U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	204-736
Drug Name:	ACIPHEX® (rabeprazole sodium) delayed-release sprinkle capsules (b) (4) 5.0 mg
Indication(s):	Treatment of gastroesophageal reflux disease (GERD) in pediatric patients 1 to 11 years of age
Applicant:	Eisai Inc.
Date(s):	Stamp Date: 9/27/2012 PDUFA Date: 3/27/2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 3
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Keywords:

Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

The sponsor is seeking approval of AcipHex® Delayed-Release Sprinkle Capsules for (b) (4) subjects 1 to 11 years. One study was conducted to support this indication. However, the study did not include a placebo control group and was not designed to test any formal statistical hypotheses. Hence, no statistical inference should be concluded, and only descriptive summary statistics should be presented in the labeling.

2 INTRODUCTION

2.1 Overview

Gastroesophageal reflux disease (GERD) is a common physiological event occurring in children, and characterized by increased exposure of the esophageal mucosa to the gastroduodenal contents, which are usually acidic and result in chronic symptoms. In older children, the pathogenesis and clinical presentation of GERD resemble those in adults. Antacids, H_2-receptor blockers, and several proton pump inhibitors (PPIs) have been approved for the treatment of GERD in adolescents. For PPIs, drug effects in children no less than one year of age are generally similar to those seen in adults in terms of the mode of action, absorption, elimination, and inhibition of acid production.

Rabeprazole sodium (referred to as rabeprazole), the active pharmaceutical ingredient in AcipHex®, is an inhibitor of the proton pump responsible for the terminal step in gastric acid secretion. Rabeprazole is classified as a gastric PPI and is currently marketed globally under the trade names AcipHex® and Pariet® as enteric-coated (EC) 10 mg and 20 mg rabeprazole tablets.

In the US, rabeprazole is available as 20 mg AcipHex® Delayed-Released Tablets and is indicated for short-term treatment in adults of erosive or ulcerative GERD; symptomatic GERD; maintenance of healing in subjects with GERD; healing and symptomatic relief of duodenal ulcers; long-term treatment of pathological hyper-secretory conditions including Zollinger-Ellison syndrome; and eradication of *Helicobactor pylori* in combination with amoxicillin and clarithromycin. AcipHex® 20 mg Delayed-Release Tablets are also indicated for short-term treatment of symptomatic GERD in adolescents 12 years and above.

The rabeprazole pediatric development program was initiated as a result of US FDA phase 4 commitments issued in conjunction with the approvals of AcipHex® Delayed-Release Tablets for the treatment of erosive GERD (original NDA, approved August 19, 1999), symptomatic GERD (S-009, approved February 12, 2002) and *Helicobactor pylori* (S-013, approved November 8, 2002) in adults. The Written Request (WR) for pediatric studies for rabeprazole was originally issued on December 31, 2001, and reissued in its final amended form (Amendment #7) on September 14, 2012. Written Request Study 4 (adolescents) which included studies E3810-

A001-119 and E3810-A001-202 was submitted as NDA 20973 S-002 on December 27, 2007, and approved on June 30, 2008. This submission is intended to meet the erosive and symptomatic GERD phase 4 commitments, as well as satisfy WR Amendment #7 requirements for neonates (WR Study 1), children aged 1 to 11 months (WR Study 2), and children aged 1 to 11 years (WR Study 3).

To investigate the use of rabeprazole in pediatric subjects aged 11 years or less, the sponsor developed a Delayed-Release Sprinkle Capsule formulation. The clinical development program evaluating this formulation is comprised of Study RABGRD1005 (PK/PD) for neonates, Study RABGRD3004 for 1 to 11 months old, and Studies RABGRD1002 (PK/PD) and RABGRD3003 for 1 to 11 years old. Although new data for these three pediatric age groups are provided in this submission, the sponsor is only seeking approval for the age group of 1 to 11 years, specifically for the following proposed dosage regime:

- For children weighing less than 15 kg, 5 mg once daily (b) (4) (with an option to increase to 10 mg after clinical reassessment).
- For children weighing 15 kg or greater, 10 mg once daily (b) (4).

Two efficacy clinical studies (Studies RABGRD3004 and RABGRD3003) were submitted in this application. However, only the efficacy study pertinent to the new indication sought by the sponsor (i.e., Study RABGRD3003; Part 1 and Part 2) is evaluated within this review, particularly in Section 3.

Since Study RABGRD3004 failed to show efficacy of rabeprazole, this review only briefly discusses it here. Study RABGRD3004 was a randomized, placebo-controlled, parallel group withdrawal study that investigated the efficacy of rabeprazole in infants 1 to 11 months of age with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically- or histologically-proven GERD. That study was conducted in two parts: an open-label (OL) phase for up to three weeks and a five-week double-blind (DB) placebo-controlled withdrawal phase. Subjects who achieved a clinical response during the OL phase were eligible to enter the DB phase. In the OL period, all subjects received 10 mg rabeprazole once daily for at least one week and up to three weeks until clinical response was achieved or the subject failed to improve after three weeks of treatment. In the DB period, eligible subjects were randomized to rabeprazole 5 mg, 10 mg, or placebo in a 1:1:1 ratio. Results of the study did not demonstrate efficacy in infants 1 to 11 months of age. There was no difference in either of the two sets of co-primary efficacy endpoints (for FDA and EMA respectively) between the placebo group and the combined rabeprazole treatment group. These primary efficacy endpoints included evaluation of the frequency of regurgitation; the weight-for-age Z-score; symptomatic assessments incorporated in a weekly multiple symptom score (Infant Gastroesophageal Reflux Questionnaire-Revised [I-GERQ-R]); and a daily multiple symptom score (Infant Gastroesophageal Reflux Questionnaire-Daily Diary [I-GERQ-DD]). The results were consistent with the Gastrointestinal Drugs Advisory Committee (GIDAC)'s decision that PPIs are not efficacious for GERD in this age group made at the GIDAC meeting on November 5, 2010.

2.2 Data Sources

Study reports, tabulate datasets in SDTM format, analysis datasets in sponsor-defined format, and SAS programs, for this submission have been submitted in electronic Common Technical Document (eCTD) format to the EDR at: \\Cdsesub1\evsprod\NDA204736\0000.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The statistical analysis plan (SAP) was finalized shortly after the Study RABGRD3003 Part 1 completion and before the database lock. Main changes to the planned analyses in the SAP after the database lock were the identification of major protocol deviations for the per-protocol (PP) population, and the exclusion of Site 113 data reportedly due to its incompliance with study oversight. Tabulation datasets were submitted in SDTM format while analysis datasets were submitted in a sponsor-defined format, which was similar to the ADaM format. Define files were submitted in PDF format. Originally, datasets for Study RABGRD3003 were submitted as one set for both Part 1 and Part 2 of the study. An information request was sent soon after the filing decision for separating the study data into two parts. The sponsor quickly provided the requested datasets. It is possible to conduct all the statistical analyses needed with the datasets provided.

3.2 Evaluation of Efficacy

Study RABGRD3003 was a multi-center, double-blind, parallel-group study to evaluate short-term safety and efficacy and long-term maintenance of two dose levels of rabeprazole sodium delayed-release pediatric bead formulation in 1- to 11-year-old pediatric subjects with endoscopically proven GERD. The study consisted of two parts: a 12-week, randomized, parallel-group, double-blind safety and efficacy study (Part 1) followed by a 24-week, double-blind maintenance treatment phase (Part 2) conducted to meet the requirements of the WR and post-marketing study requirements for healing, maintenance (NDA 20973) and symptomatic GERD (NDA 20973 S-009) issued by the FDA, and Pediatric Investigation Plan (PIP) issued by the EMA. The primary objectives of this study were to evaluate the efficacy (endoscopic or histologic healing) and safety of two target dose levels (0.5 mg/kg [10 mg maximum dose] and 1.0 mg/kg [20 mg maximum dose]) of a pediatric micro-bead formulation of rabeprazole sodium in a 12-week, parallel-group, double-blind design followed by a long-term safety and efficacy assessment in a 24-week, double-blind, maintenance treatment phase in subjects, 1 to 11 years of age, with endoscopically proven GERD.

