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RESEARCH**

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)



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 2.5 and 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:
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Table of Contents

1	EXECUTIVE SUMMARY	3
2	INTRODUCTION	3
2.1	OVERVIEW.....	3
2.2	DATA SOURCES	5
3	STATISTICAL EVALUATION	5
3.1	DATA AND ANALYSIS QUALITY.....	5
3.2	EVALUATION OF EFFICACY.....	5
4	SUMMARY AND CONCLUSIONS	8

1 EXECUTIVE SUMMARY

The sponsor is seeking approval of AcipHex[®] Delayed-Release Sprinkle Capsules for the healing, maintenance of healing, and symptom improvement of GERD in 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, H₂-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 *Helicobacter 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 *Helicobacter 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: <\\Cdsub1\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 H₂-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				Total
		Low Weight Cohort		High Weight Cohort		
Target Dose	Actual Dose	0.5 mg/kg	1.0 mg/kg	0.5 mg/kg	1.0 mg/kg	
		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/

FREDA COONER
03/13/2013

MICHAEL E WELCH
03/13/2013

STATISTICS FILING REVIEW

NDA Number: 204736 **Applicant: Eisai Inc.** **Stamp Date: September 27, 2012**

Drug Name: Rabeprazole sodium NDA Type: 505(b)(1) Indication: Healing and maintenance of delayed release sprinkle capsule Original NDA GERD in 1-11 years pediatric patients

On **initial** overview of the NDA application for RTF:

	Content Parameter for RTF	Yes	No	NA	Comments
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		X		None for gender or racial
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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Background

Eisai submits this NDA for AcipHex[®] (rabeprazole sodium) Delayed-Release Sprinkle Capsules to support an indication for healing and maintenance of healing of gastroesophageal reflux disease (GERD) and the improvement of GERD symptoms in children 1 to 11 years of age. In addition to the indication sought, this NDA also provides the final response to the Written Request (WR) for rabeprazole sodium, and is intended to satisfy Post-marketing Requirements 1 and 2 for AcipHex[®] Delayed-Release Tablets (NDA 20973).

Rabeprazole sodium (referred to as rabeprazole), the active pharmaceutical ingredient in AcipHex[®], is classified as a gastric proton pump inhibitor (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-Release 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 hypersecretory conditions including Zollinger-Ellison syndrome; and eradication of *Helicobacter 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. In the US, 10 mg Tablet is approved in adults but not currently marketed.

The rabeprazole pediatric development program was initiated as a result of 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 *Helicobacter pylori* (S-013, approved November 8, 2002) in adults. This submission is intended to meet the erosive and symptomatic GERD phase 4 commitments, as well as WR Amendment 7 requirements for neonates (WR Study 1; Study RABGRD1005), children aged 1 to 11 months (WR Study 2; Study RABGRD3004), and children aged 1 to 11 years (WR Study 3; Studies RABGRD1002 and RABGRD3003 [Part 1 and 2]). Written Request Study 4 (adolescents) which includes Studies E3810-A001-119 and E3810-A001-202 was submitted as NDA 20973 S-022 on December 27, 2007 and approved on June 30, 2008. Some results from these two studies are provided in this submission for comparison.

On November 5, 2010, a Gastrointestinal Drugs Advisory Committee (GIDAC) was convened regarding the use of PPI in symptomatic GERD in the 1- to 11-month pediatric age group. The GIDAC and FDA determined that PPIs are not efficacious for GERD in this age group. At that time, Study RABGRD3004 had already initiated and decision was made to continue. Both interim futility analysis and final analysis failed to show efficacy, consistent with the assessment and conclusions of GIDAC for other members of the PPI class. Hence, although new data for three pediatric age groups is provided in this submission, the sponsor only seeks approval in age group of 1 to 11 years. This reviewer will focus on this age group as well.

To investigate the use of rabeprazole in pediatric subjects aged less than 12 years, the sponsor developed a Delayed-Release Sprinkle Capsule formulation. During the process, the granule formulation was modified twice. Phase 1 concept granule formulation was supplied in sachets and used in the pediatric phase 1 Study RABGRD1002. This granule formulation was modified and the dosage form was changed from sachets to sprinkle capsules, used in the pediatric phase 3 Studies RABGRD3004 and RABGRD3003. The sponsor claims that the to-be-marketed granule formulation is essentially the same as the phase 3 granule formulation.

STATISTICS FILING REVIEW

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: [\\Cdseub1\evsprod\NDA204736\0000](#).

Overview of studies

This NDA includes pediatric clinical trial data with rabeprazole sodium delayed-release sprinkle capsules. The pediatric clinical program comprised 753 subjects in the following studies:

- Neonates and preterm infants, referred to as neonates (Study RABGRD1005; 69 subjects) using the EC granule formulation;
- Infants 1 to 11 months of age (Studies RABGRD1003; 50 subjects and RABGRD3004; 344 subjects) using the EC granule formulation;
- Children 1 to 11 years of age (Studies RABGRD1002; 28 subjects, RABGRD3003 Part 1; 127 subjects, and RABGRD3003 Part 2; 64 roll-over subjects) using the EC granule formulation;
- (previously submitted and reviewed under NDA 20973 S-022) Adolescents 12 to 16 years of age (Studies E3810-A001-119; 24 subjects and E3810-A001-202; 111 subjects) using 10 and 20 mg EC tablets.

