II. RABE Sodium 20 mg/day			
NRRD/ 62-5423 (F, 49)	Hypertension	9	NO/REMOTE
NRRP/ 166-3004 (M, 70)	M.I.	29	NO/NONE
NRRK/ 41-9287 (F, 79)	Hypertension SVT	105 105	NO/NONE
NRRK/ 12-9469 (M, 66)	Thrombosis	158	YES/NONE
NRRK/ 28-9794 (M, 64)	M.I.	189	NO/NONE
NRRQ/ 102-4006 (F, 75)	M.I.	353	YES/NONE
NRRQ/ 122-4001 (M, 68)	M.I. M.I.	99 168	NO/NONE YES/NONE
NRRK/ 164-4001 (M, 76)	M.I.	290	NO/NONE
NRRK (1y ext.)/ 006-19560 (F, 54)	CHF	463	YES/NONE
NRRK (1y ext.)/ 032-19545 (M, 71)	CHF	740	NO/NONE
NRRK (1y ext.)/ 001-19002 (M, 69)	Coronary Artery Disorder	738	NO/NONE
NRRK (1y ext.)/ 065-19451 (M, 80)	Coronary Artery Disorder	728	YES/NONE
NRRK (1y ext.)/ 060-19414 (F, 75)	Heart Arrest	886	YES/NONE (Death)
NRRK (1y ext.)/ 028-19808 (F, 77)	Hypotension, Postural Syncope	430	NO/NONE
NRRQ (1y ext.)/ 124-5002 (M, 74)	M.I.	462	YES/NONE (Death)
III. RABE Sodium 40 mg/day [n=0]			
IV. RABE Sodium 60 mg/day [n=0]			
V. RABE Sodium 120 mg/day [n=0]			
VI. RANITIDINE 150 mg BID			
NRRJ/ 10-8462 (F, 45)	Chest Pain	44	YES/NONE

VII. OMEPRAZOLE 20 mg/day			
NRRQ/ 181-4002 (F, 40)	Chest Pain	155	NO/NONE
NRRQ (1y ext.)/ 181-5002 (F, 41)	Angina Pectoris	420	NO/NONE
VIII. FAMOTIDINE 40 mg/day [n=0]			
IX. PLACEBO			
[redacted]	[redacted]	[redacted]	[redacted]
NRRI/ 11-4662 (M, 67)	Arterial Thrombosis	32	YES/NONE
NRRK/ 41-9754 (F, 69)	Chest Pain Hypertension	25 25	NO/PROB NO/REMOTE
NRRK/ 045-9314 (M, 45)	Chest Pain CHF	11	NO/NONE
X. Ongoing Study/Blinded Treatment			
E033-311/ 013-185 (M, 39)	Chest Pain, Syncope	10	YES/NONE
E033-311/ 013-261 (F, 20)	Heart Arrest	27	YES/NONE

Reviewer's Table

The most noticeable finding in Table 7 is an imbalance in incidence of MI. A detailed review of these cases revealed no clear relationship to RABE sodium. One patient (102-4006 in the NRRQ study), the only female in the group, had no cardiac risk factors listed. All others had either evidence of previous coronary artery disease or other cardiac risk factors (hypertension, tobacco dependency, long-term smoking, hyperlipidemia, diabetes mellitus, atherosclerosis, hypercholesterolemia etc.). Except for Pt. NRRK (ODD)/29-9197, a 32y M[3], all patients were 55y old or older. None of the events was considered by the investigator to be drug-related. As shown in Table 7, one patient in the RABE 10 mg/day and two in the RABE 20 mg/day discontinued because of the MI event. A third in the latter treatment group died because of MI. Again, the death of this 74y M in the maintenance of GERD trial NRRQ (1y extension) was considered unrelated to test medication. The most plausible explanation for the observed imbalance in MIs among the treatment groups is that the exposure in the RABE sodium group is ca. 2.31 times the exposure (in patient years) of the comparison groups (i.e. 482/209=2.31). Further analysis of the available data is presented below.

- The distribution of MIs and Exposure for controlled clinical trials was:

[3] The events surrounding this particular patient were meticulously scrutinized because of his young age. The Pt. had a 13-y Hx of smoking 20 cigarettes per day and may have had significant pre-existing coronary artery disease since he had single bypass surgery after his MI; however, no information is available regarding specific angiographic findings.

