CLINICAL REVIEW

Application Type	New NDA
Application Number(s)	204,736
Priority or Standard	Priority
Submit Date(s)	27-Sep-2012
Received Date(s)	27-Sep-2012
PDUFA Goal Date	27-Mar-2013
Division / Office	DGIEP
Reviewer Name(s)	John Troiani, MD, PhD
Review Completion Date	05-Mar-2013
Established Name	Rabeprazole
(Proposed) Trade Name	ACIPHEX sprinkle capsules
Therapeutic Class	Proton-Pump Inhibitor (PPI)
Applicant	Eisai
Formulation(s)	Sprinkle Delayed-Release Capsule
Dosing Regimen	5mg or 10mg
Indication(s)	Treatment of GERD (up to 12 weeks)
Intended Population(s)	Children with GERD, ages 11 years or less

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Children 1 to 11 years of age. I recommend approval of ACIPHEX Sprinkle Delayed-Release Capsules for the indication of Treatment of GERD in the 1-11 year age group for up to 12 weeks of treatment at a dose of 5 mg (or 10 mg if inadequate response to 5 mg) for patients weighing less than 15 kg; and at a dose of 10mg for patients weighing at least 15 kg.

Infants 1 to 11 months of age. I recommend not approving ACIPHEX for GERD in this age group.

Neonates 0 to <1 month of age or CGA <44 weeks. I recommend not approving ACIPHEX for GERD in this age group.

PMCs. The Applicant has agreed to conduct an in vitro study to assess the effect of alcohol on the drug release of ACIPHEX Sprinkle Delayed Release Capsules and commits to report the study results no later than August 8, 2013 according to the amendment dated February 15, 2013.

PREA. The Applicant was granted pediatric exclusivity on 04-Dec-2012 and has fulfilled their PREA obligation.

1.2 Risk-Benefit Assessment

Neonates 0 to <1 month of age or CGA <44 weeks. No studies were done to assess efficacy and safety for use of ACIPHEX in patients with GERD in this age group.

Infants 1 to 11 months of age. Randomized placebo-controlled multicenter trial (Study 3004) did not demonstrate efficacy of ACIPHEX in patients with GERD in this age group.

Children 1 to 11 years of age. A multicenter, randomized, two parallel-group, non-placebo-controlled trial (Study 3003) of low- and high-dose ACIPHEX sprinkles given orally once daily in 127 patients with endoscopically proven GERD was conducted. At baseline, all patients underwent esophagogastroduodenal (EGD) endoscopy with

biopsy. For enrollment patients had to have both a Hetzel-Dent (HD) score of at least 1 (0=normal; 1=inflammation without erosions; 2 and higher=erosions) and a Histologic Features of Reflux Esophagitis (HFRE) score of at least 1 (0=no abnormality; 1 or higher=histologic evidence of inflammation of esophageal mucosa).

Enrolled patients were then randomized to one of two rabeprazole dose levels—0.5 mg/kg/day (low-dose) or 1.0 mg/kg/day (high-dose). For convenience to parents and trial conduct, the actual doses given were 5 mg, 10 mg, or 20 mg, depending on the patient's bodyweight. For patients weighing 6.0 to14.9 kg (low-weight cohort), low-dose was 5mg and high-dose was 10mg. For patients weighing 15 kg or more (high-weight cohort), low-dose was 10mg and high-dose was 20mg.

In Part 1, patients received once daily rabeprazole for 12 weeks when they underwent endoscopy with biopsy. Part 2 was a double-blinded extension of Part 1, in which 12-week responders ("healing" defined as HD=0 or HFRE=0) were continued in double-blind fashion for an additional 24 weeks on once daily rabeprazole at the dose assigned in Part 1. Of 87 patients who achieved healing in Part 1, 64 patients were enrolled into Part 2. Endoscopy with biopsy was repeated at the end of Part 2 (36 weeks total rabeprazole).

