- Prospective protocols from the three studies projected the following **4 week therapeutic gains for rabeprazole**:

  NRRC = 36% over placebo (81% RAB vs. 45% PBO, p<0.05); 100 patients randomized to RAB 20 mg, RAB 40 mg, and PBO.

  NRRL = None. *"Similarity"* was to be based on 95% confidence interval; 200 patients randomized to RAB and OME.

  NRRD = 10% over ranitidine, (93% RAB vs 83% RAN, p=0.05); 370 patients randomized to RAB 20 mg and RAN.

- My review of the **NRRC** pivotal multicenter trial, revealed that rabeprazole tablets given as a single 20 mg morning dose, are effective in healing duodenal ulcers **(4 Wk delta gain +40%; Rab=79% vs PBO=39%, p=0.001)**. Rabeprazole tablets were also significantly better than placebo tablets in improving abdominal pain, particularly nighttime duodenal ulcer pain. The small USA placebo multicenter trial, revealed that duodenal ulcer healing by rabeprazole treatment is not dose related and that it requires a continuous 4 week administration to achieve healing , i.e., after the first two weeks therapy, the proportion of DU patients healed by rabeprazole did not significantly differ from placebo.

- Trial **NRRL** revealed that DU healing by **20 mg rabeprazole** tablets is comparable to the DU healing achieved by **omeprazole 20 mg, At the Wk 4 endoscopy, 98% patients on rabeprazole healed, vs. 93% patients on omeprazole healed, (p=0.083, NS)**.

- According to the observations, in study NRRD, the sponsor's claim of superior rabeprazole efficacy over ranitidine in DU healing was not **substantiated** and was apparently skewed by one center (Inv. 10). In this center, all the 13 patients randomized to rabeprazole and all the 13 patients randomized to ranitidine were unhealed after 2 weeks of continuous therapy. Additional two weeks therapy reported a rather anomalous result, e.g., almost 100% healing in rabeprazole patients (12/13), but only just 54% healing among ranitidine patients. In the absence of knowledge of progression in ulcer size during rabeprazole treatment, the peculiar healing results reported by Inv 10 are extremely difficult to explain. Further, statistical comparison assessed by the statistician reviewer revealed significant treatment-by-center interaction. Exclusion of this 26 patients rendered the proportion of healing in the remaining 93% patients, 174 rabeprazole and 175 ranitidine, **not** significantly different **(corrected 4 Wk healing revealed delta=+8%, Rab=83% vs Ran=75%, p=0.071, NS)**.

- In the gastric acid hypersecretion and ZES cases, administration of rabeprazole in doses equal or greater than 60 mg/day improved symptomatology and induced peptic ulcer healing.

- Based on my review of the submitted data, **I conclude that rabeprazole is safe and effective in the treatment of active duodenal ulcer disease, gastric acid hypersecretory states and ZES.**

iii. Reviewer Recommendations.

1. Approve the use of rabeprazole for the treatment of active duodenal ulcer

2. For the treatment of active DU, rabeprazole tablets should be continuously administered in a single 20 mg tablet, after the morning breakfast, for a period not shorter than 4 weeks.

3. The sponsor should correct the table submitted on **Page 6, Vol. 1,** proposed labeling section, by excluding the Wk 2 and Wk 4 healing reported by Inv 10. The corrected efficacy analysis of duodenal healing should include appropriate adjustment of statistical significance.

4. Approve the use of rabeprazole tablets, in doses of 60 mg or higher, for the treatment of gastric acid hypersecretion and ZES.