	RABE Sodium (mg/day)			RAN 300-600 mg/day	OME 20 mg	PL
	10	20	40			
Number of Patients with MIs	3	5	0	0	0	0
Exposure (patient years)[a]	195	281	6	49	99	60
Total pt. yrs.	482			Not Applicable		
a) Combined Acute and GERD Maintenance CCTs.						
Data Source: Sponsor's Appendix 1, Tables 4.1 and 4.2						

- The distribution of MIs and Exposure for maintenance of healing of GERD studies was:

	RABE (mg/day)		PL
	10	20	
NRRK-ODD			
Number of patients with MIs	1	0	0
Exposure (patient years)	46	57	23
Total patient years	103		23
NRRK-EVEN			
Number of patients with MIs	2	1	0
Exposure (patient years)	72	77	30
Total patient years	149		30
Data Source: Sponsor's Appendix 1, Table 4.4			

- All in all, analyses of the data revealed **no dose response**. Although all MI occurred in RABE sodium-treated patients, no consistent dose response pattern was seen in the individual trials. In the NRRK-EVEN North American study, the number of MIs in the 20-mg/day dose group was less than the number in the 10-mg/day group. The exposure to RABE sodium was ca. 5 times higher than in the PL group. Since only four MIs were observed in these trials, it is not surprising that no MI was seen in the PL group. On the other hand, the number of MIs in the European GERD maintenance study (NRRQ) in the 20-mg/day group was larger than the number in the 10-mg/day group:

	RABE Sodium (mg/day)		OME (mg/day)
	10	20	20
Number of Patients with MIs	0	3	0
Exposure (patient years[a])	74	71	74
Total patient years	145		74
a) for Study NRRO			
Data Source: Sponsor's Appendix 1, Table 4.4			

- The exposure in the RABE sodium groups was ca. 2 times that of the OME group. Since only 3 MIs were observed in these groups, it is not surprising that no MI was seen in the OME group.

- The distribution of MIs and exposure for acute controlled clinical trial NRRP was:

	RABE Sodium (mg/day)	OME (mg/day)
	20	20
Number of Patients with MIs	1	0
Exposure (patient years)[a]	11.0	10.0
a) For Study NRRP		
Data Source: Sponsor's Appendix 1, Table 4.4		

- The exposure in the RABE sodium group was about the same as that in the OME group. Since only one MI was seen in the RABE sodium group, it is not surprising that none was observed in the OME group.

2. Incidence of AEs Other Than MI That Would be Expected to Show Evidence of Dose Relationship if RABE Sodium Affected Myocardial Perfusion

An additional important comparison is that of the incidence of certain AEs, such as angina, chest pain, EKG change from normal to MI and sudden death. The data for these AEs in controlled clinical trials (see also Table 7) do not show evidence of dose relationship (Table 8). Of the four AEs listed in this Table, chest pain and EKGs that were normal at BL and shifted to "MI" at endpoint[4] had high enough incidences, 32 and 24, respectively, to allow reasonable analogies between RABE and comparators:

TABLE 8
Incidence of AEs Other Than MI That are Related to Myocardial Perfusion

Number of Patients Reporting AEs in CCTs

	RABE Sodium	PL	RAN 300-600 mg/day	OME 20 mg/day
Angina	2	1	0	0
Chest Pain[a]	32	4	12	2
EKG Change:				
Normal to MI	24	6	17	10
Sudden Death	1	0	0	0
Total	59	11	29	12
Exposure (patient yrs)[b]	482	60	49	100
a) Includes substernal chest pain.				
b) Combined Acute and GERD Maintenance Controlled Clinical Trials (CCTs).				
Data Source: Sponsor's Appendix 1, Table 4.4				

- A total of 32 RABE sodium patients had chest pain as compared to a total of 18 combined from the comparison groups. This ratio (1.78) is slightly lower than the ratio of patient exposures (482/209=2.31).

- A total of 24 RABE sodium patients had EKG changes which shifted from normal to "MI" compared to 33 in the combined comparator groups. This ratio, 0.73 is much less than the ratio of exposures (2.31) suggesting that RABE treatment is associated with less evidence of MI by EKG than the combined comparator groups.

[4] Discussed in detail in sponsor's Section 8, "Vital Signs and Body Weight, and Electrocardiogram Findings".

- When the related events are pooled together, the ratio of RABE sodium events to those of combined comparison agents (59/52=1.13) is lower than the ratio of exposures (482/209=2.31)

Taken together, the detailed analyses of these data – when exposure is taken into consideration - do not suggest that RABE affected myocardial perfusion. The MTL agrees with the sponsor that the small excess of MIs in controlled clinical trials with RABE is most likely due to a statistical fluctuation rather than to a drug effect.

> [**NOTE:** An additional statistical fluctuation is described in Dr. Gallo-Torres' review of the GU indication (November 30, 1998, page 45 and 46), for Study –NRRG, an active-active comparison trial between RABE sodium and RAN. The incidence of cardiovascular AEs in the RAN-treated group (4%) was statistically higher than RABE-treated group (1%) (p=0.030), a Δ due to reports of cardiovascular AEs among male patients (Ran=5%; RABE=0%; p=0.029). These findings are not considered clinically significant.]