The primary endpoint for Parts 1 and 2 was endoscopic healing (HD=0) or histologic healing (HFRE=0) after 12 and 36 weeks of rabeprazole, respectively. There was no prespecified hypothesis testing. The 12-week (Part 1) healing rates were as follows:

- Low-weight cohort
    - Low-dose (5 mg): 82% (14/17)
    - High-dose (10mg): 94% (15/16)
- High-weight cohort
    - Low-dose (5 mg): 76% (29/38)
    - High-dose (10mg): 78% (29/37)

Given the use of endoscopy in all patients, which is the gold standard in erosive GERD, these healing rates demonstrate efficacy in all dose-bodyweight subgroups. In the low-weight cohort, the data suggest an incremental benefit of 10mg over 5mg, but the sample sizes are small. At 5mg, rabeprazole exposure in children was less than for the 20mg dose in adults. At 10mg, rabeprazole exposure was the same as in adults. Therefore, we accept the Applicant's proposal to indicate both 5mg and 10mg (if inadequate response to 5mg) in those children 1-11 years of age weighing 6.0 to 14.9 kg.

For children weighing 15kg or more, there appears to be no incremental benefit of 20 mg over 10 mg. Therefore the Applicant's proposal to indicate a 10mg dose for children weighing 15kg or more is acceptable.

As to duration of treatment of GERD, a duration of 12 weeks is acceptable, consistent with the design of the phase 3 trial.

As to risk, the most frequent adverse drug reactions (ADRs) in Study 3003 Part 1 occurred at rates of 5%, and included abdominal pain, diarrhea, and headache. These will be included in the label. In Part 2, only 2 patients experienced ADRs after a total of 36 weeks of rabeprazole. None of the ADRs reported in the 1-11 year age group were not already reported in adults and adolescents.

In conclusion, I feel the benefit of ACIPHEX for the treatment of GERD for up to 12 weeks in children 1-11 years of age exceeds its risk, based on the submitted data.

(b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations for postmarket risk evaluation and mitigation strategies.

1.4 Recommendations for Postmarket Requirements and Commitments

No new recommendations. The Applicant has already agreed to conduct an in vitro study to assess the effect of alcohol on the drug release of ACIPHEX Sprinkle Delayed-Release Capsules, and commits to report the study results no later than August 8, 2013 according to the amendment dated February 15, 2013.

2 Introduction and Regulatory Background

2.1 Product Information

Rabeprazole is a proton-pump inhibitor that has been approved for use in patients with GERD down to 12 years of age.

2.2 Tables of Currently Available Treatments for Proposed Indications

The Applicant has proposed the following indications for GERD for the 1-11 year age group, the only age group and indications for which the Applicant is seeking approval:

(b) (4)

The currently available PPI treatments for GERD in patients 1 to 11 years of age include omeprazole, esomeprazole, and lansoprazole shown in Table 1.