/S/

Robert Prizont, M.D.

cc:
NDA 20-973
HFD-180
HFD-180/LTalarico /S/ 12-15-98
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-180/JSenior
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 12/7/98 jgw
N/20973812.0RP

Concur. December 14, 1998

/S/

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 1

NRRD. Investigator 10

OBS	CTPATNO	INV	DRUGSORT	HEAL2	HEAL3
1	5064	10			
2	5065	10			
3	5066	10			
4	5067	10			
5	5068	10			
6	5069	10			
7	5070	10			
8	5449	10			
9	5450	10			
10	5451	10			
11	5452	10			
12	5453	10			
13	5454	10			
14	5455	10			
15	5456	10			
16	5497	10			
17	5498	10			
18	5500	10			
19	5529	10			
20	5530	10			
21	5531	10			
22	5532	10			
23	5533	10			
24	5534	10			
25	5535	10			
26	5536	10			

APPENDIX 2

NRRD. Study Protocol, Sample Size Section

3.4.3. Sample Size

The study will consist of approximately 370 qualified patients randomly allocated into two treatment groups. This sample size will provide at least 80% power to detect a signficant difference between LY307640 and ranitidine, assuming 4-week healing response rates of 93% for LY307640 and 83% for ranitidine. The duodenal ulcer healing rates were based on an unpublished meta-analysis of clinical trials comparing omeprazole and ranitidine. The sample size was computed using the approximation in Casagrande et al [1] assuming a two-sided hypothesis test performed at the 5% significance level.

CSO/Strongin

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S NEW DRUG APPLICATION (NDA) REVIEW

NDA:	20-973
SPONSOR:	Eisai Inc., Glenpointe Centre West 500 Frank W. Burr Boulevard, Teaneck NJ 07666
DATE OF SUBMISSION: DATE OF RECEIPT:	31 March 1998 1 April 1998
DRUG:	Rabeprazole sodium (ACIPHEX™) tablets, 10 and 20 mg
ROUTE OF ADMINISTRATION:	Oral, 20 mg daily in morning for up to 8 weeks (healing), or 1 year (maintenance of healing)
INDICATIONS:	Healing of esophageal erosions/ulcerations associated with gastroesophageal reflux disease (GERD), and maintenance of healing of erosive esophagitis
MATERIAL REVIEWED:	Application, 60 of 283 volumes; and reports by clinical pharmacology and chemistry; proposed labeling; pertinent other information and references.
REVIEWER:	John R. Senior, M.D./ 30 November 1998

NOV 3 0 1998

Brief Overall Review Summary

Eisai, Inc., has requested approval of its delayed-release tablet formulation of rabeprazole (ACIPHEX™) 20 mg for daily morning use for up to 8 weeks for healing of esophageal erosions/ulcerations and resolution of associated symptoms in patients with GERD, and for long-term daily use in the same dosage for maintenance of healing of such lesions. In support of this request, the sponsor has submitted data from six clinical trials. For healing and acute symptoms, two studies in North America addressed rabeprazole dose-ranging (10, 20, and 40 mg/day) compared to placebo, in 103 patients, and rabeprazole 20 mg/day versus ranitidine 150 mg q.i.d. for 4 and 8 weeks; in 338 patients. Results showed rabeprazole 20 mg/day to be significantly superior to either placebo or ranitidine for healing. Two subsequent studies for one year were done in North America with 209 and 288 patients, showing superiority of 20 mg or 10 mg/day of rabeprazole to placebo in reducing recurrences of erosive esophagitis. Safety was similar to that of the control groups in these studies. European studies of healing and maintenance were also done to compare rabeprazole and omeprazole 20 mg/day. Approval of rabeprazole 20 mg/day for the healing and maintenance of healing indications is recommended, but equivalence to omeprazole and optimal dose determination for rabeprazole need further investigation.

MEDICAL REVIEW OF NDA 20-973, RABEPRAZOLE FOR TREATMENT OF EROSIVE ESOPHAGITIS

TABLE OF CONTENTS

I. Introduction

This review is part of a larger medical review that includes consideration of the use of rabeprazole for other indications, including healing of acute duodenal and gastric ulcers (reviewed by Drs. R. Prizont and H. Gallo-Torres, respectively). The focus of this review is on evaluation of clinical data submitted in support of the sponsor's request for approval of indications for:

1) healing of esophageal erosions or ulcerations associated with gastroesophageal reflux disease (GERD) and symptoms of heartburn that may accompany those lesions; and
2) maintenance of healing of such lesions and symptoms.