Nonetheless, this issue **"Does RABE affect myocardial perfusion? Is RABE associated with excess MI?" a)** should be carefully addressed in the labeling, **b)** it will be revisited in the MTL review of the safety update and **c)** should continue to be addressed by careful post-marketing monitoring.

Finally, the incidence of patients reporting one or more post-treatment SAEs (including death due to malignancy) for RABE and comparators was:

RABE Sodium	RAN	OME	FAM	PL
[n=3556]	[n=537]	[n=553]	[n=293]	[n=521]
9	3	1	0	1
(0.3%)	(0.6%)	(0.2%)	(0%)	(0.2%)

But none of these events, described in sponsor's Table 6F, was assessed by the investigator as treatment related.

F. Discontinuations Due to AEs (Table 9)

TABLE 9

AEs that were assessed as definitely, for sure, probably or possibly related to test medication, per Tx group

RABE (mg/day)								
5 [n=0]	10 [n=4]	20 [n=9]	40 [n=3]	60 [n=1]	RAN [n=3]	OME [n=7]	FAM [n=5]	PL [n=5]
	67-9249 (arrhythmia) 61-4020 (diarrhea) [61-4031] asthenia J-011/114-2 (rash, peripheral edema)	43-5290 (rash) 018-2803 (headache) 124-3001 (rash) 3-9015 (amblyopia) 30-9209 (diarrhea) 1-4002 (insomnia) 104-4025 (rash) J-011/181-3 (palpitation) J-013/7/-1 (stomatitis)	005-4665 (dizziness) 1-508 (abdominal pain) 1-575 (allergic Rx)	001-001 (CPK ↑*) SGPT ↑*)	003-8015 (nausea) 34-8234 (abdominal pain) 35-8240 (impotence)	163-4003 (nausea) 1081-5007 (CPK ↑) J-014-2-D-3 (rash) J-014-2-D-5 (LFTs Abnormal) J-014/2-G-4 (laryngismus) J-014/19-DU-2 (face edema; peripheral edema) J-014/31-G-3 (eczema)	J-013/1-2 (rash) J-013/13-3 (constipation, abdominal pain) J-013/50-1 (diarrhea) J-013-60-3 (LFTs abnormal) J-013-74-4 (LFTs abnormal)*	13-2776 (abdominal pain) 61-9425 (puruitus) 32-9736 (diarrhea) 42-9291 (dyspepsia) 1-417 (hypotension)

Reviewer's Table

This Table lists all discontinuations – from all studies - that were judged to be definitely, for sure, probably or possibly **related to test medication**. SAEs are also included in this per Tx assignment computation. SAEs that resulted in D/C but that were not appraised as related to test medication have been excluded from this calculation because an assessment of those data was given above. The data in Table 9 do not show an AE pattern leading to D/C with RABE that is too dissimilar from that seen with comparators, including PL but specially that for omeprazole and lansoprazole [data not included in this Table], the two approved PPIs. In addition, as shown below, the overall incidence of subjects with AEs leading to discontinuation was low and was similar between RABE and comparator treatment groups.

Incidence of AEs Leading to Discontinuation

RABE Sodium	RAN	OME	FAM	PL
[n=3556]	[n=537]	[n=553]	[n=293]	[n=521]
108[a]	11	19	15	10
(3.0%)	(2.0%)	(3.4%)	(5.1%)	(1.9%)

The AE which most frequently led to the D/C of patients treated with RABE sodium was g.i. carcinoma (20 of 3556 patients). However, these were all (with the exception of one case, NRRK 10-9770) considered to be pre-existing conditions detected during entry procedures. These subjects were allowed to begin Tx with test medication, but were W/D as soon as the cancers were diagnosed. Tx duration for these 19 subjects ranged from 4 to 33 days.

The next most frequent AE leading to D/C of Tx with RABE sodium was vomiting (5 patients), followed by abdominal pain and rash (4 patients each), and coronary artery disorder, diarrhea, headache, MI and skin carcinoma (3 patients each).

G. Assessment of AEs

The incidence of all Tx-emergent AEs (TESS), both serious and non-serious, was summarized in the sponsor's ISS report. A differentiation is made between acute CCTs in North America vs Europe. GERD maintenance CCTs in North America vs Europe, acute controlled Japanese studies, in the 13 other trials in patients and in the 36 Human PK et al. studies. Also presented by the sponsor were severity and relationship to test medications, drug-demographic and drug-disease interactions.

