[redacted]

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In conclusion, the following regulatory actions are recommended with regards to Eisai, Inc. NDA 20-973 [Rabeprazole sodium (ACIPHEX™)].

1. Approval of a regimen of 20 mg/day of rabeprazole for 4 to 8 weeks for healing erosions/ulcerations of the esophagus associated with GERD and symptomatic relief. Superiority to ranitidine may be claimed, but not equivalence to omeprazole.

2. Approval of rabeprazole for the maintenance of healing and reducing the relapse rate of erosions/ulcerations in patients with already healed lesions of erosive esophagitis associated with chronic GERD, and for reduction in relapse rates of heartburn symptoms in these patients, at a daily dose of rabeprazole 20 mg for one year. Superiority to ranitidine may be claimed, but not equivalence to omeprazole.

3. Approval of rabeprazole for the treatment of active duodenal ulcer, at the oral dose of 20 mg, after the morning breakfast, for a period not shorter than 4 weeks. Symptomatic relief and equivalence to omeprazole 20 mg QAM may be claimed. Neither superiority nor equivalence to ranitidine may be claimed.

4. Approval for the use of omeprazole for the treatment of gastric acid hypersecretion, including Zollinger-Ellison syndrome. The recommended adult oral dose varies with the individual patient but should start with 60 mg once a day.

5. Not approval of rabeprazole for the healing and symptomatic relief of acute benign gastric ulcer.

December 22, 1998

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.
Medical Team Leader, HFD-180

/S/ 12-22-98

Lilia Talarico, M.D.
Director, HFD-180

cc:
NDA 20-973
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n/20973811.0hg

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL TEAM LEADER'S REVIEW

NDA:	20-973
	DEC 22 1998
Sponsor:	Eisai Inc.
Date of Submission:	March 31, 1998
Drug:	Aciphex™ (Rabeprazole Sodium)
Pharmacological Category:	Antisecretory; antiulcer; inhibitor of the H^+/K^+-ATPase enzyme system (Proton Pump Inhibitor = PPI)
Proposed Indications and Dosage:	Related to Gastric Acid Production Inhibition Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease • 1 x 20 mg tablet once daily for up to 8 weeks Long-term Maintenance of Healing of Erosive or Ulcerative GERD • 1 x 20 mg tablet once daily Healing of Duodenal Ulcers • 1 x 20 mg tablet once daily for up to 4 weeks [redacted] • starting dose is 60 mg once a day, to be adjusted to individual patient needs for as long as clinically indicated
Material Reviewed:	Integrated Summary of Safety
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

EXECUTIVE SUMMARY

Summarized here is a review of the overall safety data submitted by the sponsor, as part of NDA 20-973 [8. CLINICAL DATA SECTION (Continued), H. Integrated Summary of Safety] for ACIPHEX™ (rabeprazole sodium) tablets. In the present review, the entire safety database is assessed.

The safety and tolerance of RABE have been tested in Phase I through III trials in healthy volunteers and a variety of patient populations that were studied in order to justify the claims (erosive esophagitis associated with GERD, maintenance of healed reflux esophagitis, duodenal ulcer, hypersecretory syndromes and gastric ulcer). All in all, 69 clinical trials were undertaken, 63 of which had been completed while 6 were ongoing as of the ISS cutoff date of October 31, 1997.

When searching for clues for what to look for or what to expect in terms of AEs with RABE, it is worth noting that this drug is a proton pump inhibitor (PPI) and that two of this class of compounds (omeprazole and lansoprazole) have already been approved for, roughly, the same indications being sought with RABE. Both approved PPIs are perceived as being safe for both short-term (S-T) use, where the most frequently occurring AE related to PPI is headache (see below) and long-term (L-T) use (several years) in maintenance trials. Important pre-clinical findings with PPIs after L-T administration to rats have been dose-related significant increases in carcinoid tumors and ECL cell hyperplasia of the stomach. Although the mechanism for carcinoid tumor formation has not been completely elucidated, it most certainly involves hypergastrinemia. The latter is thought to be a consequence of the profound inhibition of gastric acid secretion that these compounds are known to exert. There is, however, less and less concern about such pre-clinical findings because there are now human gastric biopsy data after L-T administration of omeprazole (more than 10 years continuous administration to GERD maintenance patients) and lansoprazole (less L-T experience), demonstrating that these compounds are associated with an increase in gastric atrophy only when *H. pylori* infection is present. However, no progression to pre-malignant states (intestinal metaplasia type III) has been seen. For RABE, biopsy data after L-T administration, are assessed in detail in my review of the SU, to gain more information on longer term administration than was available in what was submitted in the ISS. For this (and the approved PPIs) L-T follow-up with gastric mucosa biopsy continues to be required in those patients being treated with these compounds L-T (more than 2 years).