A. Approach to the review document and conventions used

This document is intended primarily as scientific support for regulatory recommendations made on the basis of careful consideration of the clinical data provided, with background reference to chemical, pharmacologic, and statistical information supplied. Is also written as a archival reference document to summarize information on the new drug and the disorders for which it was investigated. The reviewer has approached this submission first by focusing upon what the sponsor has requested, and what evidence has been submitted in support of that request. The overall structure for the review includes an introduction with a very brief mention of the drug, the sponsor, and diseases for which it was investigated, dates of submission and review, and materials reviewed. Immediately following the title page is a boxed, concise, half-page summary of the review, to provide the reader with a picture of the purpose, context, issues, major findings and conclusions, evaluation and regulatory recommendations. The organization of the review and a road map to its sections in a Table of Contents follows on the second page, and that is immediately followed by this explanation of the process used to approach the information in 60 of the 283 volumes submitted. Ancillary submissions and reviews previously reported also have been considered. Typeface conventions used to distinguish the source of the text were:

Material summarized by the reviewer from that submitted by the sponsor is shown in plain 12-point Times New Roman font, with references to the submitted Volume and page numbers;

Text taken directly from that submitted by the sponsor is shown in quotations, and tables or figures copied from the submitted material were noted "As submitted in Volume__, page___.";

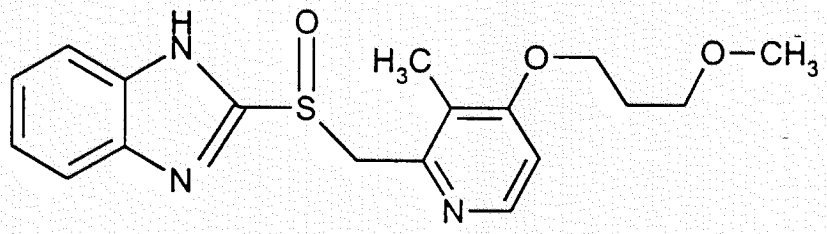
Material provided by the reviewer in explanation of the approach taken to review, or taken from other sources, whether pertinent literature or other regulatory material, is shown in 11-point font;

Commentary, opinion, discussion by the reviewer about the submitted material or about the literature or other sources (cited, wherever possible) is shown in 12-point italic font.

Sections of the review were numbered and paginated as shown in the Table of Contents, which corresponded in general with the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application," published in July 1988 by the Center for Drug Evaluation and Research of the Food and Drug Administration.

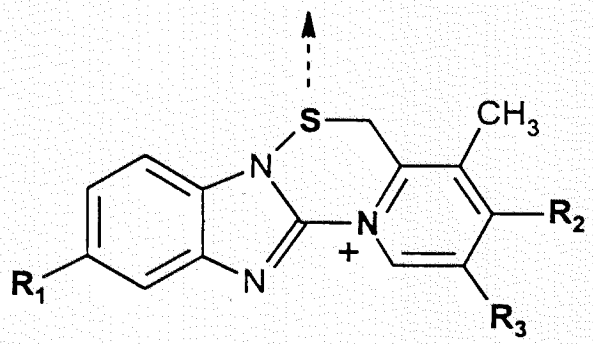
B. Description of the drug and formulation

Rabeprazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, $C_{18}H_{21}N_3O_3S$, molecular weight 359.45, was patented in 1988 by Souda, et al., to Eisai Company. It was developed as another in the series of gastric mucosal oxyntic cell inhibitors of the K^+,H^+-ATPase enzyme system for secretion of strong concentrations of HCl into the gastric lumen (also known widely as "proton-pump inhibitors", or PPIs).