Table 1 Table of currently available PPIs for proposed indications

Treatment	Indication in 1-11 year age group	Notes
NEXIUM® (esomeprazole) DR Capsules and Oral Suspension	**Section 1.1 Treatment of GERD** • *Healing of EE:* "…indicated for short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course of NEXIUM may be considered." (dose: weight<20kg:10mg; weight≥20kg: 10mg or 20mg) • *sGERD*: "…indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with GERD in adults and children 1 year or older." (dose: 10mg once daily)	In clinical trial in 1-11 year age group—multicenter parallel group with n=109 patients treated once daily for up to 8 weeks. "history of endoscopically-proven GERD" N=53 (49%) patients with EE at baseline. Patients were endoscopically characterized as to presence or absence of EE. "Although most of the patients who had follow up endoscopy at the end of 8 weeks of treatment healed, spontaneous healing cannot be ruled out because … the trial did not include a control group."
PRILOSEC® (omeprazole) DR tabs and DR Oral Suspension	**Section 1.3 Treatment of GERD (adults and pediatric patients)** • *Symptomatic GERD*: "… is indicated for treatment of heartburn and other symptoms associated with GERD in pediatric patients and adults (dose: weight "5 < 10kg": 5mg; weight "10 < 20 kg": 10mg; weight ≥20kg: 20mg). <u>NOTE</u>: treatment duration for pediatric sGERD is not specified in Highlights, Indications, or Dosage and Administration sections of label • *EE:* "…is indicated for the short-term treatment (4-8 weeks) of EE that has been diagnosed by endoscopy in pediatric patients and adults." (dose: weight "5 < 10kg": 5mg; weight "10 < 20 kg": 10mg; weight ≥20kg: 20mg) **Section 1.4 Maintenance of healing of EE (adults and pediatric patients)** "…is indicated to maintain healing of EE in	"effectiveness…for the treatment of nonerosive GERD in pediatric patients 1 to 16 years of age is based in part on data obtained from 125 pediatric patients in two uncontrolled Phase III studies." <u>sGERD Study 1</u>: n=12 pediatric patients 1 -2 years old "with history of clinically diagnosed GERD" treated for 8 weeks. 75% (9/12) had decreased vomiting/regurg episodes from baseline by at least 50%. <u>sGERD Study 2</u>: n=113 patients 2-16 years old "with a history of symptoms suggestive of nonerosive GERD" treated for 4 weeks. Successful response was defined as "no moderate or severe episodes of either pain-related symptoms or vomiting/regurgitation during the last 4 days of treatment." Response rates of 59% (58/98 in 20mg group) and 60% (9/15 in 10mg group).

Treatment	Indication in 1-11 year age group	Notes
	pediatric patients and adults." (dose: weight "5 < 10kg": 5mg; weight "10 < 20 kg": 10mg; weight ≥20kg: 20mg) NOTE: treatment duration for pediatric maintenance of healing of EE is not specified in Highlights, Indications ("Controlled studies do not extend beyond 12 months."), or Dosage and Administration sections of label.	Healing of EE: uncontrolled open-label dose-titration study in 1-16 year age group. EE healed in 90% (51/57) Maintenance of Healing of EE: uncontrolled open-label n=46. "54% of patients required half the healing dose" "41% had no relapse". 63% had "no overall symptoms"
PREVACID® (lansoprazole) DR Capsules, DR Oral Suspension, DR ODT	"**Pediatrics (8.4)**: (1-11 years of age) Short-term treatment of sGERD and short-term treatment of EE" (Highlights section, "Dosage and Administration"—none in Indications) **Section 1.7 GERD** • *Short-term Treatment of sGERD "*…is indicated for the treatment of heartburn and other symptoms associated with GERD. (dose: ≤30kg: 15mg; >30kg: 30mg--once daily for up to 12 weeks) • *Short-term Treatment of EE "*…is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of EE. For patients who do not heal with PREVACID for 8 weeks (5-10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of EE an additional 8-week course of PREVACID may be considered." (dose: ≤30kg: 15mg; >30kg: 30mg--once daily for up to 12 weeks)	Clinical trial in 1-11 year olds--uncontrolled open-label, n=66 patients "with GERD". After 8-12 weeks "50% reduction in frequency and severity of GERD symptoms". 21/27 with EE were healed at 8 weeks and 100% at 12 weeks by endoscopy.

[ref: labels]

2.3 Availability of Proposed Active Ingredient in the United States

Available.

2.4 Important Safety Issues With Consideration to Related Drugs

Osteopenia/osteoporosis/fracture and hypomagnesemia (rare) are the two main safety issues for the PPIs, and both may occur with prolonged use of PPIs. Bone fracture may also be associated with multiple daily doses of a PPI.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

31-Dec-2001. Written Request issued.

14-Sep-2012. Final Amendment (#7) to Written Request.

04-Dec-2012. Exclusivity granted.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission has acceptable quality and integrity.