- In the 12 CCTs conducted in North America and Europe, AEs were reported in 55% of patients who received RABE sodium (all doses combined). There was no apparent dose effect [RABE 10 mg=70%; 20 mg=51%; 40 mg=56%] even if incidence of individual AEs is compared. The most common AEs (i.e. ≥5%) reported in the RABE sodium individual dose and combined groups were:

COSTART Term	RABE Sodium (mg/day)			
	10	20	40	Combined
Total No. of Patients	274	1188	90	1552
Any TESS AE	103 (70%)	608 (51%)	50 (56%)	851 (55%)
Headache	15%	10%	12%	11%
Diarrhea	16%	10%	9%	11%
Rhinitis	16%	5%	8%	7%
Nausea	7%	6%	7%	6%
Abdominal Pain	9%	5%	6%	6%
Pharyngitis	11%	4%	8%	6%
Flu Syndrome	10%	4%	6%	5%
Data Source: Sponsor's Appendix 1, Tables 10.1.1 and 10.3.1				

- Not unexpectedly, on account of the longer exposure to RABE sodium, patients who participated in the GERD maintenance CCTs reported more AEs (361/488=74%) compared to those who participated in the acute CCTs (490/1064=46%). The incidence of key terms is compared below.

	Combined Results in CCTs	
	Acute	GERD Maintenance
Headache	107 (10%)	64 (13%)
Diarrhea	83 (8%)	84 (17%)
Rhinitis	42 (4%)	68 (14%)
Nausea	49 (5%)	44 (9%)
Abdominal Pain	40 (4%)	51 (10%)
Pharyngitis	32 (3%)	56 (11%)
Flu Syndrome	20 (2%)	54 (11%)
Data Source: Sponsor's Appendix 1, Tables 10.1.1 and 10.3.1		

- The incidence of any TESS for RABE sodium, RAN and PL did not show clinically significant differences and there were no apparent dose effects. A comparison of the incidence of seven key terms follows.

COSTART Term[a]	RABE Sodium (mg/day)				RAN 300-600 mg/day	PL
	10	20	40	Combined		
Total No. of Patients	192	795	90	1077	537	258
Any TESS AE	149 (78%)	485 (61%)	50 (56%)	684 (64%)	320 (60%)	145 (56%)
Headache	39 (20%)	107 (13%)	11 (12%)	157 (15%)	85 (16%)	28 (11%)
Diarrhea	39 (20%)	104 (13%)	8 (9%)	151 (14%)	61 (11%)	26 (10%)
Nausea	20 (10%)	63 (8%)	6 (7%)	89 (8%)	46 (9%)	17 (7%)
Rhinitis	40 (21%)	56 (7%)	7 (8%)	103 (10%)	37 (7%)	20 (8%)
Abdominal Pain	24 (13%)	53 (7%)	5 (6%)	82 (8%)	36 (7%)	10 (4%)
Pharyngitis	27 (14%)	50 (6%)	7 (8%)	84 (8%)	26 (5%)	16 (6%)
Flatulence	14 (7%)	44 (6%)	2 (2%)	60 (6%)	18 (3%)	9 (3%)

a) Patients with occurrences in more than one COSTART term are counted only once in the Any TESS AE total. Protocols include NRRC, NRRD, NRRG, NRRF, NRRI, NRRJ, NRRK-ODD and NRRK-EVEN.

Data Source: Sponsor's Appendix 1, Table 16.2

- Similarly, the incidence of any TESS in all CCTs conducted in Europe was 35% in patients who received RABE sodium and 31% in patients treated with OME. No clinically important differences were seen between these two Tx groups for any AE except for MI which the MTL has described and discussed in utmost detail in the section entitled SAEs related to cardiovascular system. A higher percentage of patients receiving RABE sodium 10 mg (54%) reported AEs compared to 31% of patients receiving 20 mg. These findings suggest no dose effect.

- An analysis of the incidence of AEs across Tx by duration and geographic region revealed a) comparability between RABE sodium combined (55%), RAN (60%) and PL; b) comparability between RABE sodium (25%) and OME (27%) in acute CCTs in North America and Europe, respectively.

- AEs occurring in at least 1% of patients in the RABE sodium combined group for the two GERD maintenance studies conducted in North America showed an incidence of AEs that was higher in the RABE groups than in the PL group; however, no dose effect.was shown

	RABE Sodium (mg/day)			PL [n=169]
	10 [n=165]	20 [n=163]	Combined [n=328]	
Any TESS AE	138 (84%)	134 (82%)	272 (83%)	101 (60%)

Of a number of COSTART terms analyzed, the Kaplan-Meier estimate of the cumulative probability of having **abdominal pain** was statistically significantly greater (p=0.0172 [Logrank], p-0.0156 [Wilcoxon]) in the RABE sodium 10-mg group (17.3%) than in the PL group (7.0%). No other statistically significant difference was seen between Tx groups for any other event tested in an overall model using a lifetest procedure to adjust AE frequency rates between the Tx groups. This analysis can be viewed as most valid with frequent events, such as rhinitis and diarrhea, where sufficient numbers of events occurred to have confidence that a non-significant result is meaningful. Lower frequency events must be interpreted with caution. The MTL agrees with the sponsor that many differences in TESS incidences were a function of an increased opportunity for an event to occur on RABE sodium (rather than on PL).