rabeprazole

It is similar in structure to the approved PPIs omeprazole and lansoprazole, and to pantoprazole, all of which contain the same central structure that rearranges and cyclizes in acidic environment to form an active sulfenamide derivative that reacts with key cysteine residue 813 of the extracytoplasmic loop of the transmembrane enzyme system (Bensancon, *et al.*, 1997). The PPIs are unstable in acidic environment, and exert their pharmacologic effect after absorption, delivery to the oxyntic cells via the blood circulation, and are activated by protonation of the pyridinyl-N in the acidic milieu of the secretory canaliculus of the active parietal (oxyntic) cells or in the acid-transporting, gastric-derived vesicles of those cells. The neutral PPIs can pass through the oxyntic cell membrane into the extracellular, vesicular space, but there they are protonated and cannot be reabsorbed, hence the protonated form is concentrated. The active core of the PPIs then rearranges and cyclizes to the cationic sulfenamide (Lindberg, *et al.*, 1986; Senn-Bilfinger, *et al.*, 1987) that reacts with the thiol group of the enzyme cysteine-813 to form a stable disulfide (Bensancon, *et al.*, 1997) that inhibits the proton-pumping activity.



...the reactive sulfenamide of proton-pump inhibitors in acidic milieu

When the sulfenamide reacts with the enzyme Cys-813, the N-S bond of the newly cyclized ring is broken and the new S-S disulfide bond between the enzyme and the PPI is stable. The four PPIs mentioned above differ only in the side chains $\mathbf{R_1}$, $\mathbf{R_2}$, and $\mathbf{R_3}$, but these do have influence on the stability and reactivity of the compounds. This may be of interest when the biological and clinical activities of the compounds are compared. All four of the PPIs have in common the central benzimidazole-sulfinyl-methyl-(3-methyl-pyridine moiety, but they differ in their side chains as follows:

compound	*company*	*patented*	R_1	R_2	R_3
omeprazole	Hässle/Astra	1979	$-OCH_3$	$-OCH_3$	$-CH_3$
lansoprazole	Takeda/TAP	1986	-H	$-OCH_2CF_3$	-H
pantoprazole	Byk-Gulden	1986	$-OCHF_2$	$-OCH_3$	-H
rabeprazole	Eisai	1988	-H	$-OCH_2CH_2CH_2OCH_3$	-H

These structural differences have biologic consequences, and the compounds differ in their metabolism and physiological disposition after absorption. They differ also in their rates of activation to the reactive sulfemamide, and in rates of inhibition of the gastric K^+,H^+-ATPase enzyme (data from Bensancon, *et al.*, 1997; Kromer, *et al.*, 1998)

	half-time,	*seconds*	*neutral*	*half-time*
compound	*activation*	*inhibition*	*stability*	*plasma, minutes*
omeprazole	168	390	intermediate	75
lansoprazole	120	400	intermediate	84-162
pantoprazole	276	1128	most	74
rabeprazole	78	90	least	89

Rabeprazole sodium is a white-to-slightly yellowish white amorphous solid that is very soluble in water and methanol, freely soluble in acetone, ethyl acetate, and dichloromethane, but practically insoluble in hexane and toluene.

The drug product to be marketed if approved is to be made by Eisai at its plant in and may be packaged and labeled for distribution at sites in the United States (see chemistry review for details and other information on manufacturing, quality controls, stability, etc.). It is reported (Volume 1, page 137, paragraph 4.2.9.2) that two formulations of the rabeprazole sodium 20 mg tablets were used in the North American and European clinical studies, but the difference was a minor change in grade for the diacetylated monoglycerides used as plasticizers in the enteric coating. Three formulations of the 10-mg tablets were used in the course of the clinical pharmacology and controlled clinical studies. A bioequivalence study is reported to be planned. The sponsor, as stated in the proposed labeling (see Volume 1, page 62), intends to

make available light yellow 20-mg tablets imprinted E243, and pink 10-mg tablets imprinted E241; both tablets are enteric-coated for delayed release of the active rabeprazole sodium for absorption from the small intestine. The composition of the tablets is given as (ibid., page 133):

