CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204736Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	3/8/2013
From	Ruyi He, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 204736
Applicant	Eisai, Inc
Date of Submission	9/27/2012
PDUFA Goal Date	3/27/2013
Therapeutic Class	Proton-pump inhibitor (PPI)
Proprietary Name / Established (USAN) names	ACIPHEX® (rabeprazole sodium) Delayed-Release Sprinkle Capsules
Proposed Indication(s)	Treatment of Gastroesophageal Reflux Disease (GERD) in Pediatric Patients Aged 1 to 11 Years • ACIPHEX is indicated for the healing and improvement of GERD symptoms (b) (4) • ACIPHEX is indicated for the maintenance of healing of GERD (b) (4)
Proposed Dosage forms / Strength	For patients with bodyweight < 15 kg, 5 mg once daily with the option to increase to 10 mg if no symptomatic response; for patients with bodyweight ≥ 15 kg, 10 mg once daily
Recommended:	I recommend that NDA 204736 for ACIPHEX® (rabeprazole sodium) Delayed-Release Sprinkle Capsules be approved for the Treatment of GERD in Pediatric Patients Aged 1 to 11 Years For patients with bodyweight < 15 kg, 5 mg once daily with the option to increase to 10 mg; for patients with bodyweight ≥ 15 kg, 10 mg once daily

1. Introduction

Rabeprazole 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 or 20-mg rabeprazole tablets containing (b) (4) and (b) (4) mg rabeprazole free acid, respectively.

In the United States, rabeprazole is available as 20-mg AcipHex® tablets and is indicated for short-term treatment in adults of erosive or ulcerative gastroesophageal reflux disease (GERD); symptomatic GERD; maintenance of healed erosive or ulcerative 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 tablets are also indicated for short-term treatment of symptomatic GERD in adolescents 12 years and above.

Gastroesophageal reflux is a common event occurring in children. GERD is characterized by increased exposure of the esophageal mucosa to the gastroduodenal contents, which are usually acidic and result in chronic symptoms, and may occur in children of all ages.
In older children, the pathogenesis and clinical presentation of GERD resemble those in adults. Antacids, H2-receptor blockers, and several PPIs, including rabeprazole, have been approved for the treatment of GERD in adolescents.

2. Background

The rabeprazole pediatric development program was initiated as a result of US FDA Phase 4 commitments issued in conjunction with the approvals of rabeprazole delayed-release tablets for the treatment of erosive and symptomatic GERD in adults. The pediatric clinical program comprised 753 subjects in the following studies:

• Neonates and preterm infants, (Study RABGRD1005; using the EC granule formulation
• Infants 1 to 11 months of age (Studies RABGRD1003; and RABGRD3004) using the EC granule formulation
• Children 1 to 11 years of age (Studies RABGRD1002; RABGRD3003 Part 1; and RABGRD3003 Part 2) using the EC granule formulation
• Adolescents 12 to 16 years of age (Studies E3810-A001-119; and E3810-A001-202) using 10- and 20-mg EC tablets which was approved on 30 June 2008).

Overview of Regulatory Activity
Pre-NDA meeting was held on July 12, 2011. FDA and the sponsor agreed the content and format of the proposed pediatric NDA for the use of rabeprazole for the treatment of GERD in pediatric patients aged 1-11 years.

On September 11, 2012, FDA informed the sponsor to submit pediatric study information in one NDA (not a supplement) considering this will be a new formulation (pediatric granules) and asked the population will be neonates, 1 month - 11 months inclusive, 1 year - 11 years inclusive.

3. CMC/Device

Dr. Yichun Sun is the CMC reviewer for this NDA and he concluded in his review that this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

The Office of compliance has made a final "Acceptable" recommendation on the facilities involved.

The drug product, rabeprazole sodium delayed-release capsules, is proposed to be used to treat GERD in pediatric patients aged 1 to 11 years. The strengths of rabeprazole sodium capsules are available at 2.5, 5 and 10 mg per capsule (Note: Only the 5 and 10 mg capsules are sought for marketing according to the amendment dated February 1, 2013). Rabeprazole sodium capsules are hypromellose hard capsules, each containing (b) (4) enteric coated granules. The different strengths are achieved by (b) (4). The manufacturing process of rabeprazole sodium capsules consists of (b) (4) The identity, strength, purity and quality (except for dissolution acceptance criterion) of the drug product are adequately controlled by the drug product specification. The rabeprazole sodium delayed-release sprinkle capsules are packaged into high density polyethylene (HDPE) bottles (bottles of 30 capsules). The proposed expiration dating period of 24 months is supported by the long-term and accelerated stability data provided. See Dr. Sun's review for details.

Dr. Houda Mahayni from ONDQA did review on the evaluation and acceptability of 1) the in vitro dissolution method and acceptance criteria, 2) the product stability with dosing vehicles, and 3) the waiver request for the lower dosage strengths (2.5 mg and 5 mg). Dr. Mahayni concluded that the proposed dissolution method conditions and acceptance criteria for each stage are acceptable.

The Applicant did not evaluate the alcohol dose dumping potential of their proposed modified release dosage form. On February 15, 2013, the Applicant made the postapproval commitment to assess the effect of alcohol on the drug release of AcipHex Delayed Release Sprinkle Capsules and submit the study results no later than August 8, 2013.

4. Nonclinical Pharmacology/Toxicology

Dr. Ke Zhang is the reviewer and Dr. David Joseph is the team leader for this NDA and they concluded in the review that from a nonclinical standpoint, this NDA is recommended for approval and has no recommendation for Post-Marketing Commitments, Agreements, Post-Marketing Requirements and/or Risk Management Steps.

In the 5-week oral toxicity study in the neonatal rats, E3810 was given by oral gavage to 7-day old rats at 0, 5, 25, and 150 mg/kg/day. Treatment increased the serum gastrin level and stomach weight. Histopathological examination revealed a dose-related increase in cytoplasmic eosinophilia of chief cells in the stomach. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of ECL cells was increased in males at 5 mg/kg and higher and females at 25 mg/kg and higher. These changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals.

In the 90-day oral toxicity study in neonatal dogs, E3810 was given by oral gavage to 7-day old dogs at 0, 3, 10, and 30 mg/kg/day. Treatment increased the serum gastrin level, stomach weight and gastric mucosal thickness. Histopathological examination revealed degeneration/necrosis of parietal cells and mucosal hypertrophy/hyperplasia in the fundus of the stomach in a dose related manner. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Insook Kim is the Clinical Pharmacology reviewer for this NDA and Dr. Sue-Chih Lee is the Team Leader. They reviewed the NDA and concluded that NDA 204736 is approvable. They have no recommendation for a post marketing requirement (PMR) or post marketing commitment.

Based on the review provided by Dr. Kim, Clinical Pharmacology Findings are summarized as follows:

Dose selection
The proposed dose of 5 mg for patients < 15 kg with an option of increase to 10 mg and 10 mg for patients > 15 kg is acceptable from a clinical pharmacology standpoint. For patients > 15 kg, the dose of 10 mg is recommended based on no apparent dose-response for healing of GERD between 10 mg and 20 mg. In addition, no concentration-response relationship is evident the healing of GERD. For patients < 15 kg, the dose of 5 mg is also recommended based on no apparent exposure response relationship for the healing of GERD between doses of 5 mg and 10 mg. We found the proposed dose of 5 mg acceptable as it is the lowest effective dose with an acceptable response rate. In addition, the proposed “option of dose increase to 10 mg after reassessment” is agreeable based on the limitations of the small sample size (n=16-17) for the definitive conclusion on the dose-response between 5 mg and 10 mg. On the other hand, the

mean AUC after 5 mg dosing was estimated to be lower than the observed AUC at doses of 10 mg or 20 mg in adults while the systemic exposure at10 mg is within the AUC range observed in adults at the approved 20 mg.

The to-be-marketed formulation is bioequivalent to the formulation used in the phase 3 trials in patients 1-11 year of age.

The bioequivalence between the to-be-marketed formulation as one 10 mg capsule and the phase 3 formulation as two 5 mg capsules was demonstrated. In the study, rabeprazole granules were administered after sprinkled on applesauce under fasting condition and swallowed with 240 ml of water. The geometric mean ratio of Cmax and AUC for rabeprazole and its associated 90% CI met the bioequivalence criteria. See Dr. Kim's review for details.

At the request of the Division of Clinical Pharmacology III, Dr. Jyoti Patel, from the Division of Bioequivalence and GLP Compliance (DBGLPC), conducted audits of the clinical and analytical portions for the following bioequivalence study.

Study RABGRD 1007, Study Title: "Pivotal study to assess the bioequivalence of the to-be-marketed Sprinkle capsule formulation and the Phase 3 Sprinkle capsule formulation of Rabeprazole sodium in fasted condition and to assess the effect of food on the to-be-marketed formulation in healthy adult subjects"

Following the inspections, Dr. Patel recommends that data from the analytical and clinical portions of study RABGRD 1007 are acceptable for further agency review.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Dr. John Troiani is the medical officer and Dr. Freda Cooner is the statistician for this NDA review.

Efficacy was evaluated in 2 Phase 3 studies in pediatric subjects <12 years of age, Study 3004 in infants 1 to 11 months of age, and Study 3003 in children 1 to 11 years of age.

STUDY 3004 in infants 1 to 11 months of age
Study 3004 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.

This study was conducted in 2 parts: an OL phase (for up to 3 weeks) and a 5-week DB placebo-controlled withdrawal phase. Subjects who achieved a clinical response during the OL phase were eligible to enter the DB placebo-controlled withdrawal phase.

In the OL period, all subjects received 10-mg rabeprazole once daily for at least 1 week and up to 3 weeks until clinical response was achieved or the subject failed to improve after 3 weeks of treatment. In the DB period, eligible subjects were randomized to rabeprazole 5 mg, 10 mg, or placebo in 1:1:1 ratio.

To comply with individual requirements of the US FDA and the European Medicines Agency (EMA), the co-primary efficacy endpoints were differentiated as follows:

- For FDA, changes from baseline to the end of the study in the frequency of regurgitation based on the daily event log; and changes in the weight-for-age Z-score between the active treatment and placebo groups.
- For EMA, changes from baseline to the end of the study in the Infant Gastroesophageal Reflux Questionnaire-Revised (I-GERQ-R) total score; and changes from baseline to the end of the study in the Infant Gastroesophageal Reflux Questionnaire-Daily Diary (I-GERQ-DD) total score between the active treatment and placebo groups.

For the FDA, the secondary efficacy objectives were based on changes from baseline for the various subscale scores I-GERQ-DD and changes in the volume of regurgitation. In addition, for the EMA weight-for-age Z-score was also assessed.

Study 3004 was conducted in infants 1 to 11 months of age, weighing between 3.4 and 14.0 kg, inclusive, who had a diagnosis of suspected GERD, symptomatic GERD, or endoscopically or histologically proven GERD, based on the presence of recurrent vomiting or regurgitation with at least 1 of the following characteristics: poor weight gain as defined by failure to thrive; irritability, excessive crying, or disturbed sleep considered abnormal by both the parent(s) and the physician (but not consistent with a diagnosis of colic); and/or refusal to eat even if hungry or arching back at meals.

The mean age was 4.7 months for the 90 subjects randomized to the placebo group (range: 1.35 - 11.74 months), and the 178 subjects randomized to the combined rabeprazole group (range: 0.85 - 11.58 months) during the DB period. Almost half of all subjects in each treatment group were in the ≥1 to <4 month age group: 48.9% in the placebo group and 48.3% in the combined rabeprazole group. The majority (86%) of all subjects were White, with equal percentages in all treatment groups. There were also more males in all treatment groups, 53.3% in the placebo group and 64.6% in the combined rabeprazole group. The rabeprazole 10-mg group had more males (71.6%) than the other treatment groups. The dose groups were fairly well balanced with respect to race and ethnicity; the majority of subjects in all dose groups were non-US subjects.

Primary Efficacy Analysis
Frequency of Regurgitation:

In the OL period, the average frequency of regurgitation decreased weekly from a mean of 4.9 at baseline (range 0 to 53) to a mean of 2.7 at endpoint (range 0 to 41). The mean change from baseline was -2.2, with a range of -15 to 6.

In the DB period, the mean (SD) change in the daily frequency of regurgitation for the placebo, rabeprazole 5-mg, and rabeprazole 10-mg groups were -0.8 (1.58), -0.8 (1.55), and -1.6 (3.63), respectively. The mean (SD) change for the combined rabeprazole group was -1.2 (2.79). Overall, the daily frequency of regurgitation was lower at the end of the DB period than at baseline for all 3 groups. The difference in the change from baseline between the placebo group and the combined rabeprazole group was not statistically significant ($P = 0.168$).

Weight-For-Age Z-Score:
In the OL period, the average weight-for-age Z-score decreased from a mean of -0.65 at baseline (range -5.3 to 3.3) to a mean of -0.56 at endpoint (range -5.3 to 3.2). The mean change from baseline was 0.10, with a range of -0.9 to 1.7.

The mean (SD) changes for the placebo, rabeprazole 5-mg, and rabeprazole 10-mg groups were 0.11 (0.329), 0.16 (0.322), and 0.11 (0.264), respectively. The mean (SD) change for the combined rabeprazole group was 0.14 (0.295). The difference in the change from baseline between the placebo group and the combined rabeprazole group was not statistically significant ($P = 0.440$). Therefore, the individual dose groups were not compared with placebo. Similar results were seen across all age groups.

I-GERQ-R (the Infant Gastroesophageal Reflux Questionnaire-Revised):

In the OL period, the average I-GERQ-R total scores decreased from a mean of 24.0 at baseline (range 13 to 37) to a mean of 15.5 at endpoint (range 0 to 38). The mean change from baseline was -8.5, with a range of -30 to 9.

Mean (SD) changes from DB baseline to DB endpoint in the I-GERQ-R total scores for the placebo, rabeprazole 5-mg, and rabeprazole 10-mg groups were -3.6 (6.41), -3.8 (7.5), and -4.1 (7), respectively. The mean (SD) change for the combined rabeprazole group was -3.9 (7.24). The I-GERQ-R total scores were lower at the end of study than at baseline for all 3 treatment groups and the improvements observed were similar for all 3 treatment groups. The difference in the change from DB baseline between the placebo group and the combined rabeprazole group was not statistically significant ($P = 0.960$). Therefore, the individual dose groups were not compared with placebo. Similar results were seen across all age groups.

I-GERQ-DD (the Infant Gastroesophageal Reflux Questionnaire-Daily Diary) Total Score:

In the OL period, the average I-GERQ-DD total scores decreased weekly from a mean of 15.5 at baseline (range 3 to 30) to a mean of 10.8 at endpoint (range 0 to 28). The mean change from baseline was -4.7, with a range of -26 to 13.

Mean (SD) changes from DB baseline to DB endpoint in I-GERQ-DD total score for the placebo, rabeprazole 5-mg, and rabeprazole 10-mg groups were -1.9 (4.55), -1.6 (4.85), and -2.1 (4.9),

respectively. The mean (SD) change in the combined rabeprazole group was -1.9 (4.86). The I-GERQ-DD total scores were lower at the end of the study than at baseline for all 3 treatment groups and the improvements observed were the same for all 3 treatment groups. The difference in the change from baseline between the placebo group and the combined rabeprazole group was not statistically significant (*P* =0.968).

Therefore, the individual dose groups were not compared with placebo. Similar results were seen across all age groups.

Major Secondary Efficacy Analysis
VOLUME OF REGURGITATION ASSESSMENT: AVERAGE DAILY VOLUME OF REGURGITATION PER CATEGORY DURING THE DB TREATMENT PERIOD

In the OL period, the mean number of regurgitation episodes decreased from the OL baseline to the end of the OL period in all volume categories. Similar trends were seen in all age groups (≥1 - <4 months, ≥4 - <8 months, and ≥8 - <12 months); Minimal changes were seen in the daily average number of episodes between DB baseline and DB endpoint in each volume category in all 3 treatment groups.

Table 1. Average Daily Volume of Regurgitation per Category During the DB Treatment Period – ITT Analysis Set in Study RABGRD3004

	Placebo (N=89)	Rabeprazole 5 mg (N=90)	Rabeprazole 10 mg (N=88)	Rabeprazole Total (N=178)
DB Baseline				
Less than 1 tablespoon	1.7	1.7	2.7	2.1
1 to 2 tablespoons	1.1	1.2	1.7	1.5
More than 2 tablespoons to 2 fluid oz	0.4	0.3	0.4	0.4
More than 2 fluid oz to 4 fluid oz	0.1	0.0	0.0	0.0
More than 4 fluid oz	0.0	0.0	0.1	0.1
DB Endpoint				
Less than 1 tablespoon	1.6	1.6	2.1	1.8
1 to 2 tablespoons	1.1	1.0	1.4	1.2
More than 2 tablespoons to 2 fluid oz	0.5	0.3	0.4	0.4
More than 2 fluid oz to 4 fluid oz	0.1	0.1	0.1	0.1
More than 4 fluid oz	0.0	0.0	0.0	0.0

Note(s): DB Baseline: Calculated as the average of the available results from the last 3 days of OL Treatment Period. DB Endpoint: Calculated as the average of the available results from the last 3 days of the DB Treatment Period.
Visit Interval: Weekly average calculated based on relevant relative days as described in the SAP.
Source: Module 5.3.5.1/RABGRD3004 CSR Table 11-7

Distribution of episodes was similar among the 3 treatment groups and all age groups. Similar results were seen across all age groups.

I-GERQ-DD - REGURGITATION SUBSCALE SCORE

In the OL period, the regurgitation subscale score decreased weekly from an OL baseline score of 6.6 to a score of 4.7 at the end of the OL period. The regurgitation subscale score decreased weekly from OL baseline through OL endpoint in all age groups (≥1 to <4 months, ≥4 to <8 months, and ≥8 to <12 months.

Changes from DB baseline to DB endpoint using DB LOCF for the regurgitation subscale score were similar for all treatment groups: mean (SD) changes for the placebo, rabeprazole 5-mg, and rabeprazole 10-mg groups were -0.8 (2.57), -0.8 (2.56) and -1.0 (2.38), respectively. The mean (SD) change for the combined rabeprazole group was -0.9 (2.47). The difference in the change from baseline between the placebo group and the combined rabeprazole group was not statistically significant (*P* =0.984).

I-GERQ-DD - DISCOMFORT SUBSCALE SCORE

In the OL period, the discomfort subscale score decreased weekly from an OL baseline score of 4.5 to an OL endpoint score of 3.0. The discomfort subscale score decreased weekly from OL baseline through OL endpoint in all age groups (≥1 to <4 months, ≥4 to <8 months, and ≥8 to <12 months).

Changes from DB baseline to DB endpoint using DB LOCF for the discomfort subscale score were similar for all treatment groups: mean (SD) changes for the placebo, rabeprazole 5-mg, and rabeprazole 10-mg groups were 0.0 (2.24), -0.1 (1.88) and -0.4 (1.94), respectively. The mean (SD) change for the combined rabeprazole group was -0.2 (1.9). The difference in the change from baseline between the placebo group and the combined rabeprazole group was not statistically significant (*P* =0.479).

I-GERQ-DD – EATING BEHAVIOR SUBSCALE SCORE

In the OL period, the eating behavior subscale score decreased weekly from an OL baseline score of 4.4 to an OL endpoint score of 3.1. The eating behavior subscale score decreased weekly from OL baseline through OL endpoint in all age groups (≥1 to <4 months, ≥4 to <8 months, and ≥8 to <12 months).

Changes from DB baseline to DB endpoint using DB LOCF for the eating behavior subscale score were similar for all treatment groups: mean (SD) changes for the placebo, rabeprazole 5-mg, and rabeprazole 10-mg groups were -0.1 (2.54), -0.1 (2.19) and -0.4 (2.15), respectively. The mean (SD) change for the combined rabeprazole group was -0.3 (2.17). The difference in the change from baseline between the placebo group and the combined rabeprazole group was not statistically significant (*P*=0.498).

In conclusion, based on above results, I concur with the assessment of Dr. John Troiani that Study RABGRD3004, conducted in subjects 1 to 11 months of age, did not demonstrate efficacy of rabeprazole for any of its primary or secondary endpoints, including frequency of regurgitation; weight for age Z score; I-GERQ-R weekly symptom score; or I-GERQ-DD daily symptom score.

Neither was there evidence of superiority of rabeprazole over placebo for any of the secondary endpoints including volume of regurgitation or any of the 3 I-GERQ-DD subscales including the Regurgitation, Feeding Behavior, and Discomfort subscales. This is consistent with studies conducted with other PPIs.

STUDY 3003 in children 1 to 11 years of age

Study 3003 Part 1 and Part 2 in children 1 to 11 years of age was a randomized, DB, multicenter study that investigated the efficacy of 2 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. The actual dose administered was further determined by body weight, which resulted in 4 actual dose groups (5- and 10-mg dose groups for subjects weighing 6.0 to 14.9 kg, and 10- and 20-mg dose groups for subjects weighing ≥15 kg). After completing the double-blind 12-week treatment phase, subjects who achieved healing were given the opportunity to enter the long-term, DB 24-week maintenance phase (Part 2) continuing on the same dose given in the previous DB 12-week treatment phase.

Table 1: Doses Selected for the Phase 3 Study RABGRD3003 (Parts 1 and 2)

	Low-weight Cohort (6.0-14.9 kg)		High-weight Cohort (≥ 15 kg)	
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**

The rabeprazole granule 0.5 mg/kg and 1.0 mg/kg target doses were selected based on the results from the Phase 1 PK study in children 1 to 11 years of age. The 0.5 and 1.0 mg/kg target doses were predicted to result in overall exposure in the range previously shown to be effective in adults with doses of 10 mg (AUC 400 ng h/mL) and 20 mg (AUC 800 ng h/mL). Based on the shared pathophysiology of GERD and the mechanism of action of PPIs, these levels of exposure were predicted to be efficacious in children 1 to 11 years of age.

The primary efficacy evaluation for both the 12-week treatment and 24-week maintenance treatment phases in Study 3003 was endoscopic/histologic healing of the esophageal mucosa defined as Grade 0 on the Hetzel-Dent classification scale (Hetzel-Dent) (macroscopically normal esophageal mucosa) and/or Grade 0 on the Histological Features of Reflux Esophagitis scale (histologically normal esophageal mucosa). EGD with biopsy was performed and graded based on both histologic and macroscopic mucosal appearance using the standard scoring methods mentioned above. Secondary endpoints included assessment of frequency and severity of pre-specified GERD symptoms (based on Total GERD Symptom and Severity Scale score) and GERD symptom relief (using the GERD Symptom Relief score). Treatment satisfaction was assessed by the investigator using the Global Treatment Satisfaction score.

The study population in Part 1 of Study 3003 (N=127) consisted of males and females 1 to 11 years of age with a history of at least 1 GERD symptom within the 3 months before screening and a positive EGD (Hetzel-Dent grade ≥ 1 and Histology Grade > 0). The low-weight cohort (6.0 - 14.9 kg) comprised 40 subjects (21 in the 5-mg group, 19 in the 10-mg group). The high-weight cohort (≥ 15 kg) comprised 87 subjects (44 in the 10-mg group, 43 in the 20-mg group). The 4 dose groups were fairly well balanced with respect to sex, race, and ethnicity; 58% were from the US, 42% from non-US countries. However, mean age and mean body weight were not similar across the 4 dose groups; all subjects in the 6- to 11-year-old group were in the high-weight cohort, while subjects in the 1- to 5-year-old group were in both weight cohorts. The mean ages of the low-weight cohort were 1.9 and 2.4 years in the 5- and 10-mg dose groups respectively. The mean ages of the high-weight cohort were 7.0 and 7.6 years in the 10- and

20-mg dose groups respectively. Fifty-four percent of subjects were 1 to 5 years of age and 46% were 6 to 11 years of age.

Sixty-four subjects continued into the 24-week maintenance treatment phase (Part 2). The 4 dose groups were well balanced with respect to sex, race, and ethnicity; 52% were from the US and 48% were from non-US countries. Mean age and mean body weight were not similar across the dose groups; the low-weight cohort was comprised solely of younger subjects (1 - 5 years) who weighed < 15 kg; all subjects 6 to 11 years of age were in the high-weight cohort.

Primary Efficacy Analysis

HEALING BY WEEK 12 (Part 1)

Overall, 81% of children 1 to 11 years of age achieved healing of the esophageal mucosa at the end of the 12-week treatment period. Eighty-two percent of the 5-mg group and 94% of the 10-mg group in the low-weight cohort, and 76% and 78% of the high-weight cohort (10-mg and 20-mg groups, respectively) had macroscopically and/or histologically normal esophageal mucosa as determined by a Grade 0 Hetzel-Dent or Histology score (Table 2).

Table 3: Endoscopic/Histologic Healing Rates - ITT Analysis Set in Study 3003 (Part 1)

	Study RABGRD3003 Part 1, 12 Weeks, N = 127			
	Low Weight Cohort		High Weight Cohort	
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/End of double-blind phase	(N = 21)	(N = 19)	(N = 44)	(N = 43)
N	17	16	38	37
n (%)	14 (82)	15 (94)	29 (76)	29 (78)

Abbreviations: ITT = Intent-to-treat; n = Size of subset sample; N = Total sample size.
Note: Healing rate was defined as having either Grade 0 on the Hetzel-Dent Endoscopic Classification System (macroscopically normal esophageal mucosa) or Grade 0 on the Histological Features of Reflux Esophagitis Scale (histologically normal esophageal mucosa).

The healing rate was similar amongst the 4 actual dose groups: 82% of the 5-mg group and 94% of the 10-mg group in the low-weight cohort, and 76% and 78% of the high-weight cohort (10-mg and 20-mg groups, respectively).

When subcategorized by age, the 1 to 5 year old group had a slightly higher healing rate (84%) than the 6 to 11 year old group (77%). When subcategorized by region, the non-US group had a slightly higher healing rate (87%) than the US group (76%).

Secondary Efficacy Analysis

Change from Baseline in Total GERD Symptom and Severity Score Study 3003 (Part 1)

The total GERD Symptom and Severity score in all subjects decreased from a mean of 19.3 points at baseline to 8.6 points at Week 12. This reflects a statistically significant ($P < 0.001$: paired t-test) mean decrease of 10.0 points. However, we do not know if the difference has any clinical meaningfulness.

In addition, the instrument using the total GERD Symptom and Severity score is a not valid tool for drug development in patients with GERD, especially in pediatric patients. In addition, evaluation of symptoms is a secondary endpoint; we do not recommend those information into labeling.

Mean Change in Severity of Individual Symptoms of GERD from Baseline to End of Study Study 3003 (Part 1)

Mean changes in the severity of total GERD symptoms from baseline to the end of the study (Week 12) showed an overall improvement of 46%. Within the 12-item subscale of individual symptoms, overall improvements were reported for all symptoms (range: 37% for coughing to 86% for vomiting). The largest overall improvements were reported for the symptoms of vomiting (86%), nausea (82%), hoarseness and choking (80% each), and dysphagia (79%).

When subcategorized by age, there was overall total improvement from baseline to Week 12; 54% and 37% in the 1 to 5 year old and the 6 to 11 year old groups, respectively. The greatest improvements were in dysphagia and hoarseness (both 92%) in the 1 to 5 year old group and in choking and vomiting (94% and 100%, respectively) in the 6 to 11 year old group.

GERD Symptom Relief Score Study 3003 (Part 1)

At Week 12, for all subjects, the GERD Symptom Relief scores showed that the majority of subjects reported symptom relief: 71% subjects felt better, 23% felt no change, and 7% felt worse. A slightly greater percentage of subjects in the high-weight cohort (70% and 76%) reported feeling better than in the low-weight cohort (67%).

Hetzel-Dent Endoscopic Classification System Grades Study 3003 (Part 1)

At Week 12, of all subjects, 81% had ≥1 grade improvement on their Hetzel Dent score; 72% showed improvement to Grade 0, 18% had no change, and 1% showed worsening. The results were similar across the actual dose groups: 82% in the 5 mg dose group; 81% in the 10-mg group (low weight cohort); 87% in the 10-mg group (high weight cohort); and 76% of subjects in the 20-mg actual dose group had a Hetzel Dent Score improvement of ≥1 point.

Histology Features of Reflux Esophagitis Scale Scores Study 3003 (Part 1)

Using the Histology Features of Reflux Esophagitis Scale, subjects' scores were Grades 1 through 5 at baseline. Overall, at the end of Part 1, 57% of subjects had a ≥1 grade improvement on their histology score; 38% achieved Grade 0, 28% had no change, and 15% with worsening in the histology score. There was no notable difference across the actual dose groups.

When classified by age, results followed similar trends. At Week 12, among subjects aged 1 to 5 years, 43% had Grade 0 histology scores and among subjects aged 6 to 11 years, 33% had Grade 0 histology scores.

Primary Efficacy Analysis
MAINTENANCE OF HEALING (part 2)
At the end of the 24-week maintenance treatment phase (Week 36), the extent of healing achieved in the 12-week treatment phase was maintained in 100% of subjects in both dose groups in the low-weight cohort and in 89% and 85% in the 10-mg and 20-mg groups, respectively, in the high-weight cohort (Table 4).

Table 4: Endoscopic/Histologic Healing Rates - ITT Analysis Set in Study 3003 (Part 2)

	Study RABGRD3003 Part 2, 24 Weeks, N = 61			
	Low-weight Cohort		High-weight Cohort	
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 36/End of maintenance phase	(N = 8)	(N = 7)	(N = 24)	(N = 22)
N	8	6	18	20
n (%)	8 (100)	6 (100)	16 (89)	17 (85)

Abbreviations: ITT = Intent-to-treat; n = Size of subset sample; N = Total sample size.
Note: Healing rate was defined as having either Grade 0 on the Hetzel-Dent Endoscopic Classification System (macroscopically normal esophageal mucosa) or Grade 0 on the Histological Features of Reflux Esophagitis Scale (histologically normal esophageal mucosa).

When subcategorized by age, all subjects (100%) in the 1 to 5 year old group maintained healing compared with 83% of subjects in the 6 to 11 year old group.

However, because there is lack of control group and small number of patients in each group, the results listed above are unable to conclude maintenance of therapy is necessary. I concurred with Dr. Troiani's assessment that a placebo group might have done the same as the active treatment group in healing rates. Therefore the data in Study 3003 do not support maintenance of healing indication.

Secondary Efficacy Analysis

Mean Change in Severity of Individual Symptoms of GERD from Baseline to End of Study
Mean changes in the severity of overall total GERD symptoms from baseline (end of Part 1) to the end of the study (Week 36) showed 13% improvement. Within the 12 item subscale of individual symptoms, overall improvements were reported for all symptoms (range: 30% for fullness during eating to 100% for vomiting and choking). The largest overall improvements were reported for the symptoms of vomiting and choking (100% each), nausea (79%), hoarseness and dysphagia (61% each).

When subcategorized by age, there was a slight worsening (5%) of symptoms overall from baseline to EOS in the 1- to 5-year-old group and overall 30% improvement in the 6 to 11 year old group. The greatest improvement was in vomiting and choking in both the 1 to 5 year-old group and the 6- to 11-year-old group (all 100%).

GERD Symptom Relief Score (Part 2)

At Week 36, the GERD Symptom Relief Score for all subjects showed, 64% felt better, 33% felt no change, and 3% felt worse. When subcategorized by actual dose, a lower percentage of subjects (43%) in the 10-mg group in the low-weight cohort felt better compared with the other 3 actual dose groups (range 58% - 88%).

Hetzel-Dent Endoscopic Classification System Grades (Part 2)
Shifts in Hetzel Dent scores (Week 12 to Week 36), for all subjects, revealed 83% maintained Grade 0, 2% had an improvement of ≥ 1 grade and 16% had a decline of ≥ 1 grade. Shifts were similar across the actual dose groups, except for subjects in the low weight cohort, who all maintained Grade 0.

Histology Features of Reflux Esophagitis Scale Scores (Part 2)
At the end of Part 2, 46% of subjects had Grade 0, 27% had an improvement of ≥ 1 grade and 26% had a decline of ≥ 1 grade.

When classified by age, results followed similar trends. At Week 36, in 1 to 5 year olds, 57% had Grade 0 histology scores; and in subjects 6 to 11 year olds, 38% had Grade 0 histology scores.

Change in Clinical Global Impression of Improvement (CGI-I) Score Compared with Baseline (Part 2)
The CGI-I score, for all subjects at Week 36 (Part 1 Week 12 + Part 2 Week 24 = Week 36), showed 92% scored "Good" to "Excellent", 7% "Fair" and 1% "Poor". In the low-weight cohort, scores of 50% of subjects and 43% of subjects in the 5 mg and 10-mg groups, respectively, were rated "Good" and scores of 38% of subjects and 29% of subjects in the 5 mg and 10-mg groups, respectively, were rated "Excellent." In the high-weight cohort, 46% of subjects and 36% of subjects in the 10-mg and 20-mg groups, respectively, were rated "Good," and 50% of subjects and 59% of subjects in the 10-mg and 20-mg dose groups, respectively, were rated "Excellent".

When subcategorized by age, scores in 30% of subjects were "Excellent" and 57% were "Good" (subjects 1 - 5 years old); similarly, scores in 68% of subjects were "Excellent" and 29% were "Good" in subjects 6 to 11 years old.

EFFICACY CONCLUSIONS
Study RABGRD3004, conducted in subjects 1 to 11 months of age, did not demonstrate efficacy of rabeprazole for any of its primary or secondary endpoints, including frequency of regurgitation; weight for age Z score; I-GERQ-R weekly symptom score; or I-GERQ-DD daily symptom score.

Neither was there evidence of superiority of rabeprazole over placebo for any of the secondary endpoints including volume of regurgitation or any of the 3 I-GERQ-DD subscales including the Regurgitation, Feeding Behavior, and Discomfort subscales. This is consistent with studies conducted with other PPIs.

The efficacy of rabeprazole has been demonstrated in children 1 to 11 years of age as presented in this NDA (Parts 1 and 2) and supports the use of rabeprazole granules for the treatment of GERD in children 1 to 11 years of age.

The efficacy of rabeprazole granules administered in doses of 5 and 10 mg to children 1 to 11 years of age who weighed 6 to 14.9 kg (low-weight cohort) and 10 and 20 mg doses to those ≥ 15 kg (high-weight cohort) with endoscopically-proven GERD was consistent across weight cohorts and dose groups. Twelve weeks of treatment resulted in consistent improvement in all efficacy analyses in the majority of subjects. The primary endpoint of endoscopic/histologic healing was achieved in 81% of subjects in all dose groups in both cohorts (range: 76% to 100%) In addition, results of efficacy analyses by age (1 - 5 years of age vs. 6 - 11 years of age), study region (US vs. non-US) and disease severity (erosive vs. Nonerosive GERD) were consistent with results based on the entire study population.

However, for the part 2 of the study, there is no placebo (ie, natural history) group for comparison and no re-randomization before entering Part 2. A placebo group might have done the same as the active treatment group in healing rates. Therefore the data in Study 3003 do not support maintenance of healing indication.

Based upon the principle of initiating treatment with the lowest effective dose, a rabeprazole dose of 5 mg once daily is recommended for patients 1 to 11 years old who weigh < 15 kg. For patients weighing ≥ 15 kg, a dose of 10 mg of rabeprazole once daily is recommended in order to achieve clinical efficacy with acceptable safety. If no clinically meaningful improvement is achieved, based on the clinician's judgment, the dose could be increased to 10 mg for patients 1 to 11 years old who weigh < 15 kg. Given the increased rate of treatment-related AEs in children 1 to 11 years of age given 20 mg rabeprazole, an additional dose increase in subjects weighing >15 kg is not supported.

8. Safety

The longest planned exposure to rabeprazole was in Study RABGRD3003 in children 1 to 11 years of age; the initial DB treatment phase was 12 weeks followed by an optional DB 24-week maintenance phase. Planned exposure for infants 1 to 11 months of age in Study 3004 was at least 1 week and up to 3 weeks in the OL treatment period and up to 5 weeks in the DB treatment period. Planned exposure in adolescents 12 to 16 years of age in Study E3810-A001-202 was 8 weeks. The Phase 1 PK study in infants 1 to 11 months of age, Study 1003, had a planned exposure of 5 days of dosing for Option 1 and up to 28 days for Option 2. Study 1005 had a planned exposure of at least 5 days and up to 28 days in both Part 1 and Part 2. Phase 1 studies in children 1 to 11 years of age (Study 1002) and in adolescents 12 to 16 years of age (Study E3810-A001-119) had planned exposures of 5 days, and 5 or 7 days, respectively.

DEMOGRAPHIC AND OTHER CHARACTERISTICS OF THE STUDY POPULATIONS
Demographic characteristics for parameters of sex and race were similar for all studies in the pediatric program for rabeprazole.

In Study 3004, the majority (57 placebo subjects [63.3%] and 111 rabeprazole subjects [62.4%]) were non-US subjects. Their countries of origin included Australia, Belgium, Bulgaria, Hungary, Israel, Italy, The Netherlands, Poland, and South Africa. The All Subject Set enrolled in the OL period contained similar proportions of US and non-US subjects.

The mean age was 4.7 months for the 90 subjects randomized to the placebo group (range: 1.35 - 11.74 months), and the 178 subjects randomized to the combined rabeprazole group (range: 0.85 - 11.58 months). Almost half of all subjects in each treatment group were in the ≥1 to <4 month age group: 48.9% in the placebo group and 48.3% in the combined rabeprazole group. The majority (86%) of all subjects were White, with equal percentages in all treatment groups. There were no "American Indian", "Alaskan Native", Native Hawaiian" or "Other Pacific Islanders" in the study. There were also more males in all treatment groups, 53.3% in the placebo group and 64.6% in the combined rabeprazole group. The rabeprazole 10-mg group had more males (71.6%) than the other treatment groups.

The mean age for the 127 subjects enrolled in Study 3003 was 5.7 years; 69 (54%) were in the 1- to 5-year-old age group and 58 (46%) were in the 6- to 11-year-old age group. The majority of subjects were White (78%), 10% were Black, 2% were Asian, and 9% were classified as "Other" (other races included mixed, Mexican, North African, and Caucasian, for example). There was no "American Indian", "Alaskan Native", Native Hawaiian" or "Other Pacific Islanders" in the study. By region, 74 (58%) subjects were from the US, and 53 (42%) were non-US. Note: non-US subjects consisted of 33 (26%) subjects from Europe (Belgium, Denmark, France, Italy, and Poland), 10 (8%) from Israel, 7 (6%) from South Africa, and 3 (2%) from India.

Similar numbers of subjects were randomized to each target treatment, with 65 and 62 subjects receiving target doses of 0.5 mg/kg and 1.0 mg/kg rabeprazole, respectively. Within each of these target dose groups, the subject's actual dose was further determined by the subject's body weight, resulting in 4 actual dose treatment groups. The 4 actual dose groups were well balanced with respect to sex, race, and ethnicity distributions. Median age and median body weight were not similar across the 4 actual dose groups. The low-weight cohort was comprised solely of younger subjects (1 to 5 years) who weighed less than 15 kg. All of the older subjects (6 to 11 years) were enrolled in the high-weight cohort (≥15 kg). Fewer subjects weighing <15.0 kg were enrolled than subjects weighing ≥15 kg, thus the sample size for the low-weight cohort (N=40) was smaller than that of the high-weight cohort (N=87).

Treatment-Emergent Adverse Events

Common Adverse Events

Study 3004

In this Phase 3 study in infants 1 to 11 months of age, no AEs were reported by ≥5% subjects in the OL treatment period; A summary of TEAEs reported by ≥5% subjects in any treatment group during the DB treatment period is presented in Table 5. Overall, the most commonly reported TEAEs during the DB phase were pyrexia (2.2% placebo, 7.8% rabeprazole 5 mg and 5.7% rabeprazole 10 mg) and upper respiratory tract infection (5.6% placebo, 2.2% rabeprazole 5 mg and 8.0% rabeprazole 10 mg). Gastroesophageal reflux reported as a TEAE was seen in more

placebo subjects (7.9%) than rabeprazole 5-mg subjects (2.2%) or rabeprazole 10-mg subjects (4.5%). Increased serum gastrin levels were reported in more patients in the rabeprazole 10-mg group (8.0%) compared with the rabeprazole 5-mg group (2.2%) or the placebo group (0%).

Table 5: Double-blind Treatment-emergent Adverse Events by System Organ Class and Preferred Term Occurring in at Least 5% of Subjects in any Treatment Group – Double blind Safety Set in Study 3004

System Organ Class Preferred Term	Placebo (N=89)	Rabeprazole sodium 5 mg (N=90)	Rabeprazole sodium 10 mg (N=88)	Rabeprazole sodium total (N=178)
Number of Subjects with at Least One TEAE	42 (47.2)	39 (43.3)	44 (50.0)	83 (46.6)
Gastrointestinal disorders	**15 (16.9)**	**12 (13.3)**	**12 (13.6)**	**24 (13.5)**
Gastrooesophageal reflux disease	7 (7.9)	2 (2.2)	4 (4.5)	6 (3.4)
Vomiting	5 (5.6)	4 (4.4)	1 (1.1)	5 (2.8)
General disorders and administration site conditions	**4 (4.5)**	**7 (7.8)**	**7 (8.0)**	**14 (7.9)**
Pyrexia	2 (2.2)	7 (7.8)	5 (5.7)	12 (6.7)
Infections and infestations	**21 (23.6)**	**18 (20.0)**	**21 (23.9)**	**39 (21.9)**
Upper respiratory tract infection	5 (5.6)	2 (2.2)	7 (8.0)	9 (5.1)
Investigations	**3 (3.4)**	**5 (5.6)**	**10 (11.4)**	**15 (8.4)**
Serum gastrin increased	0 (0.0)	2 (2.2)	7 (8.0)	9 (5.1)

Note(s): Percentages are based on the number of subjects in the relevant analysis set. DB TEAEs:
All adverse events starting in DB Treatment Period and within therapeutic reach.
Therapeutic Reach: 15 Days after last dose of study drug for non-serious AEs and 30 days for serious AEs.
A subject is only counted once per SOC and PT.

In the DB period, TEAEs included increased serum gastrin (reported in 2 subjects) and diarrhea, frequent bowel movements, gastroesophageal reflux, vomiting, increased β2-microglobulin in urine, increased serum creatine phosphokinase, increased white blood cell count, and hypertriglyceridemia(reported in 1 subject each).

In the DB period, 11 rabeprazole 10-mg subjects experienced TEAEs considered related to study drug. The most common of these included increased serum gastrin levels (6 subjects) and increased serum creatinine (2 subjects); however, serum creatinine elevations were within the normal range.

Study 1005 was a PK/PD study in neonates 0 to <1 month of age or <44 weeks CGA. The PD endpoint was % time with gastric pH<4 (PTGA4). Mean PTGA4 was 90%, which is consistent with levels defined for hypo- and achlorhydria. A high degree of acid suppression (90%) was observed in Study 1005 and support that neonates are typically more acid-suppressed than adults. In Study 1005, baseline mean PTGA4 was 63%, which is the level of acid suppression in adults on a PPI. The data indicate that PPI therapy in patients <1 month of age may not be necessary.

ANALYSIS OF DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS LEADING TO DISCONTINUATION

Deaths

One death was reported in Study RABGRD1005; Subject 1425008 (rabeprazole 3 mg) died due to complications of sepsis following the inciting event of respiratory failure that eventually

resulted in complications leading to the subject's death 2.5 months after participation in the study. Respiratory failure was reported as the initial TESAE, and subsequently TESAEs of pneumothorax, renal failure/necrosis, necrotizing enterocolitis, sepsis and cerebral atrophy were reported; all events were assessed by the Investigator as not related to study drug administration.

Other Serious Adverse Events
Five subjects experienced TESAEs in the OL treatment period of Study RABGRD3004, including worsening of gastroesophageal reflux (1 subject), gastroenteritis (1 subject), upper respiratory tract infection (1 subject), and viral infection (1 subject). One subject reported dehydration, failure to thrive, and metabolic acidosis.

Ten subjects experienced a TESAE during the DB period of Study RABGRD3004, including 2 placebo-treated subjects (failure to thrive and hypoacusis), 6 subjects receiving rabeprazole 5 mg (stridor, agitation and pyrexia, upper respiratory tract infection, gastroenteritis, and urinary tract infection [2 subjects]), and 2 subjects receiving rabeprazole 10 mg (increased β2-microglobulin and bronchiolitis).

Six subjects in Study RABGRD3003 experienced a total of 7 TESAEs during Part 1: 3 respiratory infections; 2 gastrointestinal infections; 1 event of humerus fracture; and 1 event of dehydration. With the exception of the 2 subjects with gastrointestinal infections who were treated with 10-mg rabeprazole (1 in each body weight cohort), all other subjects who experienced TESAEs were treated with 5 mg rabeprazole (low-weight cohort).

One subject in Study E3810-A001-202 who received rabeprazole 20 mg experienced 1 TESAE (mood swings, considered not related to study drug).

Adverse Events Leading to Discontinuation

Four subjects in Study RABGRD3004 were discontinued from study drug due to TEAEs during the OL period: Subject 6084009 had constipation and exhibited excessive crying post vaccination; Subject 8594024 had worsening GERD; Subject 1464005 had oral candidiasis; and Subject 1004001 exhibited failure to thrive.

Eleven subjects in Study RABGRD3004 (Subjects 1324004, 1534003, 5024004, 6064003, 6064004, 6064006, 6064010, 6064012, 6064020, 6114004, 6114005) were discontinued from study drug during the DB period due to TEAEs of worsening of GERD symptoms. One placebo-treated subject was discontinued due to increased β-2 microglobulin (Subject 5024004).

Three subjects in Study RABGRD3003 were discontinued from the 12-week treatment phase of the study due to gastrointestinal TEAEs (Subject 1433009 had exacerbation of vomiting and diarrhea; Subject 1433001 had intermittent diarrhea; and Subject 5023001 had abdominal pain exacerbation and nausea.

CLINICAL LABORATORY EVALUATION IN CLINICAL TRIALS

In general, mean changes in clinical laboratory parameters were small and not clinically meaningful in the pediatric studies. In all the pediatric studies that evaluated serum gastrin levels (Studies RABGRD3004, RABGRD3003, RABGRD1003, and RABGRD1002), there was an observed increase from baseline at the end of the study. Elevation of serum gastrin, even after short-term treatment with a PPI is expected, due to the marked decrease in gastric acid secretion and the induction of the negative feedback loop stimulating intragastric gastrin production and secretion.

Overall the mean laboratory values remained relatively constant from OL baseline to DB endpoint in all the treatment groups of this study.

There were no meaningful changes reported in urine β2-microglobulin values in subjects receiving placebo and 5-mg rabeprazole. However, a mean increase 0.148 mg/L was reported in subjects receiving 10-mg rabeprazole with a mean value of 0.171 mg/L at OL baseline which increased to 1.524 mg/L at DB endpoint. No elevations in either serum BUN or creatinine, or changes in the urinary sediment were associated with elevations in the urinary β2-microglobulin values. Serum iron levels were measured at the OL baseline and at the end of the DB period to evaluate a potential concern over iron malabsorption related to the hypochlorhydria induced by rabeprazole. The mean change from OL baseline to EOS in serum iron was greater in the placebo group (-2.245 μmol/L) compared with -1.740 μmol/L for the 5-mg rabeprazole group, and -0.342 μmol/L for 10-mg group. These data do not indicate decreased iron absorption while on rabeprazole.

A mean increase in serum gastrin levels from the initial OL visit to the end of the DB period was reported in subjects receiving rabeprazole. For subjects in 10-mg rabeprazole group, there was a mean increase of 163.66 ng/L (from 179.33 to 331.59 ng/L) as compared with a mean increase of 91.50 ng/L in subjects receiving 5-mg rabeprazole. However, in subjects randomized to placebo during the DB period after receiving rabeprazole 10-mg during the OL period, there was mean decrease of -13.17 ng/L.

CONCLUSIONS

In studies in infants 1 to 11 months of age, children 1 to 11 years of age and adolescents, the most common AEs were in the System Organ Classes of gastrointestinal, infectious, and respiratory/thoracic.

Neonates had a distinct profile of AEs with the most common being anemia of prematurity, apnea, bradycardia, retinopathy of prematurity, and inguinal and umbilical hernia. The neonates evaluated in Study RABGRD1005 were a relatively sick inpatient population with GERD symptoms in addition to concurrent co-morbidities. There was a trend toward more TEAEs in the higher dose groups (2 mg and 3 mg) compared with the low-dose group (1 mg).

Although this difference was attributable in part to chronic co-morbidities and conditions commonly found in premature infants, small numbers of other TEAEs/TESAEs associated with the higher dose groups included serious infections and possible sequelae of infection such as necrotizing enterocolitis, sepsis, pneumonia, and urinary tract infection. These were judged to be

not related to study drug by the investigators, but associations between certain infections (C. difficile enterocolitis, other enteric infections, and pneumonia) and the chronic use of PPIs as a class have been suggested by previous epidemiologic studies and can not be ruled out.

In the placebo-controlled study in infants 1 to 11 months of age (RABGRD3004), TEAEs occurred in both the OL (34.6%) and the DB (46.8%) periods of the study, with the majority being mild or moderate in severity. There were no notable differences in total TEAEs between the rabeprazole and the placebo group during the DB period, including TEAEs due to infections such as urinary tract infections, pneumonia, C. difficile infection, or gastroenteritis.

The safety in children 1 to 11 years of age was evaluated in RABGRD3003, the most common reported TEAEs in Part 1 were cough, vomiting, abdominal pain, diarrhea, pyrexia, headache, upper respiratory tract infection, oropharyngeal pain, and nasopharyngitis. The majority of all TEAEs were mild or moderate in severity. The incidences of TEAEs occurring in more than one subject were similar across the four actual dose groups in Part 1, with the exception of abdominal pain and headache, neither of which was reported for any subjects in the low-weight cohort. This is likely due to these subjects being younger in age and not able to verbalize these symptoms. The types and overall incidences of commonly reported TEAEs observed during the 24-week maintenance phase were not different from those observed during the initial 12-week treatment phase. The majority of all TEAEs were mild or moderate in severity.

When compared with adolescents, no qualitative differences in the safety profile for rabeprazole were observed between the 1 to 11 year and 12 to 16 year pediatric populations; however, the incidences of commonly reported TEAEs of cough, vomiting, abdominal pain, diarrhea, and pyrexia were lower in the 12- to 16-year-old study population. Similar to the studies in adolescents 12 to 16 years of age, no significant dose-response relationship was observed with respect to TEAEs in children 1 to 11 years of age. Most TEAEs were mild or moderate.

Overall, the occurrence of TEAEs, SAEs, and TEAEs leading to discontinuation in children 1 to 11 years of age was similar to that in adolescents 12 to 16 years of age. Adverse events leading to discontinuation were more common in children 1 to 11 months of age, mostly associated with worsening symptoms of GERD during the placebo-controlled DB period and withdrawal of parental consent.

In general, mean changes in laboratory parameters were small and not clinically meaningful across all the pediatric age groups. In the studies in infants and children which assessed gastrin, a trend toward a greater increase in serum gastrin was seen in the higher dose groups exposed for a longer period of time, which is consistent with the acid suppressive effect of rabeprazole.

9. Advisory Committee Meeting

No Advisory Committee was convened to discuss this NDA. In June 2010 Pediatric Advisory Committee discussed safety and efficacy in pediatric patients 1-11 months with symptomatic GERD on PPI therapy. The data indicated that PPI therapy (Esomeprazole or lansoprazole) was not shown to be effective in a randomized, placebo controlled efficacy

study in pediatric patients 1-11 months with symptomatic GERD. The data in this NDA on Aciphex is consistent with the AC conclusion on other PPIs.

10. Pediatrics

The NDA has been presented to Ped committee. The committees concurred with our assessment and provide detail labeling recommendation.

11. Other Relevant Regulatory Issues

According to Dr. Susan Leibenhaut from the Division of Good Clinical Practice Compliance, two clinical sites were inspected for this NDA and the final classification for both sites is NAI. The few issues raised during inspections are unlikely to have any effect on data integrity or efficacy outcome. The data generated by the sites appear acceptable in support of the indication targeted.

A total of 2 clinical sites were selected for inspection mainly due to high enrollment. All selected sites were inspected by the Division of Good Clinical Practice Compliance. Dr. Susan Leibenhaut from FDA DSI stated that the inspectional observations made at those clinical sites would not appear to have a substantive effect on safety and/or efficacy evaluations. The inspection of the sponsor indicated that its procedures for collecting, handling, and archiving the large amounts of data generated by these studies appear to be adequate. Other observations noted during the inspection of the sponsor would not appear to have a substantive effect on safety and/or efficacy evaluations.

Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the indication. See review by Dr. Susan Leibenhaut for detail.

The sponsor submitted financial certification and disclosures for Study 3003 and 3004. According to the sponsor, the clinical investigators who were filed to IND 33,985 and participated in support of this application, hold none of the disclosable financial arrangements with Johnson and Johnson Pharmaceutical Research & Development, L.L.C. as defined in 21CFR 54.2(a)(b)(c) and (f).

12. Labeling

Denise Baugh from DMEPA concludes that the proprietary name, ‘Aciphex Sprinkle’ and the dosage form ‘Delayed-release capsules’ are appropriate for this product and I concur.

The current proposed indication: “the healing and improvement of GERD symptoms and the maintenance of healing of GERD” is not appropriate. The indications of the healing and the maintenance of healing were granted in the past only to “erosive or ulcerative GERD”. However,

in the current NDA, study population included both non-erosive and erosive GERD. Therefore, I recommend that the wording of indication be changed to "treatment of GERD in Pediatric Patients Aged 1 to 11 Years".

I concur with labeling recommendations provided by Dr. Troiani listed in his review and concur with labeling recommendations provided by the review team.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend that NDA 204736 for ACIPHEX® (rabeprazole sodium) Delayed-Release Sprinkle Capsules be approved for the Treatment of GERD in Pediatric Patients Aged 1 to 11 Years

For patients with bodyweight < 15 kg, 5 mg once daily with the option to increase to 10 mg; for patients with bodyweight ≥ 15 kg, 10 mg once daily

- Risk Benefit Assessment

I concur with Dr. Troiani's risk-benefit assessment that benefits outweigh potential risk for pediatric patients 1-11 years old with GERD. The risk-benefit balance is in favor of approval of ACIPHEX® (rabeprazole sodium) Delayed-Release Capsules in treatment of GERD in pediatric patients 1-11 years old.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  Includes restricted distribution, components of REMS

  None

- Recommendation for other Postmarketing Requirements and Commitments

As a PMC, the sponsor should assess the effect of alcohol on the drug release of AcipHex Delayed Release Sprinkle Capsules. In the current NDA, the applicant did not evaluate the alcohol dose dumping potential of their proposed modified release dosage form.

The timeline the sponsor submitted on March 15, 2013, states that the sponsor will conduct this study and submit the study results according to following timeline:

Protocol Submission: 8 May 2013
Study Completion: 8 July 2013
Report Submission: 8 August 2013

- Recommended Comments to Applicant

  None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUYI HE
03/18/2013