- In the one GERD maintenance CCTs conducted in Europe, slightly fewer patients in the OME group (47%) reported TESS than in the RABE sodium 10-mg (54%), RABE sodium 20-mg (58%) and RABE sodium combined (56%) groups; but these differences are not considered to be clinically important. When the incidence of individual AEs in the RABE sodium combined group was compared to the OME group, no clinically important differences were noted, especially for GI-related events (i.e., abdominal pain, diarrhea, nausea and constipation). Furthermore, no clinically significant dose-related differences were observed between the RABE sodium 10- and 20-mg groups.

- In the two CCTs conducted in Japan, the incidence of AEs was low and similar across RABE sodium and FAM Tx groups. No apparent dose effect was seen in patients receiving 5, 10 or 20 mg RABE sodium.

- The AE profile in the 129 RABE-treated patients with *H. pylori* and other indications and the two patients with ZES was comparable to that seen for patients with [ ] DU, and GERD. The most common AE reported by RABE-treated patients in the studies for other indications was diarrhea (27% of the 131 patients, compared to 6% of the 33 PL patients), followed by headache (25% RABE vs 27% PL), taste perversion (15% RABE vs 0% PL), and abdominal pain (11% RABE vs 6% PL).

H. AEs Possibly or Probably Related to Test Medication

Regardless of the geographic location (North America vs Europe), the indication (acute GERD or GERD maintenance) or dose (10 vs 20 vs 40 mg of RABE per day), the proportion of TESS possibly/probably related to test medication showed no clinically important differences across Tx groups (RABE, RAN, OME, PL). There was no apparent dose effect among the patients treated with RABE sodium.

I. Treatment Emergent Signs and Symptoms by Severity

All TESS were examined by severity (mild/moderate/severe) and by type of study (acute vs maintenance) and geographic location (North America vs Europe).

1. TESS of MILD Severity

- In acute CCTs in North America, no dose effect with respect to the incidence of **mild** TESS was seen in patients receiving RABE sodium. The overall incidence of any **mild** TESS was comparable in the RABE sodium combined and the RAN groups, 38% and 40% respectively. There was a greater percentage of patients in these Tx groups with mild TESS compared to patients in the PL group (27%).

- In acute CCTs in Europe, the over incidence of any **mild** TESS was comparable between RABE sodium 20-mg/day (64/315=20%) and OME 20 mg/day (59/319=18%).

- In GERD maintenance CCTs in North America, no dose effect was seen with respect to the incidence of **mild** TESS in patients receiving RABE sodium [10-mg/day=115/165 (70%); 20-mg/day=110/163 (67%)]. The combined overall incidence was higher in the RABE sodium group than in the PL group (69% vs 44%, respectively), a difference probably related to exposure differences between these two Tx groups.

- In the GERD maintenance CCTs in Europe, the 20-mg/day RABE sodium group appeared to have a greater incidence (50%) of **mild** TESS compared to the 10-mg/day group (39%). In this study population, the overall incidence of **mild** TESS was higher in the RABE sodium combined group (44%) compared to the OME group (35%).

2. TESS of MODERATE Severity

- In acute CCTs in North America, no dose-related effects were observed in patients who received RABE sodium and the overall incidence of **moderate** TESS was comparable across all three Tx groups, i.e., RABE sodium combined (25%), RAN (25%) and PL (27%).

- In acute CCTs in Europe, the overall incidence of any **moderate** TESS was comparable in both Tx groups: RABE 20-mg, 18/315 (6%) vs OME 30/319 (9%).

- In GERD maintenance CCTs in North America, no dose-related differences between RABE sodium 10 and 20 mg were seen, but overall incidence of any **moderate** TESS was higher in the RABE sodium combined group (188/328=57%) compared to placebo (54/169=32%), most likely due to the difference in exposure as previously discussed.

- In the GERD maintenance CCTs in Europe, no apparent effect of RABE sodium dose was seen and the overall incidence of any **moderate** TESS was comparable in both groups: 28/160=18% in the RABE combined group and 18/83=22% in the OME group.

3. SEVERE TESS

- The proportion of patients with **severe** TESS in acute CCTs in North America was:

RABE Sodium (mg/day)			Combined	RAN 300-600 mg/day	PL
10	20	40			
1/27 (4%)	55/632 (9%)	13/90 (14%)	69/749 (9%)	60/537 (11%)	12/89 (13%)

From the data above, the dose of RABE sodium appeared to effect the incidence of **severe TESS;** however, the number of **severe AEs** at the individual term level was small and no clinically important dose-related differences were seen. Moreover, the overall incidence of any **severe TESS** was similar between RABE sodium combined (69/749=9%) and comparators: 60/537=11% for RAN and 12/89=13% for PL.