Ingredient	
[redacted]	
rabeprazole sodium	
mannitol	
magnesium oxide	
low-substituted hydroxypropyl cellulose	
hydroxypropyl cellulose	
magnesium stearate	
[redacted]	
[redacted]	
ethyl cellulose	
[redacted]	
[redacted]	
hydroxypropyl methyl cellulose phthalate	
diacetylated monoglycerides	
talc	
titanium dioxide	
ferric oxide (yellow)	
[redacted]	
Carnauba wax	
[redacted]	
[redacted]	
[redacted] total tablet weight	

The rabeprazole formulations used in the clinical studies whose results are here submitted for review and evaluation for possible approval will be indicated in the summary of each study as will follow below.

B. Background of previous INDs and NDAs for rabeprazole

Rabeprazole was first investigated in humans in July 1988, in a rising-dose tolerance study conducted [redacted] (E3810-J081-001), using single doses from 1 to 80 mg. This was followed by a multiple-dose-tolerance study by [redacted] (E3810-J081-002) of 20 and 40 mg in a crossover design. A full Japanese clinical development program followed (as stated in Volume 1, page 212, paragraph 7.2.4).

Eisai America, Inc (EAI) submitted IND [redacted] on 16 November 1989, and conducted four Phase I clinical studies (E3810-A001-001, and -002, -003, -004). Sponsorship of IND [redacted] was transferred to [redacted] on 15 April 1993, under whose sponsorship the clinical studies for duodenal and gastric ulcer healing, and for healing and maintenance of healing of erosive esophagitis associated with GERD were carried out in North America and Europe. After those studies were done, the IND was transferred from [redacted] Eisai Corporation North America (ECA) on 21 December 1995, and then on 31 March 1997 to Eisai, Inc. (ESI), a subsidiary of ECA. The NDA is being submitted by ESI.

Comment: This somewhat confusing history of changing sponsorship has to be borne in mind in reviewing the data submitted [redacted] contracted with [redacted] a contract research organization, for the design, execution, and reporting of the principal clinical studies upon which the requests for approval are based. With respect to this portion of the medical review, dealing with healing and maintenance of healing of erosive esophagitis associated with GERD, studies NRRI, NRRJ, NRRP, NRRK-odd, NRRK-even, and NRRQ were actually [redacted] studies. The NDA 20-973 submission is being made by ESI, with [redacted] as its contract research organization. It is not entirely clear exactly who did what in preparing the submission.

We have received reports of the six clinical studies concerning the healing of and maintenance of healing of erosive esophagitis. These include:

1) *the North American dose-ranging study (NRRI) of 0, 10, 20, and 40 mg rabeprazole for 4 or 8 weeks for healing acute erosive lesions [November 1993-March 1994];*
2) *the North American comparison (NRRJ) of 20 mg rabeprazole daily or ranitidine 150 mg q.i.d. for 4 or 8 weeks for healing acute erosive lesions [February-September 1995];*
3) *the European comparison (NRRP) of rabeprazole 20 mg or omeprazole 20 mg daily for 4 or 8 weeks for healing acute erosive lesions [April 1995-**March 1996**];*
4) *the two North American maintenance studies (NRRK-odd, NRRK-even) of 10 or 20 mg daily of rabeprazole or placebo for prevention of relapse of erosive esophagitis [February 1995 – **October 1996**];*
5) *the European comparison (NRRQ) of rabeprazole 20 mg or omeprazole 20 mg daily for prevention of relapse of erosive esophagitis [May 1995-**May 1997**].*

All of these studies appear to have been carried out by [redacted] acting under contract to [redacted] The European healing study (NRRP) and all three of the maintenance studies were still underway when the IND was transferred back to Eisai [redacted] on 21 December 1995. Who did the analyses and reports? [redacted] Eisai?

