esophagitis by prior treatment, often with proton-pump inhibitors, so that the serum gastrin levels at study entry would have been elevated. The fact that the levels remained about the same in patients on rabeprazole 20 mg/day, but fell in those on half that dose, and fell most of all in those on placebo, reinforces the point. Nothing can be concluded about the meaning of serum gastrin levels without knowing what prior treatment the patients had been on to heal their erosive esophagitis, before entering this study.