- In acute CCTs in Europe, there were no individual **severe** AEs in either the RABE sodium or the OME group with an incidence ≥1% and the overall incidence of any **severe** TESS was comparable between treatment groups, i.e., RABE sodium (2/315=1%) and OME (5/319=2%).

- In GERD maintenance CCTs in North America, no effect of RABE sodium dose was observed with respect to the incidence of **severe** TESS. In this group, the overall incidence of any **severe** TESS was slightly higher in the RABE sodium combined group (66/328=20%) compared to the PL group (24/169=14%). This difference was most likely due to exposure differences, as previously discussed.

- Finally, in the GERD maintenance CCTs in Europe, no clinically significant dose effect was noted and the overall incidence of any **severe** TESS was equal in both Tx groups: 12/160=8% for RABE combined and 7/83=8% for OME.

J. Clinical Laboratory and Biopsy (Bx) Evaluations

- In the Acute CCTs in North America and Europe, mean changes in hematology parameters from BL to Endpoint were small and were similar across Tx groups. The proportions of patients in each Tx group with modified shifts from BL and TEAVs (treatment emergent abnormal laboratory value) were also similar across Tx groups. No clinically important effect of RABE sodium dose on hematology parameters was seen. Thus, Tx with RABE sodium at doses of 10, 20 or 40 mg did not appear to affect Hct, Hb, RBC, WBC or platelet count during the controlled acute trials. Consistent with this observation, the percentages of patients with anemia, hypochromic anemia, leukocytosis, and abnormal platelets (sponsor's Appendix 1, Table 10.1.1) were <1% across all Tx groups. Anemia was reported for <1% of patients in the 20-mg RABE sodium, RAN, and OME groups. Hypochromic anemia, leukocytosis and abnormal platelets were each reported for <1% of patients in the 20-mg RABE sodium group.

- In GERD maintenance CCTs in North America and Europe, the mean changes in Hgt, Hb, RBC, WBC, and platelet count from BL to Endpoint were small and were comparable across Tx groups. The proportions of patients in each Tx group with modified shifts from BL were comparable across Tx groups for RBC and platelet count. The proportion of patients with modified shifts in Hct from within or above normal limits to below normal limits was slightly higher for RABE sodium-treated patients (46/457=10%) than for those treated with OME (5/78=6%); but was similar to the proportion of patients in the PL group (18/153=12%). In the RABE sodium-treated patients, a slightly higher proportion of patients (48/457=11%) was noted to have a shift in Hb from within or above normal limits to below normal limits compared to the OME (4/78=5%) and PL (10/153=7%) groups. These differences in Hct and Hb were not noted in the numbers (%) of patients with TEAVs.

- In acute CCTs in Japan, no abnormal hematology findings were noted for Hct and Hb. Also, the proportions of patients in each Tx group with abnormal hematology findings were comparable across treatment groups for RBC, WBC, WBC differential, and platelet count. No dose effect in the RABE sodium-treated patients was seen.

1. Liver Function Tests (LFTs)

- In acute CCTs in North America and Europe, mean changes from BL to Endpoint in LFTs were small and were similar across Tx groups. The proportions of patients in each Tx group with modified shifts from BL and with TEAVs were also similar across Tx groups, indicating that Tx with RABE sodium did not appear to affect LFTs in the three Acute CCTs. Moreover, no dose effect in patients receiving RABE sodium was seen. The percentages of patients with hyperbilirubinemia, increased GGT, increased AST (SGOT), and increased ALT (SGPT) were ≤1% across all Tx groups and no patients in the Acute CCTs were reported to have increased alkaline AP (sponsor's Appendix 1, Table 10.1.1). Hyperbilirubinemia and increased AST (SGOT) were each reported for <1% of patients in the OME group. Increased ALT (SGPT) was reported for <1% of patients in the 20-mg RABE sodium and OME groups. No patient in the RABE sodium group was reported to have increased GGT, compared with 1% of patients in the OME and PL groups.

- In GERD maintenance CCTs in North America and Europe, mean changes from BL to Endpoint in LFTs were small and similar across Tx groups. The proportion of patients with modified shifts from BL was slightly higher for OME-treated patients than for other Tx groups for AP, AST and ALT. The numbers (%) of patients with TEAVs were similar across Tx groups. The conclusion is reached that Tx with RABE sodium did not appear to affect LFTs in the GERD Maintenance CCTs. Furthermore, no dose-related difference was seen between the RABE sodium 10- and 20-mg doses. Consistent with this observation, the percentages of patients with increased AP, increased AST (SGOT), and increased ALT (SGPT) were ≤1% across all Tx groups; no patient was reported to have bilirubinemia or increased GGT (sponsor's Appendix 1, Table 10.1.1). Increased AST (SGOT) and AP were each reported for 1% of patients in the OME group. Increased ALT (SGPT) was reported for <1% of patients in the 10- and 20-mg RABE sodium groups.

- In acute CCTs in Japan, no dose-related difference in patients receiving RABE sodium was seen for the LFTs. Furthermore, the proportions of patients in each Tx group with abnormal LFTs were comparable across Tx groups.

2. Kidney Function Tests (KFTs)

- In CCTs in North America and Europe, whether acute or GERD maintenance trials, mean changes from BL to Endpoint in KFTs were small and changes were similar across Tx groups. For each kidney function parameter, the proportions of patients with modified shifts from BL and with TEAVs were also similar across Tx groups, and no apparent dose effect of RABE sodium was seen. Tx with RABE sodium did not appear to affect KFTs in these CCTs. Consistent with these results no specific kidney function TESS was reported for more than 1% of patients in any Tx group.

- Abnormal clinical laboratory findings for KFTs were reported for two patients in the two Acute CCTs conducted in Japan. Both patients (one each in the 5- and 20-mg RABE sodium groups) were reported to have increased BUN. These findings do not appear to be clinically significant since a) there were no corresponding reports of elevated serum creatinine values, and b) as described above, no clinically important findings for BUN or serum creatinine were found in the CCTs conducted in North America and Europe.

3. Cardiac Enzymes

Some inconsistent findings in CPK or AST were reported, but these were of no concern because the changes in the RABE sodium combined group were similar to those seen either in the OME or the RAN groups.

4. Thyroid Function Tests

It is worth noting that an adverse toxicity finding (minimal to slight thyroid follicular hypertrophy in mid- to high dose dogs) in preclinical studies necessitated the inclusion of thyroid function tests as an additional laboratory test requirement.

- In CCTs in North America and Europe, mean changes in thyroid function tests from BL to Endpoint for the RABE sodium-treated patients were small and were similar for the 10- and 20-mg groups. Modified shift and TEAV analyses were not performed for these laboratory data.

- TSH values were examined to determine how many patients with normal values at BL had values above or below normal at Endpoint. Only one OME-treated patient had a normal Baseline TSH value which was above normal at Endpoint.

- In addition, thyroid function tests were assessed in 6 pharmacology trials. The main conclusion from each of these studies is given below.

	Main Conclusions
1. Study A001-601	No clinically significant changes in thyroid function values for individual subjects and no evidence of any effect of RABE sodium on mean values for the dose groups (10, 20, 30 and 40 mg of RABE sodium) or PL.
2. Study A001-002	One 10-mg subject with a low BL T_3 uptake had a further decrease on Days 5 and 16, but normal T_3, T_4 and T_7 levels. The decrease was considered unrelated to RABE sodium.
3. Study A001-003	The study population consisted of 10 healthy volunteers and 10 men with renal failure. There were no clinically significant changes in the thyroid function values for individual subjects and no evidence of any effect of RABE sodium on mean values.
4. Study A001-004	The study population consisted of 13 healthy men, 10 men with chronic compensated cirrhosis of the liver. There were no clinically significant changes in thyroid function values for individual subjects and no evidence of any effect of RABE sodium on mean values. RABE sodium was well tolerated by subjects with stable chronic hepatic cirrhosis.
5. Study E044-106 (NRRY)	No clinically important differences between RABE 20 mg/day and PL were noted for thyroid function results in this crossover study in 12 healthy volunteers treated with test medication for 14 days.
6. Study E044-307 (NRRP)	No statistically significant differences were seen between RABE sodium and OME (evaluated at BL and at Week 8) in patients with erosive esophagitis. The parameters evaluated included thyroxine, TSH, T_3 uptake, and free T_4 index Endpoint values.

5. Fasting Serum Gastrin

The findings when evaluating this parameter were as expected of a PPI. The effect on gastrin was predictably dose-related, well-differentiated from the effect of RAN and PL but similar to that of the OME control (another PPI). This information should be included in the labeling.

6. Biopsy Evaluations

The MTL agrees with the sponsor that predictably, dose-related differences were seen with respect to ECL hyperplasia and these findings were consistent with the pharmacological actions of this PPI. There were no significant distinctions between RABE sodium and OME, another PPI, for the histological parameters evaluated. Nonetheless, the predictable dose-related differences demonstrated for serum gastrin and ECL hyperplasia should be reflected in the labeling.

[A very detailed evaluation on Bx data, based on the report by Dr. J. Gardner, an expert in this field, is carried out during the MTL's review of the October 21, 1998 Safety Update.]

K. Vital Signs

When all CCTs are considered, no clinically important dose-related effects in RABE-treated patients were observed. The mean changes in systolic and diastolic BP, pulse (and body weight) were small and comparable across Tx groups.

L. EKG Findings

In CCTs in North America and Europe mean changes in heart rate and PR, QRS and QTC interval were small. No dose effect in RABE sodium-treated patients was seen and no clinically significant differences across Tx groups were noted.

M. Additional Safety Issues

- Except for the expected dose effect in serum gastrin and ECL hyperplasia, the 20 mg/day RABE dose is considered as safe as the 10 mg/day dose.

- RABE, as OME, 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 (all metabolized by the P_{450} system).

- In clinical trials, antacids were used concomitantly with the administration of RABE sodium and, in a specific study designed to define this interaction, no interaction with liquid antacids was observed. It was also determined that – based on clinical results – RABE sodium can be given with and without food. However, expected interactions have been seen with compounds where absorption is pH dependent. Co-administration of RABE sodium results in ca. a 33% decrease in the AUC and C_{max} of ketoconazole and ca. a 20% increase in trough digoxin levels. Therefore individual patients may need to be monitored to determine if a dosage adjustment is necessary when such drugs are taken concomitantly with RABE sodium.

- The bioavailability of RABE sodium, as determined in a formal interaction study, appeared to increase with age as did the mean peak plasma concentration of RABE sodium; however, no clinically meaningful differences were seen between elderly and young patients with respect to adverse events, vital signs, or laboratory values. Furthermore, review of TESS and TEAVs for the twelve Controlled Clinical Trials in North America and Europe showed no clinically meaningful differences with respect to age and gender. There were too few non-Caucasian patients to make any meaningful comparison across racial groups. The PK differences seen between M and F patients are believed to be due to differences in body weight rather than gender.

December 22, 1998

/S/

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-973
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-180/JSenior
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 12/16/98 jgw
N/20973811.4HG

/S/ 12-22-98

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 18 December 1998

FROM: John R. Senior, M.D., Medical Officer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Comments on Pharmacology/Toxicology review of NDA 20-973 (rabeprazole)

TO: Lilia Talarico, M.D., Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180 /S/ 12-21-98

VIA: Hugo Gallo-Torres, M.D., Medical Team Leader, HFD-180

This memorandum addresses your request for comment on Dr. Ke Zhang's pharmacology/toxicology review of preclinical data for rabeprazole sodium (ACIPHEX™, E3810, LY307640; Eiasai, Inc.) dated 16 December 1998.

Dr. Zhang recommended approval of the drug from a preclinical standpoint, with which the paharmacology/toxicology team leader, Dr. Jasti Choudary, concurred on 18 December. However, concerns were mentioned by Dr. Choudary that the compound was tumorigenic (gastric enterochromaffin -like cell carcinoids) in female Sprague-Dawley rats even at lowest tested doses of 5 mg/kg or 30 mg/m^2, only twice the recommended human dosage based on body surface area. Growth of such tumors is agreed to be multifactorial, and not just a function of gastrin alone. The drug was also mutagenic in microbial (Ames/Salmonella) and mamalian cell (Chinese hamster ovary/HGPRT and mouse lymphoma cell line L5178Y/TK$^{+/-}$) tests. For these reasons, the preclinical data suggest that approval of rabeprazole for long-term use in nonpathological conditions should not be recommended.

Comment: All of the proton-pump inhibiting agents have shown the ECL-carcinoids in rodent species, but the previously approved omeprazole and lansoprazole have shown somewhat different tumorigenicity and mutagenicity. The two approved compounds have now been administered to millions of people for quite long periods of time, up to 10 or 15 years for omeprazole and up to about 5 years for lansoprazole. The human experience appears to be different from that seen in the rodent species. Caution is advisable despite this, and the long-term use of potent gastric acid suppressants such as the family of gastric mucosal proton-pump inhibitors will need to be monitored closely. The long-term concern in humans is mainly the possibility of gastric mucosal atrophy, metaplasia, dysplasia, and gastric carcinoma. The major clinical use for long-term proton-pump inhibitors will very likely be maintenance of healing and reduction of the risk of relapse of erosive esophagits in patients with gastroesophageal reflux

disease (GERD). The pharmacology/toxicology concerns are noted. My recommendation of 23 November 1998 for approval of rabeprazole sodium at a dose of 20 mg/day for healing of erosive esophagitis of GERD, and for maintenance of healing, is reiterated. Post-approval concern for possible carcinoids and other tumors, especially adenocarcinoma, will continue to be needed as more and more human experience with this class of drugs continues to accumulate. Erosive esophagitis is a serious pathologic condition, with potentially dangerous complications and sequelae. At present, the proton pumps inhibitors are the best pharmacologic therapy for the disease, and only surgical fundoplication has been shown to be of comparable effectiveness in preventing those complications.

/S/ 18 Dec '98

John R. Senior, M.D.
Medical Reviewer, DGCDP
date

cc:
NDA 20-973
HFD-180
HFD-180/LTalaric /S/ 12-21-98
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD –180/JChoudary
HFD-181/BStrongin

Concur. December 18, 1998
/S/

APPEARS THIS WAY
ON ORIGINAL