D. Requested labeling for erosive esophagitis healing and maintenance

Eisai is requesting approval of indications both for healing of the erosions/ulcerations of erosive esophagitis associated with GERD within 8 weeks and for maintenance of healing of those lesions, using a recommended daily dose of 20 mg each morning. The language requested is:

"**INDICATIONS AND USAGE**

"**Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)**
ACIPHEX™ is indicated for up to eight weeks treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD).

"**Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease GERD)**
ACIPHEX™ is indicated for maintaining healing in patients with erosive or ulcerative gastroesophageal reflux disease (GERD maintenance)."

"**DOSAGE AND ADMINISTRATION**

"**Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)**
The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily for up to eight weeks. (See INDICATIONS AND USAGE).

"**Long-term Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD Maintenance)**
The recommended adult oral dose is one ACIPHEX™ 20 mg delayed-release tablet to be taken once daily. ACIPHEX™ 10 mg tablet taken once daily has been demonstrated to be effective versus placebo in the maintenance of healing of GERD. (See INDICATIONS AND USAGE)."

In support of these indications and dose recommendations, the sponsor wishes to include in the labeling a page-and-a-half (Volume 1, pages 54-5) of abbreviated, partial results of their clinical studies NRRI, NRRJ, NRRP, and combined NRRK-odd and NRRK-even.

Comment: Not mentioned are the North American dose-ranging results for 10 and 40 mg of rabeprazole (Study NRRI), or the European year-long comparison of rabeprazole 20 mg and omeprazole 20 mg daily on reducing the recurrence rate (Study Q), will be discussed below.

E. Marketing of rabeprazole

Rabeprazole was approved in Japan on 14 October 1997 and was first marketed there under the name "Pariet™" on 12 December 1997 (see Volume 1, page 128). The drug has not yet been approved or marketed elsewhere in the world, although other applications are pending review (in the U.K *(Volume 1, page 212, end of second paragraph in section 7.2.4)*.

II. Controlled Clinical Studies for Healing Erosive Esophagitis

Three studies have been done and reports submitted for the healing indication, and three for the maintenance indication. They included both placebo (NRRI and NRRK) and active drugs (NRRJ, NRRP, NRRQ) as the control groups

Study	*Where Done*	*Start*	*Finish*	*Treatments*	*Weeks*	*Pts*	*Invs*
Healing							
NRR**I**	North America	Nov '93	Mar '94	P; R 10,20,40	4 or 8	103	20
NRR**J**	North America	Feb '95	Sep '95	R 20; r 150 q	4 or 8	338	63
NRR**P**	Europe	Apr '95	Mar '96	R 20; O 20	4 or 8	202	27
Maintenance							
NRR**K-odd**	North America	Feb '95	Oct '96	P; R 10, 20	52	203	27
NRR**K-even**	North America	Feb '95	Oct '96	P; R 10, 20	52	293	24
NRR**Q**	Europe	May '95	May '97	R 20; O 20	52	243	21

Note: Treatments: P, placebo; R 10, rabeprazole 10 mg/day; R 20, rabeprazole 20 mg/day; R 40, rabeprazole 40 mg/day; O 20, omeprazole 20 mg/day; r 150 q, ranitidine 150 mg four times/day.
Pts, number of patients randomized; Invs, number of investigators participating.

The three healing studies had the same basic design, and the three protocols are almost identical. Each called for recruiting patients with at least 3 months of GERD symptoms, determining by endoscopy specified in the protocol to be done and evaluated by a gastroenterologist. All of the studies used a standardized grading scale for the esophageal lesions, a modified Hetzel-Dent scale.

Grade 0 = normal mucosa, no abnormalities noted; or
Grade 1 = no macroscopic erosions, but presence of erythema, hyperemia, and/or friability of the esophageal mucosa; or
Grade 2 = superficial ulceration or erosions involving less than 10% of the mucosal ; surface of the last 5 cm of esophageal squamous mucosa; or
Grade 3 = superficial ulceration or erosions involving of greater than or equal to 10% but less than 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa; or
Grade 4 = deep ulceration anywhere in the esophagus or confluent erosion of more than 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Grade 5 = stricture, as defined by a narrowing of the esophagus that does not allow easy passage of the endoscope without dilatation (patient must be discontinued).