The sponsor seeks approval of AcipHex[®] Delayed-Release Sprinkle Capsules for the healing, maintenance of healing, and symptom improvement of GERD in subjects 1 to 11 years of age. This submission contains CMC, nonclinical and clinical data intended to support the following proposed dosage regimen:

- 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 no less than 15 kg, 10 mg once daily (b) (4).

This reviewer will mainly evaluate Study RABGRD3003 (Part 1 and Part 2) in children 1 to 11 years of age, which was a randomized, double-blind, multicenter study that investigated the efficacy of two target dose levels of rabeprazole granules (0.5 mg/kg and 1.0 mg/kg). In the treatment phase (Part 1), rabeprazole was administered for 12 weeks. After completing the double-blind 12-week treatment phase, subjects who achieved healing were given the opportunity to enter the long-term, double-blind 24-week maintenance phase (Part 2) continuing on the same dose given in the previous double-blind 12-week treatment phase. The study designs of the two phase 3 studies (Studies RABGRD3004 and RABGRD3003 [Part 1 and Part 2]) are summarized in the table on next page.

Issues for 74-day letter

1. It appears that you have submitted all the data and program files for both Part 1 and Part 2 of Study RABGRD3003 in the folder named “rabgrd3003-pt1”. You should also submit separate data files for the two parts of the study to facilitate our review.
2. You have conducted efficacy analyses in age and region subgroups. You should also conduct efficacy analyses in gender and race subgroups.

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Study ID	Number of Study Centers/ Location	Study Start/ End Date/ Duration	Study Design	Study Drugs Dose, Regimen	Subjects by Dose Group Entered/ Completed	Age Range, Sex (M/F), % (B/W/O), %	Diagnosis/ Key Inclusion Criteria	Efficacy Endpoints
RAB GRD3004	70/US, Australia, Belgium, Bulgaria, Hungary, Israel, Italy, the Netherlands, Poland, South Africa.	November 4, 2009 – November 16, 2011 10 weeks	Open-label to Double-blind, placebo-controlled, parallel-group randomized treatment withdrawal design	Granules Open-label – 10 mg qd Double-blind 5 mg qd 10 mg qd Placebo	268/231 90/77 88/78 90/76	1–11 months 65/35 (14/84/2)	Suspected or, symptomatic GERD, or endoscopically or histologically proven GERD, based on recurrent vomiting or regurgitation with at least 1 of the following: failure to thrive, irritability not consistent with colic, or refusal to eat	Primary: (FDA) Change from BL in frequency of regurgitation and weight-for-age Z-scores (EMA) Change from BL in I-GERQ-R total score and I-GERQ-DD total score Secondary: (FDA) Volume of regurgitation; regurgitation, discomfort, eating behavior subscales of I-GERQ-DD (EMA) FDA endpoints + weight-for-age Z-score
RAB GRD3003, Part 1	41/US, Belgium, Denmark, France, Italy, Poland, Israel, South Africa, India	January 30, 2009 – August 19, 2010 12 weeks	Double-blind, parallel-group; Randomized treatment	Granules 5 mg qd 10 mg qd actual doses (for low-weight cohort: 6.0-14.9 kg) 10 mg qd 20 mg qd actual doses (for high-weight cohort: ≥15 kg)	21/17 19/16 44/38 43/37	1-11 years 56/44 (10/78/12)	≥ 1 GERD symptom within 3 months prior to screening; positive EGD	Primary: Endoscopic/histologic healing at Week 12 Secondary: Changes in frequency and severity of GERD symptoms, Symptom relief, Treatment satisfaction, CGI-I, Endoscopy and Histology Scores, and Antacid use

STATISTICS FILING REVIEW

Study ID	Number of Study Centers/ Location	Study Start/ End Date/ Duration	Study Design	Study Drugs Dose, Regimen	Subjects by Dose Group Entered/ Completed	Age Range, Sex (M/F), % (B/W/O), %	Diagnosis/ Key Inclusion Criteria	Efficacy Endpoints
RAB GRD3003, Part 2	30/US, Belgium, Denmark, Italy, Poland, Israel, South Africa, India	April 21, 2009 – January 19, 2011 24 weeks	Double-blind, parallel-group; maintenance treatment	Granules 5 mg qd 10 mg qd actual dose (for low-weight cohort 6.0-14.9 kg) 10 mg qd 20 mg qd actual dose (for high-weight cohort ≥15 kg)	9/8 8/6 24/18 23/18	1-11 years 58/42 (9/80/11)	Achieved healing at end of Part 1; ≥ 1 GERD symptom within 3 months prior to screening; positive EGD	Primary: Maintenance of endoscopic/histologic healing at Week 36 Secondary: Changes in frequency and severity of GERD symptoms, Symptom relief, Treatment satisfaction, CGI-I, Endoscopy and Histology Scores

Abbreviations: B = Black; CGI-I = Clinical Global Impression of Improvement; EGD = Esophagogastroduodenoscopy; F = Female; GERD = Gastroesophageal reflux disease; M = Male; O = Other; qd = Once daily; US = United States; W = White.

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/s/

FREDA COONER
10/31/2012

MICHAEL E WELCH
10/31/2012