These publications do not provide additional or new safety data regarding Aciphex™.[14]

X. CLINCAL LABORATORY EVALUATIONS

Laboratory analyses were presented for the GERD Extension Clinical Studies conducted in North America (Studies A001-309-1,2,3) and Europe (Studies E044-310-1,2). Descriptive summaries were presented for the Human Bioequivalence Study conducted in North America (A001-118), for the study of two Tx regimens of Aciphex™ and OME for acute GERD (E033-311) conducted in Europe and for the Open-Label Study of 11 patients with ideopathic GAHS or ZES. Clinical laboratory evaluations included selected serum chemistries, such as serum gastrin, hematology tests, and urinalysis. Three types of analyses of the laboratory data were performed for the pooled data from the GERD Extension Clinical Studies conducted in North America (Studies A001-309-1,2,3) and Europe (Studies E044-310-1,2):

- Mean changes from BL to Endpoint.

- A modified shift analysis that showed by Tx group the numbers and percentages of patients who had at least one laboratory value that shifted from a normal or low value (values within or below the normal range) at BL to a high value (a value above the normal range) post-BL; and the number and percentage of patients who had at least one value that shifted from a normal or high value (values within or above the normal range) at BL to a low value (a value below the normal range) post-BL calculated and presented by Tx group.

- The numbers and percentages of patients with a potentially clinically significant Tx emergent abnormal laboratory value (TEAV)[15], summarized by Tx group.

- Tx with Aciphex™ at doses of 10 or 20 mg per day did not appear to have a clinically significant effect on Hct, Hb, RBC, WBC, or platelet count during the controlled GERD extension studies. No meaningful dose-related effects on hematology parameters were seen with Aciphex™ sodium 10 or 20 mg dose Tx.

- As discussed above, abnormalities in the hemic/lymphatic system were reported in ca. 5% of the patients in the North American and European GERD Extension studies. Twelve of 292 patients (4%) demonstrated anemia (including iron deficiency anemia). Leucopenia, thrombocytopenia, and abnormal WBC were reported in less than 1% of patients across all Tx groups.

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[14] The non-clinical papers were also included in sponsor's Appendix 6 with the three non-clinical toxicology reports discussed in sponsor's chapter 5 of the SU document.

[15] A TEAV was defined as a post-BL laboratory value that was outside (above or below) the potentially clinically significant range, but was within the potentially clinically significant range at BL; or a value that represented a potentially clinically significant worsening of an abnormality present at BL. The criteria for defining TEAVs was found in the sponsor's Statistical Methodology Section (Section 2) and in the discussion of the various laboratory parameters summarized in the various categories. All criteria to define "worsening" were established by Eisai Inc. Criteria for worsening were established to identify patients who had abnormal values (i.e., met the TEAV criteria) at BL that worsened during Tx so that all patients could be considered in the TEAV Tx group.

- Tx with Aciphex™ at doses of 10 or 20 mg did not appear to have a clinically significant effect on liver function during the controlled GERD Extension studies. No meaningful dose-related effects on hepatic functional parameters were not seen with Aciphex™ 10 or 20 mg dose Tx.

- As previously discussed, abnormal laboratory findings for LFTs were reported for 2% of the patients in the North American and European GERD Extension studies. Bilirubinemia and increased GGT were reported for 1 of 292 patients (<1%). Increased ALT (SGTP) was observed in 3 patients (1%) across all Tx groups. No AST (SGOT) increase was noted in these studies.

- Tx with Aciphex™ at doses of 10 or 20 mg did not appear to have a clinically significant effect on kidney function tests during the controlled GERD extension studies. No meaningful dose-related effects on kidney functional parameters were seen with Aciphex™ 10 or 20 mg dose Tx. As previously discussed in Chapter 6, abnormal laboratory findings for kidney function tests were not among the AEs reported across all Tx groups in the North American and European GERD Extension Studies.

- Tx with Aciphex™ at doses of 10 or 20 mg did not appear to have a clinically significant effect on serum cardiac enzymes (CPK and SGOT) values during the controlled GERD extension studies. No meaningful dose-related effects on these parameters were seen with Aciphex™ 10 or 20 mg dose Tx. Comparison of the cardiac enzymes activity between NDA and GERD extension studies did not reveal clinically important differences.

- No clinically meaningful changes were noted for thyroid function in the Aciphex™ combined group. No clinically noticeable dose-effect was observed in the Aciphex™ 10- and 20-mg groups as well. Mean changes in thyroid function tests from BL to Endpoint for the Aciphex™-treated patients in GERD Extension Studies were small and generally consistent with those in GERD Maintenance Studies. Some shifts in thyroid function tests to abnormal level (high or low) from BL to Endpoint were noted in the GERD Extension studies for the Aciphex™ combined group. Two patients' (9%) thyroxine values shifted below the normal range. In contrast, T3 uptake shifted above the normal range in 4 (18%) patients. At the same time, three (13%) of patients shifted BL abnormal thyroid tests to normal range at Endpoint in the Aciphex™ combined group. Shifts to abnormal Free T4 Index values were also reported in 1 (25%) patient in the PL group and in 2 (40%) patients in the OME group.[16]

[16] The largest changes were observed for the OME-treated group, where mean thyroxine values dropped a total of 20.25 nmol/L compared to a small decrease in the Aciphex™ combined group (-4.26 nmol/L) and placebo group (-4.51 nmol/L). The decrease in thyroxine values was slightly greater in the Aciphex™ 20-mg group (-6.58 nmol/L) compared to the Aciphex™10-mg group (-0.91 nmol/L). The most sensitive parameter of thyroid activity, TSH mean value, increased by 1.10 mIU/L in the OME group compared to a small decrease (-0.05 mIU/L) in the Aciphex™ combined group and PL group (-0.68 nmol/L). Mean changes in Free T4 also were more noticeable in the OME group. T3 uptake changes in the Aciphex™ combined group were very similar to changes observed in the PL group during the Tx.

In summary, laboratory parameters for the controlled North American and European GERD extension studies were pooled and analyzed for mean changes, the numbers and percentages of patients with high and low shifts from BL values, and the number and percentages of patients with TEAVs. Also, a descriptive analysis for three other clinical studies was provided. No clinically relevant findings were seen for hematology, serum chemistry, urinalysis, or thyroid function tests in Aciphex™-treated groups of patients. Changes in serum gastrin values in Aciphex™ groups were not dose-related in the GERD Extension Studies. For other parameters, the GERD Extension Studies results were generally consistent with those in the GERD Maintenance Studies. No important differences were noted between Aciphex™ and OME sodium.

XI. SUMMARY OF GASTRIC BIOPSY EVALUATIONS

(Reanalysis of Gastric Biopsy Data from NRRK and NRRQ)

a) Generalities

In this section authored by Dr. Jerry Gardner, a recognized clinical expert in this field, the sponsor presented analysis of gastric biopsy data from the NDA GERD Maintenance and post-NDA extension studies. Dr. Gardner utilized tabulated data, as well as an electronic database, to sort information for his independent analyses. Data Listings 22-28 (sponsor's Volume 14, Appendix 11) contained patient specific gastric Bx listings.

It is noted that gastric infection with *H. pylori* is accompanied by duodenal ulceration and inflammation in both the antrum and the corpus (body) of the stomach. Treating patients who are infected with *H. pylori* with PPIs, such as omeprazole or lansoprazole, decreases inflammation in the gastric antrum, but increases in the gastric corpus.[17] These changes in the corpus also occur with RAN treatment[18] and with vagotomy [E.J. Kuipers et al. NEJM 334:1018-1022 (1996)].

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[17] R. Lamberts et al. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth and gastritis. Gastroenterology 104:1356-1370 (1993)
E. Solicia et al. Effects of Eradication of Helicobacter pylori on gastritis in duodenal ulcer patients. Scand J Gastroenterol 29(uppl 201):28-34 (1994).
E.C. Klinkenberg-Knol et al. Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and Safety. Ann Intern Med 121:161-167 (1994)
M. Stolte et al. Relationships between the degree of Helicobacter pylori colonization and the degree and activity of gastritis, surface epithelial degeneration and mucus secretion. A Gastroenterol 33:9-93 (1995).
R.P.H. Logan et al. Changes in the intragastric distribution of Helicobacter pylori during treatment with omeprazole. Gut 36:2-16 (1995).
E.J. Kuipers et al. Atrophic gastricis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. NEJM 334:018-1022 (1996).
M. Stolte et al. Changes in Helicobacter pylori-induced gastritis in the antrum and corpus during 12 months of treatment with omeprazole and lansoprazole in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 12:47-253 (1998).

[18] J.E. Madsen et al. Helicobacter pylori and chronic active inflammation of the duodenum and stomach in duodenal ulcer patients treated with ranitidine, misoprostol, or an acid-neutralizing agent. Scand J Gastroenterol 26:465-470 (1991)
A. Meining et al. H_2-receptor antagonists and antacids have an aggravating effect on Helicobacter pylori gastritis in duodenal ulcer patients. Aliment Pharmacol Ther 11:729-734 (1997).

In 1996, Juipers and colleagues [(locus cited) (1996)] reported that Dutch patients with *H. pylori* infection treated with omeprazole for severe esophagitis developed **atrophic gastritis.** In contrast, Swedish patients with *H. pylori* infection treated with gastric fundoplication for esophagitis did not develop atrophic gastritis. This report led to a meeting of the Gastrointestinal Drugs Advisory Committee of the FDA in November 1996 to review the data on which the Kuipers' paper was based as well as relevant data from Astra-Merck obtained with omeprazole and from Tap Holding Co. obtained with lansoprazole[19]. No firm conclusions were drawn regarding the effects of PPIs on pathologic changes in the gastric mucosa, and the participants recognized that more data were needed to assess the effects of PPIs on the gastric mucosa of patients infected with *H. pylori*.

The sponsor has conducted two separate randomized, double-blind studies that examined the abilities of 10 and 20 mg RABE vs comparators to prevent recurrence of ulcerative or erosive esophagitis in patients whose esophagitis had healed during previous Tx, usually with a PPI. Both studies lasted up to 52 weeks. One study (NRRQ) was conducted in Europe and included 20 mg omeprazole as an active comparator. The other (NRRK) was conducted in the US and included a PL control group. Results from study NRRK were analyzed as two separate studies by assigning study sites to one of two groups based on study site number (NRRK-odd and NRRK-even). In the present analysis, however, results from NRRK-odd and NRRK-even were combined and referred to as simply from NRRK. In both the European and the US study, gastric Bxs taken at BL and at prespecified times during the 52-week Tx period were assessed for *H. pylori* and gastritis using the Sydney classification system[20], and for enterochromaffin-like (ECL) cell hyperplasia using the classification proposed by Solcia and colleagues[21]. Reproduced here are the main conclusions from Dr. Gardner's analyses.

In several instances, the number of patients per cell was too small to draw meaningful conclusions. The parameters evaluated included active patients (in L-T on-going trials), adequate samples, H. Pylori infection, acute inflammation ("activity"), chronic inflammation ("inflammation"), atrophy, metaplasia and enterochromaffin-like (ECL) cell hyperplasia.

b) **Comparison of Changes in Gastric Corpus Mucosa in Studies NRRK and NRRQ**

Pathological changes in the gastric corpus mucosa in study NRRK and NRRQ are summarized in Table 8.

M. Roland et al. A histological study of gastric mucosa before and after proximal gastric vagotomy in duodenal ulcer patients. Scand J Gastroenterol 10:181-186 (1975).

[19] Transcript of meeting of Gastrointestinal Drugs Advisory Committee, Food and Drug Administration, November 4-5, 1996, Bethesda, MD.

[20] A.B. Price. The Sydney system: histological division. J Gastroenterol Hepatol 6:209-222 (1991).

[21] E. Solcia et al. Histopathological classification of nonantral gastric endocrine growths in man. Digestion 41:185-193 (1988).

TABLE 8
NDA 20-973 SU

Summary Comparison of Changes in Gastric Corpus Mucosa in NRRK and NRRQ

	Incidence BL	Prevalence Onstudy	Increase in Grade Onstudy	
Measurements	(all pts)	($10 & R20)	NRRK	NRRQ
% Adequate Samples	Q>K	Q>K	–	–
H. pylori	Q>K	Q>K	No	No
Activity	Q>K	Q>K	No	No
Inflammation	Q>K	Q>K	Yes: R20 No: R10 & PL	Yes: R10, R20 & Om20
Atrophy	Q>K	Q>K	No	No
ECL Cell Hyperplasia	Q>K	Q>K	Yes: R20 No: R10 & PL	Yes: R10, R20 & Om20

- In NRRK, nearly half of the PL patients dropped out of the study by 4 weeks; therefore, meaningful comparisons between PL and active Tx groups were not possible. It is possible that all changes observed in active Tx groups in both NRRK and NRRQ are unrelated to the treatment and simply reflect the natural course of *H. pylori* pathology.

- In each Tx group in both studies, only a minority of patients had an adequate Bx at week 52.

- NRRQ had significantly higher values than NRRK with respect to incidence at BL and prevalence onstudy for *H. pylori* infection, activity, inflammation, atrophy and ECL cell hyperplasia. The incidence or prevalence of metaplasia did not differ between NRRK and NRRQ, but there were only a small number of patients with metaplasia.

- For *H. pylori* infection, activity, inflammation, atrophy and ECL cell hyperplasia in NRRK and NRRQ, prevalence did not change or decrease over the course of the 52-week study.

- There were **no consistent changes** in the active Tx groups when BL grade for *H. pylori* infection, activity or atrophy was compared to endpoint grade.

- For both inflammation and ECL cell hyperplasia, the increases in grade from BL to endpoint were similar in all three active Tx groups in NRRQ and the 20-mg RABE in NRRK, and were significantly greater than those in the PL and 10-mg RABE groups in NRRK.

c) Effect of H. Pylori

The analysis of results stratified on the basis of *H. pylori* infection are summarized in Table 9.

TABLE 9
NDA 20-973 SU

Summary Comparison Effect of *H. pylori* Infection on Changes in Gastric Corpus Mucosa in NRRK and NRRQ

	H. pylori-positive greater than H. pylori-negative			
	Baseline		Onstudy	
Measurement	Incidence	Grade	Prevalence	Increase Grade
% Adequate Samples	Neither	--	Neither	--
Activity	K & Q	K & Q	K & Q	K&Q
Inflammation	K & Q	K & Q	K & Q	K&Q
Atrophy[a]	Q	Neither	Q	Q
ECL Cell Hyperplasia	Neither	Q	Not done	K

a) Only 15 samples had atrophy in NRRK

- There were no significant differences in the percentages of adequate samples between patients with *H. pylori* infection and those without infection in any Tx group in NRRK or NRRQ.

- Nearly all the differences between BL incidence and onstudy prevalence of activity and inflammation in NRRK and NRRQ can be accounted for by the difference in incidence in *H. pylori* infection in these two studies.

- In the active Tx groups in NRRK and NRRQ, the onstudy increases in grade of inflammation from BL to endpoint were significantly higher in patients with *H. pylori* infection than in those without infection.

- In the active Tx groups in NRRQ, the onstudy increases in grade of atrophy from BL to endpoint were significantly higher in patients with *H. pylori* infection than in those without infection.

- In the active Tx groups in NRRK and NRRQ, the onstudy increases in grade of ECL cell hyperplasia from BL to endpoint were not significantly different in patients with *H. pylori* infection from those in patients without infection.

d) Comparison of Changes in Antral and Corpus Mucosa in Study NRRQ

The analyses of pathologic changes in the gastric antral and corpus mucosa are summarized in Table 10.

TABLE 10
NDA 20-973 SU

Summary: Comparison of Changes in Antral (Ant) and Corpus (Corp) Mucosa in NRRQ

	Compare Antrum to Corpus				Compare Prevalence BL to Endpoint	
	BL[a]	Endpoint	Grade at BL	Onstudy Change	Antrum	Corpus
H. pylori						
R10	Corp>Ant	Same	Same	Same	Same	Same
R20	Corp>Ant	Corp>Ant	Same	Same	Same	Same
Om20	Corp>Ant	Corp>Ant	Same	Same	Base>End	Same
Activity						
R10	Corp>Ant	Same	Same	Corp>Ant	Same	Same
R20	Corp>Ant	Corp>Ant	Same	Corp>Ant	Same	Same
Om20	Corp>Ant	Corp>Ant	Different	Corp>Ant	Base>End	Same
Inflammation						
R10	Same	Same	Same	Same	Base>End	Same
R20	Same	Same	Same	Same	Same	Same
Om20	Same	Same	Same	Same	Base>End	Same
Atrophy						
R10	Same	Same	Same	Same	Same	Same
R20	Same	Corp>Ant	Same	Same	Same	Same
Om20	Same	Same	Same	Same	Same	Same
Metaplasia						
R10	Ant>Corp	Same	n.d.	Ant>Corp	Same	Same
R20	Ant>Corp	Same	n.d.	Same	Same	Same
Om20	Ant>Corp	Same	n.d.	Same	Same	Same

[a] These evaluations compared all 3 Tx groups combined. n.d. -determined because metaplasia was graded as 0-100%.

- At BL, the prevalence of H. pylori and activity of the infection were significantly higher in corpus biopsies than in antral biopsies, whereas the prevalence of metaplasia was significantly higher in antral biopsies than in corpus biopsies. The prevalence of inflammation or atrophy at baseline did not differ significantly between antral and corpus biopsies.

- At endpoint, the prevalence of H. pylori and activity of the infection were significantly higher in corpus biopsies than in antral biopsies in two of the three Tx groups (20-mg RABE and omeprazole groups). Except for atrophy at endpoint in the 20 mg RABE group, for which the prevalence in corpus biopsies was significantly higher than in antral biopsies, the prevalence of inflammation, atrophy or metaplasia at endpoint did not differ significantly between antral and corpus biopsies.

- The grades of H. pylori, inflammation, and atrophy at BL did not differ significantly between antral and corpus biopsies. For activity, corpus Bxs had a significantly higher percentage of moderate activity and a lower percentage of mild activity compared to antral biopsies.

- On study changes in H. pylori , activity, inflammation, atrophy, and metaplasia did not differ significantly between antral and corpus biopsies, except for metaplasia in the 10 mg RABE group for which antral biopsies had significantly more change than did corpus biopsies.

- In corpus biopsies, prevalence of H. pylori, activity, inflammation, atrophy, and metaplasia at endpoint did not differ significantly from that at BL. In antral BXs, prevalence of inflammation for the 10-mg RABE and omeprazole groups was significantly higher at BL than at endpoint. In antral biopsies, prevalence of H. pylori and activity for the omeprazole group was significantly higher at BL than at endpoint.

e) Comparison of Results from NRRQ with Published Results from Others

It is noted that results of NRRQ differ markedly from results of comparable studies published previously by others. Others for example, have found that BL grades of H. pylori activity and inflammation were clearly higher in antral Bxs than in corpus Bxs, whereas in NRRQ, BL grades of H. pylori, activity and inflammation were higher in corpus Bxs than in antral Bxs. Furthermore, others have found that when patients were treated with omeprazole or lansoprazole, grades of H. pylori, activity and inflammation decreased significantly in antral biopsies and increased significantly in corpus biopsies. In NRRQ, however, grades of H. pylori, activity and inflammation for corpus or antral biopsies did not change significantly during Tx with either RABE or omeprazole.

It is speculated that these differences occurred because nearly all patients in NRRQ as well as NRRK had been previously treated for up to eight weeks with RABE or omeprazole to produce healing of their erosive GERD. The findings in NRRQ that grades of H. pylori, activity and inflammation at baseline were significantly greater in corpus Bxs than antral Bxs were the same as the findings by others after 2 to 3 months of treatment with omeprazole or lansoprazole. Furthermore, in these other trials, statistically significant changes were detected after only 4 weeks of Tx, we were maximal after 2 to 3 months, and remained stable thereafter. Thus, the changes in H. pylori and gastric mucosal pathology that have been observed with omeprazole and lansoprazole by others had probably already occurred in the patients in NRRQ and NRRK by the time that they were randomized into these studies. It is also possible that results in NRRQ differed from those from others because of some important difference between RABE, which was used in NRRQ, and omeprazole or lansoprazole, which were used in the other studies. In NRRQ, however, results for H. pylori, activity and inflammation with rabeprazole were essentially the same as those with omeprazole. The latter findings argue against some important difference in RABE.

f) Analysis of Results from Antral Biopsies in NRRQ Stratified on the Basis of H. Pylori Infection

As mentioned above, Bxs from the gastric corpus with H. pylori infection, had pathologic changes that were substantially greater than those in Bxs that did not show H. pylori infection. To examine possible relationships between H. pylori and pathology in biopsies from the gastric antrum, results from these Bxs were analyzed after stratifying for H. pylori infection. The results are summarized in Table 11.

Table 11
NDA 20-973 SU

Summary: Comparison Effect of H. pylori Infection on Changes in Gastric Antral Mucosa In NRRQ

	Compare H. pylori-pos to H. pylori-neg Grade at			Compare Prevalence BL to Endpoint	
	BL[a]	Endpoint	BL[b]	Change	Hp-pos	Hp-neg
Activity						
R10	Pos>Neg	Pos>Neg	Same		Same	Same
R20	Pos>Neg	Pos>Neg	Same		Same	Same
Om20	Pos>Neg	Pos>Neg	Same		Same	Same
Inflammation						
R10	Pos>Neg	Pos>Neg	Different		Same	Same
R20	Pos>Neg	Pos>Neg	Different		Same	Same
Om20	Pos>Neg	Pos>Neg	Different		Same	Same
Atrophy						
R10	Same	Same	Same		Same	Same
R20	Same	Same	Same		Same	Same
Om20	Same	Same	Same		Same	Same
Metaplasia						
R10	Same	Same	n.d		Same	Same
R20	Same	Same	n.d		Same	Same
Om20	Same	Same	n.d		Same	Same

[a,b]) These comparisons compared all 3 treatment groups combined.
n.d.- not determined because metaplasia was graded as 0-100%.

- For all Tx groups, the prevalence of activity and inflammation at BL and at endpoint was significantly higher in patients with H. pylori infection than in those without H. pylori infection. The prevalence of atrophy or metaplasia at BL or endpoint in patients with H. pylori infection did not differ significantly from that in patients without H. pylori infection.

- At baseline, patients with H. pylori infection had a significantly higher proportion of samples with moderate inflammation and a correspondingly lower proportion of samples with mild inflammation compared to patients without infection. At baseline, the distribution of grades of activity or atrophy in patients with H. pylori infection did not differ significantly from that in patients without infection.

- The prevalence of activity, inflammation, atrophy or metaplasia at endpoint did not differ from that at BL for any Tx group for patients with or without H. pylori infection.

- The prevalence of ECL cell hyperplasia in the gastric corpus at BL in patients with H. pylori infection in the gastric antrum did not differ from that in patients without infection in the antrum.

g) Changes in Gastric Mucosa as a Function of Rabeprazole Dose

Analysis of possible changes in gastric antral and corpus mucosa as a function of the RABE dose is summarized in Table 12.

TABLE 12
NDA 20-973 SU

Changes in Gastric Mucosa as a Function of RABE Dose

Corpus Mucosa in NRRK and NRRQ

NRRK

Measurement	Prevalence Week 52 (% adequate samples) PL	R10	R20	p-values Pl v R10	Pl v R20	R10 v R20
H. pylori	14	9	8	N.S.	N.S.	N.S.
Activity	14	6	11	N.S.	N.S.	N.S.
Inflammation	28	22	17	N.S.	N.S	N.S.
Atrophy	14	0	3	N.S.	N.S.	0.050.
ECL Hyperplasia	0	6	11	N.S.	N.S.	N.S.

NRRQ

Measurement	Prevalence Week 52 (% adequate sample) R10	R20	p-values R10 v R20
H.pylori	28	44	0.089
Activity	26	49	**0.017**
Inflammation	35	56	**0.027**
Atrophy	4	18	**0.017**
ECL Hyperplasia	13	18	N.S.

Corpus and Antral Mucosa in NRRQ

Measurement	Antrum Prevalence Week 52 (% adequate samples) R10	R20	p-values R10 v R20	Corpus Prevalence Week 52 (% adequate samples) R10	R20	p-values R10 v R20
H. pylori	18	19	N.S.	26	41	N.S
Activity	12	19	N.S.	26	47	**0.048**
Inflammation	26	47	**0.048**	32	53	**0.050**
Atrophy	3	3	N.S.	3	16	**0.026**
Metaplasia	2	2	N.S.	0	1	**0.041**

P.values are from Chi square test. Values≤0.05 are in bold.

There were no significant differences among the PL and RABE Tx groups with respect to H. pylori, activity, inflammation, atrophy or ECL cell hyperplasia.

- For corpus Bx at week 52 in NRRQ, prevalence of activity, inflammation and atrophy was **significantly higher** with 20 mg RABE than with 10 mg RABE and prevalence of H. pylori was borderline significantly higher with 20 mg RABE than with 10 mg RABE. Prevalence of ECL cell hyperplasia did not differ significantly between 10-mg and 20-mg RABE groups.

- For antral biopsies at week 52 in NRRQ, prevalence of inflammation was significantly higher with 20 mg RABE than with 10 mg RABE, but prevalence of H. pylori, activity, atrophy or metaplasia did not differ significantly between 10-mg and 20-mg RABE groups. Corpus Bxs at week 52 in NRRQ from the same patients who had antral Bxs showed the same significant differences between 10-mg and 20-mg RABE as did the entire group of corpus Bxs described in the preceding paragraph. In addition, corpus Bxs at week 52 in NRRQ from the same patients who had antral Bxs also showed a significant difference between 10-mg and 20-mg RABE with respect to metaplasia; however, this difference was based on one patient.

- There were significant, RABE **dose-related effects** for several pathological features associated with H. pylori infection in corpus Bxs from NRRQ, but not in those from NRRK. The difference between these two studies probably results from the relatively small number of patients who had adequate Bxs at week 52 in NRRK. A similar phenomenon might account for the lack of dose-related effects in atral Bxs from NRRQ. With numbers from atral Bxs that were of similar magnitude to those from corpus Bxs from the same patients, there was a significant difference between RABE dose groups with respect to inflammation in antral Bxs.

h) **Analysis of Results from Mucosal Biopsies of Gastric Corpus and Antrum from Extension Studies for NRRK (A001-309) and NRRQ (E044-310) (Table 13)**

Table 13
NDA 20-973 SU
Summary: Summary of Changes Related to H. pylori in Gastric Mucosa

	Corpus Bxs		Antral Bxs	
	Prevalence	**Grade**	**Prevalence**	**Grade**
H. pylori	No change over course of study	Mild or moderate at beginning; moderate at end	No change over course of study	Mild predominates at all times
Activity	No change over course of study	Mild or moderate at beginning; moderate at end	No change over course of study	Mild predominates at all times
Inflammation	No change over course of study	Mild or moderate at beginning; moderate at end	No change over course of study	Mild predominates at all times
Atropy	Increase in R20 group	Mild predominates at all times	No change over course of study	Mild predominates at all times

- In **corpus mucosa**, the prevalence of H. pylori, activity of the infection and inflammation did not change over the course of the study.

- For these same measures, a grade of moderate predominated on the last Bx of the extension study.

- In a grade of mild predominated at BL, there was an increase to a grade of moderate during the course of the study and the increase in grade of H. pylori infection occurred before the increases in grades of activity and inflammation.

- If a grade of moderate predominated at BL, there was no further increase in grade during the study.

- In **antral mucosa**, the prevalence of H. pylori, activity and inflammation did not change over the course of the study and a grade of mild predominated for each measure over the course of the study.

- **The prevalence of atrophy in the corpus mucosa** increased in the 20-mg RABE group but not in the 10-mg RABE group. The grade of mild atrophy predominated in both corpus and antral mucosa over the course of the trial.

XII. Vital Signs, Body Weight and EKGs

- No clinically meaningful changes in systolic and diastolic BP and PR were seen in Aciphex^{tm} treated patients or patients who received omeprazole or PL.

- Results of the GERD extension studies were comparable to those for GERD maintenance studies (NDA).

  - Modest changes seen in vital signs were variable and not dose-related. – approximately 1% to 2% of patients experienced systolic and diastolic hypertension in the Aciphex^{tm} and omeprazole groups in the GERD Extension Study.

  - (No BP or HR TEAVs were noted in the PL treated group.)

  - Bradycardia of less than 50 bpm was reported for one patient from the Aciphex^{tm} 20 mg group (1%) and for one patient from the omeprazole group (2%).

  Thus, very few potentially clinically significant changes were noted both for the Aciphex^{tm} and omeprazole-treated patients.

  - No apparent dose-related effect was evident in patients receiving Aciphex^{tm} Tx.

- Body weight appeared to increase slightly over time for all patients, regardless of Tx. Body weight appeared to increase over time in all Tx groups. The mean increase was 0.5, 1.0, 1.3, 1.3 pounds in omeprazole, Aciphex^{tm} 10 mg, Aciphex^{tm} 20mg , and PL treated group, respectively. Weight gain was observed also in the GERD Maintenance

Studies, and was likely related to improvement in the function of the g.i. system due to GERD Tx.

- Electrocardiographic results were generated per Dr. Hahne in Study A001-118 (bioequivalence trial).

  - All 36 subjects enrolled in that study had an EKG examination at the time of Screening.

  - Because subjects were very physically active healthy young men with a low resting HR, sinus bradycardia was reported for PRs less than 50 bpm rather than 60 bpm as usual.

  - At screening, the following minor abnormalities were noted: two subjects (002 and 003) had right axis deviation; one subject (005) had left axis deviation; two subjects (002 and 035) had incomplete RBBB and two subjects (005 and 028) had sinus bradycardia. None of these minor abnormalities was considered by the PI to be clinically significant.

- All End of Study EKGs were normal except for the 5 subjects who also displayed non-clinically significant abnormalities at Screening.

- Three End of Study EKGs (subject 19, 27, and 32) contained computer-generated errors in QTc interval measurement (prolonged QTc interval). Re-measurement of the EKG tracings by a cardiologist revealed QTc intervals WNR for these subjects.

XIII. Drug-Demographic Interactions

A summary of the incidence of TESS and clinical laboratory TEAVs by age, gender, and race in the GERD Extension Controlled Clinical Studies in North America and Europe was presented in this section. A summary of TESS and clinical laboratory TEAVs was not conducted for the stand alone studies (A001-501, A001-118 and E003-311).

- No clinically meaningful differences were noted between Tx groups with respect to the incidence of specific TESS both in the GERD Extension and the GERD Maintenance Studies.

- No dose effect was observed when TESS were analyzed by gender.

XIV. Listing Labeling Modification of Adverse Events

In this last section of the SU, the sponsor suggested modifications to the Adverse Reactions section of the proposed product labeling submitted in NDA 20-973. The suggested modifications have been made for a number of sound reasons and the specific criteria to do this was discussed in a teleconference between Eisai, Inc. and the MTL on

October 4, 1998. The proposed revised US labeling, including a "strike-through" version which specifically detailed all deletions and additions, was appended to the SU report (Ref. Sponsor's Volume 4, Appendix 4, p. 19). It is worth noting that no additional AE information was added to the proposed labeling since the filing of the NDA.

A meticulous review of the proposed modifications was carried out. This included a comparison of the new and previous version of the proposed product labeling. Examples of AEs and the specific reasons for their removal are given in Table 14. It is concluded that the sponsor's proposal is, in the main, acceptable.

Table 14
NDA 20-973 SU
Examples of AEs Listings to be Removed From the Draft Labeling Submitted in NDA 20-973

Reason For Removal	Examples of AEs

December 22, 1998

/S/

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

/S/ 12-22-98