Patients with grade 5 strictures were not eligible, nor were those with no actual erosions/ulcerations (grades 0 or 1). Healed was assessed at endoscopy at approximately 4 weeks, and if not healed to grade 0 or 1, then again at 8 weeks on study medication. A number of secondary measures of efficacy were also used in each of the three studies, including frequency of heartburn, severity of day and night heartburn, overall well-being, doses of antacids needed per day. It was not required in the protocols to record patients endoscoped but rejected for study.

A. Dose-ranging Study NRRI (November 1993-March 1994)

Study H4M-MC-NRRI, entitled "[redacted]307640 Versus Placebo: Dose-Response Study in Patients with Erosive or Ulcerative Gastroesophageal Reflux Disease" was planned in July 1993 by [redacted] for conduct by [redacted] (It is also referred to in this application as Study E3810-L001-203 by Eisai Inc. For brevity it will be referred to as "Study I" in this section of the medical review of this NDA 20-973.) The protocol *(Volume 176, pages 109-35)* called for enrollment of approximately 100 adults with erosive GERD of at least 3 months' duration and of severity/extent of grade 2 to 4.

The study size was based on an assumption that no more than 28 % of patients randomized to placebo would show healing to grade 0 or 1 after 8 weeks of treatment, and that at least 71% of patients randomized to rabeprazole ([redacted]307640/E3810) would show healing at that time. The healing rate on placebo was based on data from trials of nizatidine that were on file [redacted] It was estimated that 25 patients per study arm would provide 80% power to detect a significant difference between placebo and rabeprazole-treated groups, using the Casagrande et al. (1978) formula. Since it was planned to study rabeprazole doses of 10, 20 and 40 mg/day, they estimated that 100 patients would be needed.

Patients with Barrett's changes but not strictures were acceptable, but patients with primary esophageal motility disorder, previous gastric/esophageal surgical procedures, varices or pyloric stenosis were excluded. Patients were not allowed to have been treated with any PPI or H2-blocker, prostaglandin, sucralfate, within 2 weeks, or with corticosteroids, NSAIDs, anticoagulants, motility agents (metoclopramide, cisapride), anticholinergics, antidepressants, anti neoplastic agents concurrently. Patients were excluded also if they had active peptic ulcers or gastrointestinal bleeding, Zollinger-Ellison syndrome, or clinically significant renal, hepatic, cardiopulmonary, neoplastic, or other disease or drug abuse. They were advised to avoid foods that they knew exacerbated symptoms, and to limit intake of caffeine, alcohol, and tobacco.

If qualified and consenting, patients were randomized to receive sets of three tablets per day, containing 10 mg of [redacted]307640 or placebo, 20 mg of [redacted]307640 or placebo, 20 mg of [redacted]307640 or placebo, so that they would be receiving blindly either 10, 20, or 40 mg of rabeprazole or placebo , taken each morning with water for 4 or 8 weeks. Mylanta® antacid tablets were also dispensed for symptomatic relief if needed, the use to be recorded. After the screening endoscopy the patients were scheduled to return at 4 weeks (28±3 days) and, if not healed to grade 0 or 1, at 8 weeks (56±3 days) after starting blinded medication. The primary measure of treatment success was to be healing of the esophagitis to grade 0 or 1 by endoscopy. Disposition of patients healed at 4 weeks was not stated, but results were to be interpreted as showing healing at 8 weeks also.

Secondary measures of effectiveness of treatment were to be graded, on daily diaries for the first week of blinded treatment and by the investigators at each visit for the previous day *(Case Report Form, Volume 176, page 314-35)*. Frequency, daytime and nighttime severity of heartburn, and overall well-being, were to be noted, as listed in paragraph 3.9.1.2. in the protocol *(Volume 176, pages 120-1)*. Scales used for rating secondary measures were as follows: