his **rheumatoid arthritis** and took no more study medication after 20 July (Day 28). Subsequently, shave biopsy of his nose showed a **basal cell carcinoma** in a lesion he had noticed first about 7 or 8 months before.

Patient 052-9363, a 61-year-old Caucasian man, has a history of rotator cuff tendonitis 1942 and obesity since 1983; environmental allergies; hypersomnia, mastoidectomy and bronchitis 1984; back pain and musculoskeletal pain since 1990; allergies to Monopril, atenolol, Vistaril, Tenormin; hypertension and chronic cough, sleep apnea since 1994; deviated septum, anxiety, and erosive esophagitis since 1995 *(Volume 204:89-91)*. He entered the study *de novo* on 9 June 1995, the day after endoscopy showed grade 0 healing, and he was randomized to **rabeprazole 10** mg/day. He remained healed (grade 0) on 7 July, but on 25 July he reported chest pain and shortness of breath with exercise over the week before. Stress testing revealed exercise-induced angina but no arrhythmias. Recurrent symptoms on 30 July led to hospitalization for **angioplasty for his coronary artery disease**. He continued on study, and showed grade 1 findings on 8 September, grade 0 on 11 December 1995 and 11 June 1996 *(Volume 205:218-20)*

Patient 020-9635,a 48-year-old Caucasian man, had a history of rheumatic fever in 1950, asthma, pneumonia, and hepatitis in 1954-5, Fanconi syndrome 1957, acne 1967, fibromyalgia and rheumatoid arthritis since 1980, penicillin allergy, right knee meniscus tear 1988, muscle spasms 1992, anxiety, insomnia, depression since 1994, and erosive esophagitis *(Volume 204:80-2)*. He entered the study *de novo* on 6 June 1995 with grade 1 healing and was randomized to rabeprazole 10 mg/day. He maintained healing (grade 0) on 5 July, but on 23 July developed low grade fever, with stiffness, swelling, redness, pain and effusion in the left knee about 5 weeks after surgical debridement (synovial plica) of the knee on 15 June. There was no evidence of additional trauma or sepsis in the joint, and he was treated with intraarticular steroids and analgesics. It was felt he had a **rheumatoid flare after knee surgery**. He continued on study and maintained healing, with grade 0 findings on 6 September and 7 December 1995, and completed the study without relapse on 6 June 1996 *(Volume 205:137-9)*.

Patient 018-9125, a 72-year-old Caucasian man, had a history chronic constipation since childhood, lactase deficiency, hay fever since 1965, penicillin allergy. eczematous dermatitis, right knee injury 1975, prostatic hyperplasia since 1982, hiatal hernia since 1983, hypercholesterolemia since 1986, multiple hepatic cysts and impotence since 1992, irritable bowel syndrome, cataracts, degenerative joint disease since 1994, anxiety, and erosive esophagitis *(Volume 204:77-9)*. He entered the study on 14 June 1995 (018-8124) after healing in Study J on rabeprazole 20 mg/day for 56 days, from grade 3 to grade 0. He was re-randomized to rabeprazole 10 mg/day, and maintained healing on 11 July but was found to have a 7-cm plaque on his anterior chest skin, confirmed to be basal cell carcinoma. He continued on study and maintained grade 0 healing on 19 September, 12 December 1995 and completed the year on 12 June 1996 without relapse *(Volume 205:123-5)*.

Patient 006-9640, a 46-year-old Caucasian woman, had a history of two caesarian sections in 1971 and 1975, fibrocystic uterus and hysterectomy in 1987, ulcerative colitis in 1990 and erosive esophagitis. She entered this study de novo on 5 June 1995, after healing to grade 0

by endoscopy 3 days before, and was randomized to receive **rabeprazole 10** mg/day. She maintained healing on 30 June and 8 September, but the next day she was hospitalized for an apparent **suicidal attempt and depression**. She was discharged after a week in hospital, but continued depressed and was thought to require tricyclic antidepressant medication. She quit the study on 26 November, maintaining healing at grade 0 on 1 December 1995.

Patient 006-9710, a 60-year-old Caucasian man, had a history of anxiety since 1990 and depression since 1993, with alcoholism of indeterminate duration *(Volume 204:62-4)*. He entered the study *de novo* on 22 August 1995, after showing grade 1 healing the day before, and was randomized to **rabeprazole 10** mg/day *(Volume 205:25-7)*. He maintained grade 1 healing on 18 September and 20 November 1995, but was admitted to hospital on 26 January 1996 after being treated in a detoxification center for **alcoholism** where he had episodes of dyspnea, sweating, nausea. He was found to have electrocardiographic evidence of **anterior myocardial infarct** of undetermined age, emphysema on chest x-ray. He continued on study, maintaining grade 1 healing on 26 February and 19 August 1996 *(Volume 205:25-7)*.

Patient 012-9079, a 64-year-old Caucasian man, had a history of bleeding duodenal ulcer in 1970 and 1993, hemorrhoidectomy 1971, hypertension since 1989, fractured left fibula 1989, back pain, right carpal tunnel syndrome, degenerative disease of the spine, leg cramps, cataracts, hyperlipidemia, seborrheic dermatitis, psoriasis, peripheral neuropathy, sigmoid polyp, macular degeneration, right eye vein occlusion, hiatal hernia, elevated liver enzymes, GERD and erosive esophagitis *(Volume 204:23-5)*. He entered this study de novo on 24 February 1995 with grade 0 healing, and was randomized to **rabeprazole 10** mg/day. He maintained grade 0 healing on 24 March, and 2 June 1995 *(Volume 205:81-2)*, but was admitted from an emergency room on 30 July 1995 (Day 157) after taking an **overdose of diltiazem** (960 mg) in mistake for Tylenol. He was dehydrated, acidotic, weak, sweaty and had mid-abdominal pain. The record showed a history also of alcohol abuse that he had concealed. Findings of lactic acidosis, hyperglycemia, renal insufficiency, pulmonary edema and complete heart block required intravenous fluids, bicarbonate, ranitidine, and he recovered after a few days. Study medication had been stopped 27 July, and final endoscopy on 2 August showed continued healing at grade 0.

Patient 010-9770, a 66-year-old Caucasian woman, had a history of menopause 1970, headaches since 1975, cholecystectomy 1988, hypertension since 1988, cataract, sulfa allergy and hiatal hernia 1990, diverticulosis and hyperlipidemia since 1992, diverticulitis 1995, erosive esophagitis and Barrett's changes 1995 *(Volume 204:21-2)*. She entered the study de novo on 31 July 1995 with grade 0 healing, and was randomized to **rabeprazole 10** mg/day. She remained healed on 28 August and 30 October 1995. On 4 December barium enema revealed a possible **colon cancer**, and she was hospitalized 22 December for colectomy that revealed Duke's stage 2B adenocarcinoma. She stopped study medication 21 December. Deep vein thrombosis of the left leg occurred two weeks postoperatively and she was readmitted for anticoagulation. Her last endoscopy on 12 January 1996 at 26 weeks showed grade 1 findings three weeks after stopping rabeprazole *(Volume 205:76-7)*.

Patient 006-9473, a 40-year-old Caucasian man, had a history of seasonal allergies since childhood, degenerative disk disease and laminectomy in 1985, pancreatitis and pancreatic cyst

1985, depression 1990, and erosive esophagitis *(Volume 204:56-8)*. He entered the study after healing on ranitidine in Study J (006-8038), 56 days from grade 2 on 1 March 1995 to grade 1 on 26 April. He was re-randomized to **rabeprazole 10** mg/day, and remained healed at grade 1 on 24 May, 24 July, and 25 October 1995 *(Volume 205: 7-9)*. On 18 November (Day 207) he had epigastric pain radiating through to the back and serum amylase elevated to 588 u/L, diagnosed as **acute pancreatitis**, for which he was hospitalized. Scans suggested chronic pancreatitis and fatty liver, and he responded to treatment over his 12 days of hospitalization. He missed from 2 to 12 doses of study medication while in hospital, but resumed taking it. Another hospitalization occurred on 10 January 1996, for **surgical repair of his left knee**, which had been injured in and automobile accident on 27 September 1995. He completed the study without relapse (grade 1) on 22 April 1996.

Patient 030-9210, a 55 year-old Caucasian man, had a history of peptic ulcer 1970, osteoarthritis since 1990, internal hemorrhoids since 1993, hyperlipidemia, chronic anxiety, tobacco dependency, and rectal bleeding in 1995 *(Volume 204:37-9)*. He entered this *study de novo* on 12 July 1995 after endoscopy the day before showed grade 0 healing, and he was randomized to **rabeprazole 10** mg/day. He remained healed on 10 August, 17 October 1995, and 2 January 1996. On 11 April 1996 (Day 276) he complained of chest pain, and was found to be hypertensive at 200/130 mm Hg. Electrocardiographic readings and serum enzyme confirmed **myocardial infarction**, and catheterization showed right coronary artery occlusion. Bypass graft was done the next day and he was discharged 4 days later. He was withdrawn from the study as of 12 April, but a final endoscopy showed no relapse on 10 July 1996 *(Volume 205:180-2)*.

Patient 066-9827, a 63-year-old Caucasian man, had a history of papule on right forearm since 1960, rectal cyst 1980, back pain since 1985 and right axillary skin tags, alcohol abuse 1989, seborrheic dermatitis of the scalp, and erosive esophagitis *(Volume 204:95-6)*. He entered this study *de novo* on 27 September 1995, after endoscopy that day showed grade 0 healing, and he was randomized to **rabeprazole 10** mg/day. He remained healed on 25 October 1995 and on 8 January and 3 April 1996 *(Volume 205:246-8)*. On 13 August 1996 (Day 322) he noticed a lump on his left neck, later shown to be a **keratoacanthoma**. He completed the study without relapse on 26 September 1996.

Placebo (99 patients)

Patient 010-9771, a 30-year-old Caucasian woman, had a history of amblyopia and right cataract since birth, asthma since childhood, Caesarian sections in 1985 and 1987, hyperlipidemia since 1994, tubal ligation and erosive esophagitis 1995 *(Volume 204:71-3)*. She entered this study de novo on 5 September 1995 with grade 0 healing, was randomized to **placebo** and showed grade 0 esophagus on 3 October, grade 1 on 5 December, and grade 0 on 27 February 1996. She was hospitalized for **elective hysterectomy and bilateral oophorectomy** on 29 May 1996, but completed the study without relapse on 3 September 1996.

Comment: None of these serious events, on rabeprazole or placebo, would appear to have been caused by rabeprazole, but were consequences of pre-existing disorders or intercurrent events.

Discontinuations for Non-Serious Adverse Events

In addition to the deaths and serious adverse events, there were 5 patients who discontinued study because of non-serious adverse events, 3 who had been on rabeprazole 20 mg/day, and 2 on placebo.

Rabeprazole 20 mg/day (94 patients):

030-9209	Fc38*	Diarrhea	Day 13
060-9418	Fc23*	Gallstones	Day 26
034-9237	Mc57*	Vomiting	Day 149

Placebo (99 patients)

042-9291	Mc60	Upset stomach, dyspepsia	Day 2
032-9736	Mc51	Diarrhea	Day 10

Patient 030-9209, a 38-year-old Caucasian woman, had a history of traumatic injuries to her head and right eye in 1963 with eventual blindness in that eye in 1980, tubal ligation 1978, penicillin allergy 1986, back pain since 1993, rhinitis and erosive esophagitis 1995 (Volume 204:48-9). She entered the study de novo on 9 June 1995 with grade 1 healing, and was randomized to **rabeprazole 20** mg/day. After the second dose on 10 June she began to have headaches, and noted decreased libido, followed 4 days later by **diarrhea**. She quit study drug on 21 June (Day 13), and all symptoms disappeared within a week. She then had symptoms of bronchitis on 28 June and myalgias 1 July, after stopping the study drug. She had relapsed to grade 3 esophagitis when she was examined 7 July 1995 *(Volume 206:91)*.

Patient 060-9418, a 23-year-old Caucasian woman, had a history of surgical procedures on her left shoulder 1990, right knee arthroscopy 1993, and ovarian cystectomy 1994. She was allergic to codeine, and had allergic conjunctivitis and glaucoma, before her erosive esophagitis *(Volume 204:54-5)*. She entered the study on 27 April 1995, after healing to grade 0 on 28 days of ranitidine in Study J (060-8417), and was randomized to **rabeprazole 20** mg/day. On 21 May she had an attack of severe epigastric pain and was found to have **gallstones**. She had her last endoscopy on 24 May, showing no relapse, and she quit study medication that day.

Patient 034-9237, a 57-year-old Caucasian man, did not have a narrative history in Volume 204. He entered the study *de novo* on 29 November 1995 with grade 0 healing *(Volume 206:117)*, and was randomized to **rabeprazole 20** mg/day. He is listed as having withdrawn for **vomiting** after 149 days on study, but no further endoscopy reports are listed.

Patient 042-9291, a 60-year-old Caucasian man, had a history of ganglion cyst removal from his right wrist 1977, arthritis since 1985, carpal tunnel repair and pinning of a broken right heel 1991, hypertension and atrial fibrillation 1992, quadruple coronary artery bypass and transurethral resection of the prostate in 1992 *(Volume 204:52-3)*. He entered the study on 5 May

1995 after healing to from grade 2 on 7 April to grade 0 on 28 days of ranitidine in Study J (042-8293), and was randomized to **placebo**. After the first two daily doses of placebo, he developed **nausea**, and quit the study 6 May (Day 2).

Patient 032-9736, a 51-year-old Caucasian man, had a history of tonsillectomy at age 13, mononucleosis age 17 (1960), rhinoplasty 1962, left shoulder subluxation 1982, GERD 1985, substance abuse 1988, insomnia since 1988, left amblyopia of unknown duration and hypertension since 1995 *(Volume 204:50-1)*. He entered this study *de novo* with grade 0 healing on 30 May 1995 and was randomized to **placebo**. After the first dose of placebo he complained of **stomach cramps and diarrhea**, which persisted until he stopped study medication on 8 June (Day 10).

Other treatment-emergent adverse events

Other adverse events that did not cause discontinuation and were not serious were reported by 77/94, 81.9% of patients on rabeprazole 20 mg/day, 80/95, 84% of patients on rabeprazole 10 mg/day, but in significantly ($p < 0.001$) fewer patients on placebo (58/99, 58.6%). Adverse events reported most frequently were rhinitis, headache, pharyngitis, diarrhea, all in more than 20% of patients taking rabeprazole. Back pain, abdominal pain, surgical procedures were reported in significantly more patients on rabeprazole than on placebo, all in over 10% of rabeprazole-assigned patients. Also significantly more frequent were chest pain, constipation, dizziness, and insomnia, in between 5 and 10% of patients *(Volume 200, pages 108-19)*. When these adverse events were considered on the basis of exposure time, none of the events were significantly more frequent in rabeprazole-treated than in placebo-treated groups.

Comment: Again, the design of the study did not allow for comparing equal period of exposure to drug and close observation/reporting of symptoms. The differences seem to be explained by the 2.7 and 2.5 times longer exposure times for rabeprazole 20 and 10-mg/day doses than for placebo. However, this point is not conclusively proved, only speculated upon using a plausible explanation.

Serum chemistries, blood counts, thyroid function testing, urinalyses, electrocardiograms, vital signs, ophthalmological examinations, gastric mucosal biopsies did not change significantly differently in patients on rabeprazole compared to placebo. Serum gastrin fell significantly on placebo, but did not change appreciably in patients on either rabeprazole dose.

Comment: These findings confirmed and closely resembled those of Study K-odd. Since most of the patients had been healed on strong acid-suppressing agents before entering Study K-even, it is not surprising that rabeprazole did not cause any further increase, while placebo administration led to a significant decline in serum gastrin levels.

Conclusions on Study K-even

The sponsor concluded that both 10 and 20-mg/day doses of rabeprazole were more effective than placebo in reducing the relapse rate of erosive esophagitis, and that the 20-mg daily dose "consistently performed better than 10 mg, although this difference reached statistical significance in only a few efficacy parameters."

Comment: It was convincing that rabeprazole is far superior to placebo for reducing erosive esophagitis relapse, but the data of this study do not support the superiority of the 20-mg daily dose over the 10-mg daily dose. The statement should be turned around to say that the two doses were not significantly different except for minor isolated cases .It should be recognized that the study was designed and powered to show superiority of rabeprazole to placebo, not for showing a significant difference between the rabeprazole doses. The protocol (Volume 201:38-9) indicated that the writers assumed a difference between relapse rates in patients on placebo and patients on rabeprazole would be at least 24% with 80% power to detect the difference with α = 0.05 (two-sided). For this, it was estimated that 80 patients per study arm would be needed, or 240 in all. When it was decided to do two studies, the numbers were simply doubled and the study was broken into two with identical protocols but odd- and even-numbered investigators.

As it turned out, the two studies were not of exactly the same size, since the 27 investigators of Study K-odd actually enrolled only 209 patients (<8/site), compared to the 288 patients enrolled into Study K-even by 24 investigators (12/site). Although the placebo relapse rate was very similar in the two studies, 50/70 (71.4%) in Study K-odd and 70/99 (70.7%), the relapse rates in patients on rabeprazole was not exactly confirmed, and there was a significantly greater relapse rate on 10 mg/day (18/66, 27.3%) than on 20 mg/day (7/67, 104%) in Study K-odd (p=0.015). In Study K-even, the difference between relapse rates in the two groups on rabeprazole (21/93, 22.6% on rabeprazole 10 mg/day, and 13/93, 14.0% on rabeprazole 20 mg/day) was less marked and not statistically significant (p=0.18).

In order to size such a study to detect a difference between the two rabeprazole groups at 80% power and α = 0.05 (two-sided), as many as 150 patients per arm would be needed. This was actually reached by the two studies combined, which included 497 patients. In such a combined study, the relapse rate on rabeprazole 20 mg/day was 20/160 (12.5%), compared to 39/159 (24.5%) on rabeprazole 10 mg/day, which was highly significant (p=0.006).

C. Study NRRQ (May '95-May '97): rabeprazole 10 or 20 vs. omeprazole 20 mg/day

Study Q was carried out in Europe by 21 of the 27 investigators who had conducted the healing Study P on 202 patients between 3 April 1995 and 15 March 1996. Its objective was to demonstrate equivalence between rabeprazole 20 mg/day or rabeprazole 10 mg/day with omeprazole 20 mg/day for reducing relapse rates of erosive esophagitis in patients with healed erosions/ulcerations.

Study H4M-MC-NRRQ, entitled ' 307640 Versus Omeprazole: Preventing Relapse in Erosive or Ulcerative Gastroesophageal Reflux Disease" was planned in August 1994 by for conduct by (It is also referred to by Eisai Inc. in this application as Study E3810-E044-308. For brevity it will be referred to as "Study Q" in this section of the medical review of this NDA 20-973.)

The protocol (see Volume 211, pages 72-101) called for enrollment of 240 adults with recently (within 90 days) healed erosive GERD of at least 3 months' duration and of pre-healing severity/extent of grade 2 to 4 on a modified Hetzel-Dent scale, as evaluated at endoscopy done by a gastroenterologist, as had been specified also for Studies NRRI, NRRJ, NRRK, and NRRP.

The number of patients was based on estimated relapse rates of 20% of patients on rabeprazole 20 mg/day and the same for those on omeprazole 20 mg/day, with 80% power to detect an 18% difference at $\alpha = 0.05$ (two-tailed), by the Casagrande (1978) formula. This yielded a requirement for 80 patients per study arm, or 240 in total.

The protocol for this Study Q was very similar to that for Study NRRK which was expanded to double the size (480 patients) and divided into two identical studies of about 240 patients each referred to above as Studies K-odd and K-even, conducted in the United States. Entry criteria for patients, endoscopic proof of healing by the same methods and scale for determining relapse to grade 2, 3, or 4 by the modified Hetzel-Dent system, secondary measures of relapse of heartburn, use of antacids, and details of study conduct were all consistent with the other studies in this series as described in more detail above.

Patients could enter into Study Q either by continuation after healing in Study P, or *de novo* if shown endoscopically to have been healed to grade 0 or 1 from a previous grade 2-4 erosive esophagitis, using an approved drug regimen. The same rules as were used for Study K-odd/even were applicable.

The protocol was amended on 10 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 Q was executed from 1 May 1995 to 7 May 1997 by 21 investigators who were under contract to Besselaar to recruit and study patients *(Table 1.1, Volume 210, pages 132-3)*:

Investigator, City	*R10*	*R20*	*O20*	*total*
001/ Pierre Hoang, Brussels, Belgium	1	1	2	4
021/ Jorgen Pederson, Solrod Strand, Denmark	0	1	1	2
023/ Bohumil Pluncar, Solrod Strand, Denmark	3	1	1	5
061/ B. Thjodliefsson, Reykjavik, Iceland	16	16	13	45
081/ John Patrick Crowe, Dublin, Ireland	3	2	3	8
082/ Paul William Napoleon Keeling, Dublin, Ireland	1	2	2	5
101/ Cornelius Dekkers, Breda, Netherlands	17	19	16	52
102/ Johannes Beker, Leischendam, Netherlands	19	14	19	52
121/ A. Gabrylewicz, Bialystok, Poland	2	3	4	9
122/ Eugeniusz Butruk, Warsaw, Poland	2	3	2	7
123/ Tadeusz Popiela, Krakow, Poland	3	3	3	9
124/ Krzysztof Marlicz, Szczecin, Poland	3	2	1	6
125/ Leslek Szczepanski, Lublin, Poland	3	2	4	9
144/ Juan Herrerias Gutierrez, Sevilla, Spain	0	1	0	1
161/ Irma Wright, Göteborg, Sweden	1	0	0	1
163/ Arnold Söderlind, Visby, Sweden	2	1	2	5
164/ Dan-Axel Hallbäck, Larlskoga, Sweden	0	2	0	2
166/ Hans Tanghöj, Eskilstuna, Sweden	0	2	2	4
181/ Graeme Kerr, Shrewsbury, England.	2	1	3	6
183/ Paul Swain, London, England	0	0	1	1
187/ K. D. Bardhan, Rotherham,England	4	2	4	10
total, 21 investigators	*82*	*78*	*83*	*243*

Investigators from Study P (see page 45 of this review) who did not participate in Study Q were: 041, Christiane Klein, of Künzing, Germany; 044, Dieter Raps, of Schopfheim, Germany; 048, R. Burlefinger, of Munchen, Germany; 142, Manuel Diaz-Rubio, of Madrid, Spain; 185, P. J. Finch, of Surrey, England; and 186, John S. A. Collins, of Northern Ireland (*Volume 211, pages 167-9*).

The investigators at the 21 centers enrolled 243 patients: 162 men (66.7%), 62 women; 236 Caucasian, 1 African descent, and 6 other; 62 (25.5%) were of age 65 or older, the mean age was 52.7 years, median 52, range 20-83; most used caffeine (93.0%) and alcohol (52.2%), but only 21.8% used tobacco and 9.5% were using antacids. Most had been healed to grade 0 (188/243, 77.4%), and the rest to grade 1 except for 1 patient with missing data. Most of the patients had no heartburn (138/243, 56.8%) and another 22.6% had only occasional heartburn less than 25% of the time. The randomized groups showed no significant differences in any of these characteristics *(Table 2.1, Volume 210, pages 138-42)*.

Of the 243 patients who entered the European maintenance treatment, nearly all (210/243, 86.4%) completed the full 52 weeks of study, with only modest losses due to adverse effects, relapse, or lack of perceived. Other reasons were provided to explain the losses from the study due to failure to return, and protocol violations. There were no significant differences in the rates of drop-outs for any reason among the three treatment groups.

DISPOSITION OF PATIENTS IN EUROPEAN STUDY Q

	total	R20	R10	O20	---------	p-value	---------
Enrolled	243	78	82	83	*R20vR10*	*R10vO20*	*R20vO20*
- Lack of efficacy	-3	-1	-1	-1			
- Lost/moved	-3	-1	-1	-1			
- Patient decision	-6	-4	-1	-1			
- Violated protocol	-8	-0	-3	-5			
- Adverse event*	-13	-4	-5	-4			
Completed study	210	68	71	71	*0.983*	*0.934*	*0.980*
% completing	*86.4%*	*87.2%*	*86.6%*	*85.5%*			

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

The results of the study, as reported by the sponsor, showed relapse rates in all three study arms that were about equivalent, in the range of 4 to 6% over the year of study:

RELAPSE OF EROSIVE ESOPHAGITIS IN STUDY NRRQ, (ITT)

	R10	R20	O20	---------	p-value	---------
	82 patients	78 patients	83 patients	*R20vR10*	*R10vO20*	*R20vO20*
By 13 weeks	1 (1.2%)	2 (3.0%)	1 (1.2%)	0.54	0.81	0.41
By 26 weeks	1 (1.2%)	3 (4.8%).	1 (1.2%)	0.30	0.81	0.18
By 52 weeks	4 (5.1%)	3 (4.8%)	4 (5.1%)	0.74	0.83	0.96

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

Comment: These results are remarkably lower than observed in the United States in Studies NRRK-odd/even. The comparison of relpase rates over a year for rabeprazole 20 mg/day is less than a third of that observed in NRRK (combined). Are they too good to be true? It is noted that three of the 21 investigators enrolled 149 of the 243 cases, and the other 18 sites enrolled only an average of 5.4 patients each. The two Dutch investigators, #101 and #102, who had reported such perfect results in Study P, each claiming 20/20 healed perfectly to grade 0 at just 4 weeks on both of the agents, also reported no relapses in any of 52 patients each in Study Q. There were no relapses among the 45 patients at Site 061, either. Such perfection is seldom seen in clinical trials, and certainly was not in the North American studies. Whether it is useful to analyze and review the results of Study Q further, until some of the questions concerning the European studies are resolved, is moot.

If the denominators of the study groups in the European studies are reduced by elimination of data from site 101,102, and 061, then the relapse rates would become 4/30 (13.3%) for rabeprazole 10 mg/day, 3/29 (10.3%) for rabeprazole 20 mg/day, and 4/35 (11.4%) for omeprazole 20 mg/day. These results would be far more consistent with the results reported in the United States for rabeprazole 20 mg/day in the combined NRRK studies, which showed 20 relapses among 160 (12.5%) patients on that dose.

Secondary analyses of relapse included increased heartburn frequency, also reported to be similar and not statistically different for any of the three paired comparisons (Report, Volume 210, page 80-2). This was also true for both daytime and nighttime heartburn severity (Volume 210, pages 82-8), well-being scores (pages 88-91), and antacid use (page 92).

Comment: The rates of relapse of heartburn frequency, daytime severity, and nighttime severity were also much less as reported in Study Q than had been reported for Study K-odd/even in which relapse of these symptoms occurred 2 to 3 times as often. The explanation does not appear to lie in the definitions, scoring systems, criteria for patient entry or management; the protocols were almost identical. The validity of these results is questionable.

Safety problems were reported in this Study Q, including centers 101,102, and 061, and patients were discontinued from the study at those centers because of adverse events, as well as at other sites. There were no deaths reported among the 243 patients studied. Serious adverse events and discontinuations from study were reported *(Volume 210: 97-100 & Volume 213: 85-99)*:

Serious Adverse Events Occurring During Study NRRQ

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 (78 patients):

102-4024	Mc55	Overdose	Day 1
061-4029	Fc49	Hysterectomy	Day 4
061-4039	Mc59	Spinal operation, wound infection	Day 4, 8
		Spinal operation	Day 32
122-4001	Mc67	Myocardial infarction	Day 15, 24
061-4004	Fc47	Hysterectomy	Day 22
164-4001	Mc75	Myocardial infarction	Day 42
102-4006	Fc74	Myocardial infarction	Day 51

Rabeprazole 10 mg/day (82 patients):

101-4003	Fc59	Small cell carcinoma of lung	Day –12
		Right ovarian tumor; nephrectomy	Day 16
123-4001	Fc52	Cholelithiasis	Day 22
061-4023	Fc49	Hysterectomy	Day 23
124-4006	Mc42	Coronary artery disease, bradycardia	Day 41
101-4051	Mc68	Chronic obstructive lung disease	Day 42
101-4043	Mc64	Repair abdominal hernia	Day 46
102-4050	Mc41	Overdose	Day47

Omeprazole 20 mg/day (83 patients):

061-4027	Fc54	Suspected overdose of study medication	Day 5
102-4004	Fc83	Gastroenteritis	Day 5
181-4002	Fc40	Headaches, numbness, twitching	Day 21
		Chest pain	Day 23
125-4007	Mc59	Lung cancer	Day 29
061-4014	Fc76	Pericarditis	Day 39
102-4018	Fo64	Overdose	Day 40
		Right hip fracture	Day 48
121-4009	Fc42	Thyroid nodules, partial thyroidectomy	Day 50
101-4005	Mc78	Diverticulosis, rectal bleeding	Day 52

Comment: If anything, centers 101, 102, and 061 appear to be over-represented in the SAE listing, 15 of the 22 (68.2%) patients for whom serious adverse events were reported. This is even higher than their 149/243 (61.3%) share of Study Q enrollment. There were just 5 SAEs for each of the three drugs reported by these centers, which may be coincidence. There seems to be an inordinate number of hysterectomies, overdoses, especially at center 061. It is also of some concern that 3 cases of myocardial infarction were reported among patients on rabeprazole 20 mg/day. In addition to the narrative summaries provided in Attachment NRRQ.13, Volume 213, pages 4-66 it would be of interest to review the actual case reports for patients with SAEs and for those discontinued from study for adverse events. Copies of endoscopy reports for European studies NRRP and NRRQ have already been requested.

Discontinuations for Non-Serious Adverse Events

In addition to the deaths and serious adverse events, there were 7 patients who discontinued study because of non-serious adverse events, 2 who had been on rabeprazole 20 mg/day, 3 on rabeprazole 10 mg/day, and 2 on omeprazole 20 mg/day *(Volume 210:100)*.

Rabeprazole 20 mg/day (78 patients):

001-4002	Fc75	Insomnia	Day 26
102-4025	Mc60	Skin rash	Day 94

Rabeprazole 10 mg/day (82 patients):

061-4031	Mc52	Tiredness	Day 26
023-4004	Fc63	Gallstone pain	Day 91
061-4020	Mc53	Diarrhea	Day 368

Omeprazole 20 mg/day (83 patients):

163-4003	Mc64	Nausea	Day 15
081-4001	Fc20	Amnesia following alcohol intake	Day 185

Other treatment-emergent adverse events

Other adverse events that did not cause discontinuation and were not serious were reported by 45/78, 58% of patients on rabeprazole 20 mg/day, 44/82, 54% of patients on rabeprazole 10 mg/day, but in somewhat but not significantly (p = 0.636) fewer patients on omeprazole 20 mg/day (39/83, 47%). Adverse events reported most frequently were flu syndrome, diarrhea, all in less than 10% of patients taking rabeprazole. There were no statistically significant differences in frequency of any of these treatment-emergent adverse events.

Comment: The 3 cases of myocardial infarction in the patients on rabeprazole 20 mg/day, compared to none in either of the groups who were taking omeprazole 20 mg/day or rabeprazole 10 mg/day, was not significant (p = 0.11) although notable.

Conclusion About Study Q

The sponsor concluded that all three drug regimens were equivalent in preventing relapse of erosive esophagitis and symptoms of GERD, and were equally safe.

Comment: This study showed unexplained major differences in relapse rates for patients who were treated with rabeprazole, compared to results in the United States (Studies K-odd and K-even. In view of the questions raised about Study Q, as well as for Study P that preceded it, it seems that the clinical equivalence of rabeprazole 20 mg and omeprazole 20 mg/day is suggested but not convincingly proved. Further data are needed, and the details of conduct and reporting of the two European studies need to be investigated and reviewed more closely.

A rough estimation of the odds of finding 20 patients in sequence with exactly the same severity of initial lesions before treatment indicates it would be extremely unlikely, and having them all heal exactly to grade 0 at exactly 4 weeks is even more unlikely. For it to happen with each of the drugs and at both Dutch centers is even more extremely unlikely. For example, if the frequency of grade 2 and grade 3 lesions initially is counted for the 60 patients randomized to rabeprazole elsewhere in Europe than the two Dutch centers in Study P, then the odds of finding 20 patients in a row with grade 3 lesions is about 1.2 in 100,000, and for 20 grade 2 lesions in a row about 1.3 in a trillion. If the odds are further calculated that all the grade 3 lesions would be healed to grade 0 in 4 weeks, the odds shrink to 1.3 in a billion, and for the grade 2 lesions all to heal to grade 0 in 4 weeks, 1 in a quintillion.

IV. Integrated Summary of Effectiveness (ISE)

A. Healing of erosive esophagitis

The sponsor summarizes the data in support of healing erosive esophagitis associated with GERD in Volume 228:127-194 (also pages 105-172 of the ISE section). The principal support for the claim of effectiveness is attributed to Study I and Study J done in North America with 103 and 338 patients, respectively, that show clear superiority of rabeprazole 20 mg/day to placebo and to ranitidine 150 mg q.i.d. Healing rates at 4 and 8 weeks were as follows:

	rabeprazole			*placebo*	*ranitidine*
	10 mg/day	20 mg/day	40 mg/day		150 mg q.i.d.
Study I					
4 weeks	17/27 (63%)	14/25 (56%)	14/26 (54%)	0/25 (0%)	
8 weeks	25/27 (93%)	21/25 (84%)	22/26 (85%)	3/25 (12%)	
Study J					
4 weeks		98/167 (59%)			60/169 (36%)
8 weeks		146/167 (87%)			112/169 (66%)