Clinical study reports from clinical trials were evaluated for safety. The overall experience consists of 5,442 subjects. This includes 5,252 patients/volunteers, 68% of which (3,556) were exposed to one or more doses of RABE sodium in the clinical trials, 10% to placebo (PL), 10% to ranitidine (RAN), 11% to omeprazole (OME), 6% to famotidine (FAM) and <1% to prenzepine (PIRENZ). Most patients in S-T trials received RABE 20 mg for up to 8 weeks. Of the 740 patients in GERD maintenance trials, 488 received RABE; of these, roughly half received 20 mg/day, the other half, 10 mg/day. Of the patients receiving RABE, approximately 54% were exposed to RABE sodium daily for 6 months, and at least 33% for one year [longer-term exposure is addressed in my review of the SU].

The bulk of the study population consisted of Caucasians. In individual clinical trials, demographic and baseline disease characteristics were well-matched across treatment groups. In general, there was a greater exposure to RABE sodium than placebo because patients in the latter group – especially in L-T maintenance trials – withdrew prematurely due to insufficient therapeutic effect.

All in all, RABE appears to be safe and well tolerated. None of the deaths or serious adverse events or discontinuations that occurred in trials of safety and efficacy was considered definitely related to test medication. Throughout the review of the safety data in the NDA and now in the ISS, special attention

was given to the occurrence of cardiovascular AEs (both serious and non-serious and whether they resulted in drug discontinuation or not). The most noticeable finding (Table 7) was an imbalance in the incidence of MI. But an exhaustive assessment of the individual cases revealed no clear relationship to RABE sodium. More importantly, this MI imbalance did not persist when comparative data were corrected by length of treatment and total number of exposure. Furthermore, from the review of the evidence, the conclusion was reached that this drug does not affect myocardial perfusion. This conclusion was based on the fact that there was no difference between RABE sodium and comparators (RAN and OME, Table 8) in the incidence of AEs related to myocardial perfusion (angina, chest pain, EKG change: normal to MI, sudden death).

The overall incidence of AEs at least possibly related to test medication and those leading to discontinuation, was similar between RABE and comparator treatment groups. Not unexpectedly, on account of the longer exposure to RABE sodium, patients that participated in the GERD maintenance controlled clinical trials (CCTs) reported more AEs (361/488 = 74%) than those that participated in the acute CCTs (490/1064 = 46%). But the most frequently occurring AEs in both groups of patients were headache and diarrhea; there were no apparent dose effects.

For CCTs in which causality assessment was made routinely for AEs, there were no important differences among treatment groups (RABE, RAN, OME, PL) in the proportion of TESS possibly/probably related to test medication. This was shown regardless of the geographic location (North America vs Europe), the indication (acute GERD vs maintenance) or dose (10 vs 20 vs 40 mg RABE per day). Also, there were neither clinical dose effects nor significant differences among treatment groups when all TESS were examined on the basis of severity.

The overall incidence of laboratory abnormalities was not unusual. An evaluation of markers of hepatocellular injury and hepatic dysfunction (elevated ASAT and ALAT values) showed no overt clinical problem. Most of the observed abnormalities were minor or explainable on the basis of underlying disease or concurrent condition. RABE sodium did not appear to affect kidney function, cardiac enzymes or thyroid function tests, in the controlled clinical trials. The elevations of fasting serum gastrin were as expected of a PPI. Although RABE is metabolized through the cytochrome P_{450} system, drug interaction trials have not demonstrated an effect of RABE sodium on the PKs of anhydrous theophylline, warfarin, phenytoin, or diazepam; these are drugs that are metabolized by the P_{450} system.

Finally, from the review of the available evidence, it is concluded that the 20 mg/day RABE dose is as safe as the 10 mg/day dose.