The 12-week, double-blind treatment phase (Part 1) initiated on January 30, 2009 and ended on August 19, 2010. Subjects were enrolled at 41 sites in the US, Belgium, Denmark, France, Italy, Poland, Israel, South Africa, and India. Part 1 consisted of a 21-day screening period and a 12-week, double-blind treatment period. End-of-study or early-withdrawal assessments were performed for each subject at the end of the 12-week double-blind treatment phase or upon early

withdrawal from the 12-week double-blind treatment phase. The parent or caregiver used an electronic handheld device to complete a daily diary and recorded the presence and severity of pre-specified GERD symptoms and the frequency and amount of antacid use. Each subject was expected to attend five scheduled office visits (screening, baseline, and Weeks 4, 8, and 12) and complete two telephone visits.

The diagnosis of GERD was established on the basis of clinical signs and symptoms and the presence of erosive or non-erosive GERD confirmed by endoscopy and histology (biopsy) during the screening period. Esophagogastroduodenoscopy (EGD) (with biopsy) was performed locally and graded based on both histologic and macroscopic esophageal mucosal appearance using standard scoring methods (Hetzel-Dent scoring system). Subjects had to have a positive EGD with a Hetzel-Dent classification, grade no less than 1 and Histological Features of Reflux Esophagitis scale, grade greater than 0, to be eligible for the study. If the subject was currently taking GERD therapy, the GERD therapy was discontinued before its entry into the study, and therapy with a PPI or H_2-antagonist had to be discontinued for at least three days before the start of treatment with study drug.

During the 12-week double-blind treatment phase, subjects were randomized in a double-blind manner to receive a target dose of either 0.5 mg/kg or 1.0 mg/kg. No placebo control arm was included in this study. The actual dose given was dependent of the subject's body weight. The dosing was further broken down by body weight:

- For subjects weighing 6.0 to 14.9 kg, the actual dose administered was:
    - Low-dose group: 5 mg (0.5 mg/kg target dose)
    - High-dose group: 10 mg (1.0 mg/kg target dose)
- For subjects weighing 15.0 kg or more, the actual dose administered was:
    - Low-dose group: 10 mg (0.5 mg/kg target dose)
    - High-dose group: 20 mg (1.0 mg/kg target dose)

In addition to the study drug, subjects were permitted to take antacids as rescue medication. Antacids were not permitted to be administered within two hours before or after study drug administration.

A subject was considered to have completed the first portion of the study if the subject completed all study treatment (per the protocol: the subject received 75% or more of the study drug for 12 weeks) and completed assessments at Weeks 12, including endoscopy. Subjects who had achieved healing (Grade 0 on the Hetzel-Dent classification or Grade 0 on the Histological Features of Reflux Esophagitis scale) by the end of Part 1 had the option to continue in Part 2, the 24-week double-blind maintenance treatment phase of the study. Subjects in Part 2 continued the same dose taken in Part 1.

Part 2 of the study started on April 21, 2009 and ended on January 25, 2011. Subjects were enrolled at 30 sites in the US, Belgium, Denmark, Italy, Poland, Israel, South Africa, and India. Baseline for the maintenance treatment phase coincided with the end-of-study visit for the 12-week treatment phase in Part 1. Subjects whose endoscopy and histology (biopsy) results were available at the end of the 12-week treatment phase, enrolled into the maintenance treatment phase, and received the study drug up to Week 24 of Part 2, did not return for the end-of-study visit of Part 1. However, the subjects who did not receive endoscopy results at Week 12 were

called back for Week 13 (end-of-study) visit to decide on their continuation into maintenance treatment phase. If it was decided to continue the subject into the maintenance treatment phase (Part 2), the subject was assigned study drug up to Week 24 of Part 2. Subjects were expected to complete five scheduled office visits during the 24-week double-blind maintenance treatment phase of the study. At the final visit (Week 24 of Part 2) of the maintenance treatment phase or upon early withdrawal, end-of-study or early withdrawal assessments including EGD with gastric biopsy, were performed for each subject.

The primary efficacy endpoint for Part 1 was healing rate, or the percentage of subjects with healing, by Week 12 (end of 12-week double-blind treatment phase), where healing was defined as Grade 0 on the Hetzel-Dent classification or Grade 0 on the Histological Features of Reflux Esophagitis scale. Similarly, the primary efficacy endpoint for Part 2 was the healing rate by Week 36 (end of 24-week maintenance treatment phase). Summary statistics, such as healing rate estimates and 95% confidence interval (CI), were presented descriptively for each Part of the study separately, using sponsor-defined intent-to-treat (ITT) population (i.e., all subjects who entered the study and had at least one post baseline efficacy measurement). No formal hypotheses were planned to be tested in the study. Based on the recommendations from the FDA and EMA, a total sample size of 100 was determined to be appropriate to evaluate the efficacy and safety profile of two rabeprazole target doses.

Two hundred thirty-nine (239) subjects were screened for this study Part 1. Of these, 127 subjects were randomized, received at least one dose of study drug, and had at least one post-baseline efficacy measurement. One hundred eight (85%) subjects completed the study and 19 (15%) subjects withdrew before study completion. Of the 127 subjects enrolled in Part 1, 74 (58%) were from the USA, and 53 (42%) were non-USA. Overall, similar numbers of subjects were randomized to each target treatment group, with 65 (51%) and 62 (49%) subjects in the lower and higher target dose of rabeprazole group, respectively. The 127 pediatric subjects had a mean age of 5.7 years (range: 1 to 11 years). The majority of subjects in the study were white (99 [78%] of 127 subjects), 13 (10%) were black, 3 (2%) were Asian, and 12 (9%) were classified as “other”. Of the 127 subjects enrolled, 69 (54%) subjects were in the 1- to 5-year-old age group and 58 (46%) subjects were in the 6- to 11-year-old age group.

Of the 65 subjects randomized to the low target dose group, 21 subjects received an actual dose of 5 mg in the low-weight cohort, while 44 subjects received an actual dose of 10 mg in the high-weight cohort. Of the 62 subjects randomized to the higher target dose group, 19 subjects received an actual dose of 10 mg in the low-weight cohort and 43 subjects received an actual dose of 20 mg in the high-weight cohort. Pediatric subjects in the older age group (6 to 11 years) were all above 15 kg and hence in the high-weight cohort. Overall, 42% of the pediatric subjects aged 1 to 5 years were above 15 kg.

Among the 87 subjects who achieved healing in Part 1, 64 subjects were enrolled into Part 2 of the study: 33 (52%) and 31 (48%) subjects in the lower and higher target dose group, respectively. Of these subjects, 50 (78%) subjects completed the study and 14 (22%) withdrew before study completion. The 64 subjects participated in Part 2 of the study had a mean age of 6.0 years (range: 1 to 11 years, inclusive). The majority (51 [80%]) subjects in the study were

white. Of these subjects, 32 (50%) subjects were in the 1- to 5-year-old age group and the remaining 32 (50%) subjects were in the 6- to 11-year-old age group.

The descriptive results for both Part 1 and Part 2 of the study are presented in the table below. A large portion of ITT subjects (81%) achieved healing during the 12-week double-blind treatment phase. Of the 64 subjects enrolled in Part 2, 52 were included in ITT population and 47 (90%) subjects maintained healing during the 24-week double-blind maintenance treatment phase.

Table: Endoscopic/Histologic Healing Rates (ITT population)

		Rabeprazole Sodium Treatment Group				
		Low Weight Cohort		High Weight Cohort		Total
Target Dose		0.5 mg/kg	1.0 mg/kg	0.5 mg/kg	1.0 mg/kg	
Actual Dose		5 mg	10 mg	10 mg	20 mg	
Week 12 (Part 1)	N	17	16	38	37	108
	n (%)	14 (82)	15 (94)	29 (76)	29 (78)	87 (81)
	95% CI[a]	(0.57, 0.96)	(0.70, 1.00)	(0.60, 0.89)	(0.62, 0.90)	(0.72, 0.88)
Week 24 (Part 2)	N	8	6	18	20	52
	n (%)	8 (100)	6 (100)	16 (89)	17 (85)	47 (90)
	95% CI[a]	(0.63, 1.00)	(0.54, 1.00)	(0.65, 0.99)	(0.62, 0.97)	(0.79, 0.97)

CI: Confidence Interval
[a]: Exact CI
Source: Reviewer's table (results concurred with the sponsor's)

4 SUMMARY AND CONCLUSIONS

The efficacy study (Study RABGRD3003) designed to support the GERD treatment indication for pediatric subjects of 1 to 11 years old did not include a placebo control group, but only two dose groups of rabeprazole sodium. Furthermore, no formal hypothesis was specified to be tested. All results can be considered descriptive only. Medical officers will judge efficacy based on clinical judgment and historical knowledge of these patient groups.

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/s/

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03/13/2013

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03/13/2013