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INTEGRATED SUMMARY OF SAFETY

In this document, a detailed review of the Integrated Summary of Safety (ISS) is carried out. The appraisal that follows was based on the sponsor's submission vol. 249 through 251 of NDA 20-973, sections 8. CLINICAL DATA SECTION (continued), and H. Integrated Summary of Safety. The Safety Update (SU), submitted October 21, 1998, is reviewed separately.

A. Drug Exposure

- 69 clinical trials were undertaken to assess the safety and/or efficacy of RABE sodium: 63[1] of these trials had been completed and 6 were ongoing as of the ISS cutoff date of October 31, 1997.

- The number of patients/volunteers that participated in the clinical trials in the ISS and who were exposed to RABE, active comparators or placebo – as a function of Tx group – is summarized in Table 1. The overall total of 5442 subjects included 5252 patients/volunteers in the 63 completed clinical studies and 190 unique subjects in the Ongoing Clinical Studies. Of the 5252 subjects who participated in the completed clinical trials, 3556 patients/volunteers (68%) were exposed to one or more doses of RABE sodium in the clinical studies conducted in North America, Europe and Japan. Less than 12% of patients/volunteers were exposed to [placebo=PL (10%)] or a comparative agent, [ranitidine=RAN (10%)], [omeprazole=OME (11%)], [famotidine=FAM (6%)], or [pirenzepine=PIRENZ (<1%)].

[1] Of the 63 completed studies, 12 were Controlled Clinical Studies (CCS) in which patients in North America and Europe were treated for erosive or ulcerative GERD, DU,[ ] and 2 studies were CCS in Japan for patients with DU [ ] The remaining 49 completed studies were categorized as 13 Other Studies in Patients and included 8 Uncontrolled Clinical Trials and 5 Studies for Other Indications, other than GERD, DU,[ ] indications, i.e., stomach ulcers, ZES, and chronic antral gastritis or PUD. The remaining 36 studies were Human PK, Bioavailability, and Clinical Pharmacology Trials.

- Of the 6 Ongoing Studies in North America and Europe, one is an acute study for Tx of patients with erosive or ulcerative GERD; 4 are L-T extension studies for the maintenance of healing in erosive or ulcerative GERD patients, and the other is for the Tx of patients with ZES or idiopathic gastric acid hypersecretory states (GAHS).

TABLE 1
Summary of Pts./Volunteers by Tx Group – All Pts./Volunteers Treated

Study Grouping/Indications	Total n	RABE Sodium	RAN	OME	FAM	PIRENZ	PL
I. CONTROLLED CLINICAL TRIALS (CCTs) (n=14)							
North America							
Acute GERD, DU and [redacted]	1375	749	537	-	-	-	89
GERD Maintenance	497	328[b]	-	-	-	-	169[c]
Europe							
Acute GERD, DU and [redacted]	634	315	-	319	-	-	-
GERD Maintenance	243	160[d]	-	83[e]	-	-	-
Subtotal North America and Europe	2749	1552	537	402	-	-	258
Japan							
Acute DU and [redacted]	994	709	-	-	285	-	-
Total CCTs	3743	2261	537	402	285	-	258
II. OTHER STUDIES IN PATIENTS (n=13)							
Uncontrolled Studies (8)	648	543	-	105	-	-	-
Japan (GERD, DU and [redacted])	648	543	-	105	-	-	-
Studies for Other Indications (5)	164	131	-	-	-	-	33
North America (*H. pylori*)	74	41	-	-	-	-	33
Europe (Chronic antral gastritis w/ or w/o PUD)	75	75	-	-	-	-	-
Japan (ZES or active stomal ulcers)	15	15	-	-	-	-	-
Total Other Studies in PTS.	812	674	-	105	-	-	33
III. PK, BIOAVAIL., AND CLIN. PHARM STUDIES (n=36)							
North America[f]	437	370	-	-	-	-	123
Europe	67	67	-	23	-	-	60
Japan	193	184	-	23	8	8	47
Total PK, etc. Studies	697	621	-	46	8	8	230
Total No. of Pts./Volunteers in Completed Studies	5252	3556	537	553	293	8	521
Total Ongoing Studies	190[g]	NA	-	NA	-	-	-
TOTAL n	5442						

a) Acute GERD, DU and [redacted] indications for the healing of erosive or ulcerative GERD, DUs and [redacted] respectively; GERD maintenance indication for the maintenance of healing of erosive or ulcerative GERD.
b) Includes 61 pts. exposed to RABE and 46 pts. exposed to RAM in acute GERD CCT
c) Includes 33 pts. exposed to RABE and 26 pts. exposed to RAN in acute GERD CCT.
d) Includes 39 pts. exposed to RABE and 42 pts. exposed to OME in acute GERD CCT
e) Includes 19 pts. exposed to RABE and 24 pts. exposed to OME in acute GERD CCT.
f) All are volunteers with the exception of 20 GERD patients in E3810-L001-A/H4M-LC-NRRA and 38 patients with *H. pylori* in E3810- L001-B/H4M-LC-NRRB.
g) A total of 190 unique subjects in two ongoing studies (A001-501 and E033-311) which are blinded.

Data Source: Sponsor's Appendix 1, Table 2.1b, Table 2.1c, and Table 3.1; Appendix 2, Patient Data Listing 3; and Individual Study Reports

- In the 9 North American and European Acute Controlled Clinical Studies comprised of 2009 GERD, DU and [redacted] patients, 53% were exposed to RABE sodium for up to 8 weeks.

- In the 3 North American and European **GERD Maintenance Controlled Clinical Trials** comprised of 740 patients (Table 2), at least 54% were exposed to RABE sodium daily for 6 months, and at least 33% for one year. In the three GERD Maintenance Controlled Clinical Trials, patients who received RABE sodium, RAN or OME in an acute GERD study [i.e., E3810-A001-303 (NRRJ) or E3810-E044-307 (NRRP)] could "rollover" into the GERD Maintenance Controlled Clinical Trial or patients could start in the GERD Maintenance Controlled Clinical Trial de novo. The de novo

patients are referred to as "Starters". The "rollover" and "Starter" patients combined are referred to as the "Total". Of the 740 GERD Maintenance Controlled Clinical Trial patients, most (61%) were Starters; whereas, 39% were rollovers.

TABLE 2
GERD Maintenance Patient Treatment Categories
GERD Maintenance Controlled Clinical Studies – North America and Europe

Treatment	Treatment Category	Number (%) of GERD Maintenance Patients		
		North America (NRRK-ODD/EVEN)	Europe (NRRQ)	Total n (%)
RABE Sodium 10 mg QAM	Total n	165	82	247
	Rollovers	32%	49%	38%
	Starters	68%	51%	62%
RABE Sodium 20 mg QAM	Total n	163	78	241
	Rollovers	33%	53%	39%
	Starters	67%	47%	61%
OME 20 mg QAM	Total n	-	83	83
	Rollovers	-	52%	52%
	Starters	-	48%	48%
PL	Total n	169	-	169
	Rollovers	35%	-	35%
	Starters	65%	-	65%
Total for all GERD Maintenance Txs		497 67%	243 33%	740 100%

Data Source: Sponsor's Appendix 2, Patient Data Listing 3

- Most of the GERD maintenance patients who received RABE sodium (61%) or PL (65%) were Starters. The percentage of Starters (48%) and rollovers (52%) were comparable among the Total patients exposed to omeprazole.

- Of the **290 rollover patients** exposed in both the acute GERD and GERD maintenance Tx programs, 188 RABE sodium GERD maintenance patients were rollovers from the acute RABE sodium or comparator treatment groups.

  - A total of 100 patients received RABE sodium in both Acute GERD and GERD Maintenance CCTs conducted in North America and Europe; thus in the 63 completed clinical trials of the ISS **the total number of "unique" patients exposed to RABE sodium was 3456.**

- Exposure in the 14 controlled clinical trials according to geographic location and indication, is summarized in Table 3. Nearly half of the patients were studied in North America and a majority (60%) were exposed to RABE sodium. There were no PL patients enrolled in either Europe or Japan.

TABLE 3

Patient Exposure by Geographic Location and Indication –
Controlled Clinical Studies – North America, Europe, and Japan

Geographic Location and Indication[a]	RABE Sodium n (%)	RAN n (%)	OME n (%)	FAM n (%)	PL n (%)
I. North America (n=1872)					
GERD: Acute	247 (23%)	169 (31%)	-	-	25 (10%)
Maintenance	328 (30%)	-	-	-	169 (66%)
Acute DU	255 (24%)	188 (35%)	-	-	33 (13%)
Total North America					
II. Europe (n=877)					
GERD Acute	100 (21%)	-	102 (25%)	-	-
Maintenance	160 (34%)	-	83 (21%)	-	-
Acute DU	102 (21%)	-	103 (26%)	-	-
Total Europe					
III. Japan (n=994)					
GERD: Acute	-	-	-	-	-
Maintenance	-	-	-	-	-
Acute DU	337 (48%)	-	-	142 (50%)	-
Total Japan					
Total 14 Controlled Clinical Trials – North America, Europe, and Japan	**2261**	**537**	**402**	**285**	**258**

a) Acute GERD, DU and [redacted] indications for the healing of erosive or ulcerative gastroesophageal reflux disease (GERD), duodenal ulcers, and [redacted], respectively; GERD maintenance indication for the maintenance of healing of erosive or ulcerative GERD.

Data Source: Sponsor's Appendix 1, Table 1.1; and individual Study Reports

- Exposure in the 14 controlled clinical trials according to indication and dose is summarized in Table 4. Of the total of 2009 patients enrolled in the 9 acute GERD, DU and [redacted] controlled clinical studies, 1064 were studied in North America/Europe and 89% of these received RABE 20 mg once-a-day.

  - Of the total 740 patients in the GERD maintenance trials, 488 received RABE. Of these, ca. half received 20 mg/day; the other half, 10 mg/day.

TABLE 4
Patient Exposure by RABE Sodium Dose –

	Total n	RABE Sodium n	RABE (mg/day) ≤5 n (%)	10 n (%)	20 n (%)	40 n (%)
I. ACUTE CONTROLLED CLINICAL TRIALS – NORTH AMERICA/EUROPE						
A. Acute GERD Indication						
NRRJ	338	169	-	-	169 (100%)	-
NRRP	202	100	-	-	100 (100%)	-
NRRI	103	78	-	27 (35%)	25 (32%)	26 (33%)
B. Acute DU Indication						
NRRD	376	188	-	-	188 (100%)	-
NRRL	205	102	-	-	102 (100%)	-
NRRC	100	67	-	-	34 (51%)	33 (49%)
[redacted]	[redacted]	[redacted]	-	-	[redacted]	-
			-	-		-
			-	-		
Total 9 Acute GERD, DU and [redacted] Controlled Clinical Trials – North America/Europe	[redacted]					
II. GERD MAINTENANCE CONTROLLED CLINICAL TRIALS – NORTH AMERICA/EUROPE						
A. GERD Maintenance Indication						
NRRK (ODD)	209	139	-	70 (50%)	69 (50%)	-
NRRK (EVEN)	188	189	-	95 (50%)	94 (50%)	-
NRRQ	243	160	-	82 (51%)	78 (48%)	-
Total 3 GERD Maintenance Controlled Clinical Trials –North America/Europe	**740**	**488**	-	247 (51%)	**241 (49%)**	-
Total 12 Controlled Clinical Trials – North America/Europe	**2749**	**1552**	-	274 (18%)	**1188 (77%)**	90 (6%)
III. ACUTE CONTROLLED CLINICAL TRIALS – JAPAN						
A. Acute DU and [redacted] Indications						
J081-011 / NRJK	199 DU	199 DU	65 (33%)	66 (33%)	68 (34%)	-
J081-013 / NRJM	280 DU	138 DU	-	-	138 (100%)	-
Total 2 Acute DU and [redacted] Controlled Clinical Trials – Japan	**479 DU**	**337 DU**	65 (19%)	66 (20%)	**206 (61%)**	-
Total 14 Controlled Clinical Trials – North America/Europe and Japan	**3743**	**2261**	137 (6%)	416 (18%)	1618 (72%)	90 (4%)

Data Source: Sponsor's Appendix 1, Table 2.1a and Table 3.1; and Individual Study Reports

- Exposure by geographic location, indication and duration of Tx is summarized in Table 5. In acute controlled clinical trials, a total of 3003 patients participated, 1773 of whom received RABE. The duration of Tx in 471 of these was ≤4 weeks, >4 to ≤6 weeks in 671, >6 to ≤8 in 552 and >8 in only 79 patients. Of the 488 RABE patients (out of the total of 740) who participated in GERD maintenance controlled clinical studies, 382 received medication (10 or 20 mg/day) for >39 to ≤52 weeks and 242 were given RABE for >52 weeks.

TABLE 5

Duration of Rabeprazole Sodium Treatment by Geographic Location and Indication
Acute Controlled Clinical Trials

Geographic Location and Indication	All Txs	RABE Sodium n	Duration of Exposure (Weeks) ≤4	>4 - ≤6	>6 - ≤8	>8
I. Acute Controlled Clinical Trials (9) – North America/Europe						
GERD	643	347	71	145	52	79
DU	681	357	237	120	-	-
Total Acute Controlled Clinical Trials – North America/Europe						
II. Acute Controlled Clinical Trials (2) – Japan						
DU	479	337	-	337[a]	-	-
Total Acute Controlled Clinical Trials – Japan	**994**	**709**	-	**337**	**372**	-
III. All Acute Controlled Clinical Trials (11)						
GERD	643	347	71	145	52	79
DU	1160	694	237	457	-	-
Total 11 Acute Controlled Clinical Trials – North America/Europe and Japan	**3003**	**1773**	**471**	**671**	**552**	79

GERD Maintenance Controlled Clinical Trials

Summarization	All Txs	RABE Sodium n	Duration of Exposure (Weeks) ≤4	>4 - ≤13	>13 - ≤26	>26 - ≤39	>39 - ≤52	>52
Patients Only Exposed for Specific Exposure Period	740	488	23	38	28	17	140	242
Total Patients Exposed	**740**	**488**	488[b]	465	427	399	**382**	**242**

a) For these studies, duration of exposure for all subjects has been defaulted to the maximum exposure category.
Data Source: Sponsor's Appendix 1, Table 2.1a and Table 2.2a; and Individual Study Reports

b) All 488 RABE sodium-treated GERD maintenance patients were exposed for up to at least four weeks and 242 of these patients continued treatment for greater than 52 weeks..
Data Source: Sponsor's Appendix 1, Table 3.2.

B. Demographics and Baseline Characteristics

Examination of the data presented by the sponsor and reviewed by Drs. Senior, Prizont and Gallo-Torres, shows that demographic and BL characteristics were well-matched across all treatment groups. The incidences of pre-existing conditions were in general comparable across treatment groups. In the **Acute Controlled Clinical Trials,** age and gender were comparable between North America and Europe; there was a higher percentage of Caucasian patients in the European studies and a higher percentage of patients of African Descent enrolled in the North American studies. Of the 1064 patients receiving RABE sodium, the majority were male Caucasians, with a mean age of 52.8 y. Across treatment groups, there were no clinically important differences in age, gender, race, or body weight. In the **GERD Maintenance Controlled Clinical Trials,** the majority of patients were male Caucasians, with a mean age of 53.5 y. As in the Acute Controlled Clinical Trials, there was a slightly higher incidence of Caucasian patients in Europe, and a slightly higher incidence of patients of African Descent in North America. The demographic characteristics across treatment groups were similar, with the exception of age; however, these differences were not clinically meaningful.

C. Disposition of Patients by Tx Group (Table 6)

Reasons for discontinuation are listed in this Table. In acute, North America trials, 8% of RABE and 5% of RAN patients discontinued. Both %s were lower than the proportion of patients on placebo who discontinued, primarily due to lack of efficacy or AEs. In acute, Europe studies, the proportion of patients discontinued was nearly identical in the RABE (3%) vs the OME group (4%). In the GERD Maintenance Controlled Clinical Trials in North America, the percentage of PL patients who D/C was significantly greater than the number of RABE sodium patients who D/C (79% compared to 31%, respectively). Again, the largest percentage of PL patients terminated prematurely (70%) due to clinical relapse (i.e., Lack of Efficacy). A slightly higher percentage of RABE sodium patients (as compared to PL patients) withdrew due to an AE (6% vs 2%). The MTL agrees with the sponsor that this may be due in part to the considerably greater exposure to RABE sodium as compared to PL, rather than to a drug effect. In the European GERD Maintenance Controlled Clinical Studies, the percentage of patients withdrawing prematurely from study participation was comparable across Tx groups and across reason for D/C.

TABLE 6

Summary of Disposition of Patients by Treatment Group

I. North America and Europe								
A. Acute Controlled Clinical Trials								
Geographic Location/ Reason	RABE Sodium (mg/day)				RAN 300-600 mg/day	OME 20 mg/day	PL	Total
	10	20	40	Combined				
North America								
Number Exposed	27	632	90	749	537	-	89	1375
Completed	27 (100%)	581 (92%)	82 (91%)	690 (92%)	509 (95%)	-	70 (79%)	1269 (92%)
Number (%) D/C	0 (0%)	51 (8%)	8 (9%)	59 (8%)	28 (5%)	-	19 (21%)	106 (8%)
AE	0%	2%	1%	2%	2%	-	6%	2%
Lack of Efficacy	0%	1%	1%	1%	<1%	-	11%	1%
Lost to F/U	0%	<1%	2%	<1%	1%	-	1%	1%
Other	0%	5%	4%	4%	2%	-	3%	3%
Europe								
Number Exposed	-	315	-	315	-	319	-	634
Completed	-	304 (97%)	-	304 (97%)	-	305 (96%)	-	609 (96%)
Number (%) D/C	-	11 (3%)	-	11 (3%)	-	14 (4%)	-	25 (4%)
AE	-	<1%	-	<1%	-	2%	-	1%
Lack of Efficacy	-	1%	-	1%	-	<1%	-	1%
Lost to F/U	-	<1%	-	<1%	-	1%	-	<1%
Other	-	2%	-	2%	-	2%	-	2%

B. GERD Maintenance Controlled Clinical Trials[b]							
North America							
Number Exposed	165	163	328		-	169	497
Completed	104 (63%)	122 (75%)	226 (69%)		-	35 (21%)	261 (53%)
Number (%) D/C	61 (37%)	41 (25%)	102 (31%)		-	134 (79%)	236 (47%)
AE	7%	6%	6%		-	2%	5%
Lack of Efficacy	18%	8%	13%		-	70%	32%
Lost to F/U	3%	2%	2%		-	1%	2%
Other	8%	10%	9%		-	6%	8%
Europe							
Number Exposed	82	78	160		83	-	243
Completed	71 (87%)	68 (87%)	139 (87%)		71 (86%)	-	210 (86%)
Number (%) D/C	11 (13%)	10 (13%)	21 (13%)		12 (14%)	-	33 (14%)
AE	6%	5%	6%		5%	-	5%
Lack of Efficacy	1%	1%	1%		1%	-	1%
Lost to F/U	1%	1%	1%		1%	-	1%
Other	5%	5%	5%		7%	-	6%

II. ACUTE CONTROLLED CLINICAL TRIALS – JAPAN[c]			
Reason	RABE	FAM	Total
Number Enrolled	709	285	994
Completed	614 (87%)	243 (85%)	857 (86%)
Number (%) D/C	95 (13%)	42 (15%)	137 (14%)
Adverse Event	4%	6%	5%
Other	9%	9%	9%

a) Protocols include NRRI, NRRJ, NRRP, NRRC, NRRD, NRRL.
Data Source: Sponsor's Appendix 1, Tables 7.1.2 and 7.1.3

b) Protocols include NRRK-EVEN, NRRK-ODD and NRRQ.
Data Source: Sponsor's Appendix 1, Tables 7.2.2 and 7.2.3.

c) Protocols include NRJK and NRJM.
Data Source: Individual Clinical Trial Clinical Trial Reports. Data were pooled for the ISS.

D. Deaths

- As of February 3, 1998, a total of 12 deaths were reported:

  1[a] during screening
  3[b] during treatment period
  8[c] reported post-treatment

a) The screen death was in a 78-y-old Caucasian F with a Hx of hypertension who signed an IC form but, because of nonqualifying endoscopic findings in the Acute Controlled Clinical Study, – NRRG, was not randomized to Tx. The patient died of an M.I. ca. 11 days later

b) None of these [RABE, n=2; OME, n=1] was related to test medication
c) None of these [RABE, n=5=lung carcinoma, metastatic lung cancer, liver carcinoma, ovarian carcinoma and cecal carcinoma; RAN=2=denocarcinoma, lung cancer and PL, 1=cardiac arrhythmia, was related to treatment.

- The incidence of deaths in the RABE group (0.2%) was comparable to that in the RAN (0.4%), OME (0.2%) and PL (0.2%) groups:

		Deaths		
RABE Sodium	RAN	OME	FAM	PL
[n=3556]	[n=537]	[n=553]	[n=293]	[n=521]
7	2	1	0	1
(0.2%)	(0.4%)	(0.2%)	(0%)	(0.2%)

E. Serious Adverse Events (SAEs)

- All in all, 216 patients reported SAEs. Of these, 6[2], 196, and 14, respectively reported SAEs during the screening, treatment and post-treatment periods.

- The incidence of SAEs during treatment in completed and ongoing trials for RABE sodium was comparable to those seen with comparators:

		SAEs[a] [Total n=196]		
RABE Sodium	RAN	OME	FAM	PL
[n=3556]	[n=537]	[n=553]	[n=293]	[n=521]
141	10	25	9	11
(4.0%)	(1.9%)	(4.5%)	(3.1%)	(2.1%)

a) The data cutoff date for ongoing trials is February 3, 1998. Post-treatment events are not included.

- In their Table 6E, the sponsor presented a listing of subjects who reported one or more SAEs during treatment. This Table contained information on study number, subject number, gender, age, reported term and COSTART term, treatment and dose, duration of treatment at time of SAE, whether or not the subject was discontinued due to the SAE, and relationship to test medication as assessed by the investigator.

- Most of the SAEs listed in sponsor's Table 6E were considered to be unrelated to test medication as judged by the investigator. Events considered to be possibly/probably related to test medication were:

[2] These consisted of: g.i. hemorrhage [n=2], cerebrovascular accident/cerebral ischemia [n=11], g.i. carcinoma [n=2], and MI (post screening failure resulting in death) [n=1].

Study/Patient (Gender, Age)	SAE COSTART Term	Ca. Days at Time of SAE	Discontinued/ Relationship to Test Med.
-NRRQ (1y ext.)/61-5045 (M, 62) (RABE sodium 10 mg)	Hepatitis[a]	374	NO/POSS
-NRRK (1y ext.)/047-19328 (F, 56) (RABE sodium 20 mg)	GI Neoplasia (Hyperplastic Gastric Polyp)[b]	362	NO/POSS
-A001-501 (M, 75) (RABE sodium 60 mg)	CPK ↑[c] SGPT ↑[d]	90	YES/POSS
J-013/74-4 (M, 55) (FAM, 40 mg)	LFTs Abnormal	17	YES/PROB
-NRRK/41-9754 (F, 69) (Placebo)	Chest Pain	25	NO/PROB
a) See MOR, Dr. J. Senior (12/1/98) b) These are considered incidental findings, unrelated to test medication c, d) Information to be included in the labeling.			

1. SAEs Related to the Cardiovascular System

These are listed in Table 7.

TABLE 7

SAEs Related to the Cardiovascular System by Treatment Group

I. RABE Sodium 10 mg/day			
		Approx. Days at Time of SAE	Disc./Relationship to Test Med.
NRRK/ 1-9006 (F, 48)	Syncope	206	NO/NONE
NRRK/ 29-9197 (M, 32)	M.I.	78	YES/NONE
NRRK/ 6-9710 (M, 60)	M.I.	165	NO/NONE
NRRK 30-9210 (M, 55)	M.I.	275	NO/NONE
NRRK/ 52-9363 (M, 61)	Chest Pain Dyspnea Coronary Artery Disorder	47 47 53	NO/NONE
NRRQ/ 124-4006 (M, 43)	Coronary Artery Disorder	286	YES/NONE
NRRK (1y ext.)/ 041-19283 (M, 64)	Syncope	655	NO/NONE
NRRK (1y ext.)/ 030-19205 (F, 45)	Bradycardia	520	NO/NONE
NRRK (1y ext.)/ 001-19006 (F, 49)	Chest Pain	534	NO/NONE
NRRK (1y ext.)/ 001-19003 (M, 65)	Coronary Artery Disorder	339	NO/NONE
J-011/111-3 (M, 57)	Dizziness	7	YES/UNKNOWN