3.2 Compliance with Good Clinical Practices

The Applicant states that it is in compliance with Good Clinical Practices.

3.3 Financial Disclosures

Based on the Applicant's submitted financial disclosure information, none of the investigators had financial conflicts of interest or disclosures to make.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

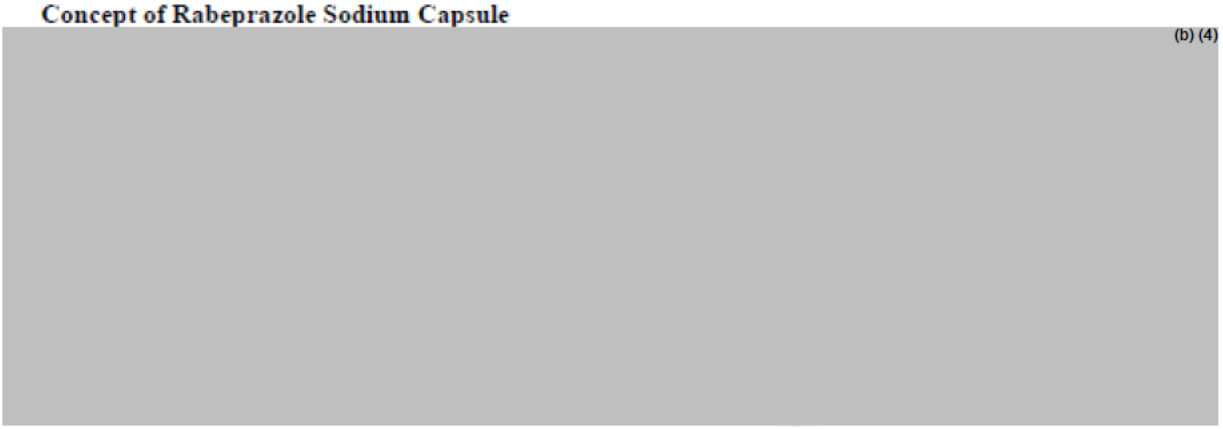
4.1 Chemistry Manufacturing and Controls

Labeling issues have not yet been resolved as of this review.

The Applicant has already agreed to conduct an in vitro study to assess the effect of alcohol on the drug release of AcipHex Sprinkle Delayed Release Capsules and commits to report the study results no later than August 8, 2013 according to the amendment dated February 15, 2013.

Drug Product. The drug product, AcipHex Sprinkle (rabeprazole sodium) Delayed-Release Capsules, is hypromellose hard capsules containing enteric coated granules of rabeprazole sodium (b) (4). Each capsule contains either (b) (4) 5 or 10 mg of rabeprazole sodium. (b) (4) The 5 mg strength is a transparent blue and opaque white No. 2 capsule. The 10 mg strength is a transparent yellow and opaque white No. 2 capsule. These (b) (4) strengths of sprinkle capsules contain (b) (4) enteric coated rabeprazole sodium granules.

Concept of Rabeprazole Sodium Capsule



Cross-Sectional Image of Enteric Coated Granule

Sprinkle Capsule

Manufacture. The manufacturing process of rabeprazole sodium capsules consists of drug substance (b) (4) . The in-process controls implemented during the manufacturing process are: (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 doses are adjusted by (b) (4) each hypromellose (HPMC) capsule. Two administration methods were expected for pediatric populations. One is a sprinkle administration (for children) and the other is (b) (4) The product was designed to satisfy both administration methods.

The rabeprazole sodium delayed-release sprinkle capsules are packaged into high density polyethylene (HDPE) bottles (bottles of 30 capsules). with a (b) (4) screw cap closure with an induction liner. Silica gel canisters are included as a desiccant in each bottle. The rabeprazole sodium capsule are developed for patients in age below 12 years old because tablets are hard to swallow for the target patients. The capsules should be opened and the enteric coated granules in the capsule should be sprinkled on a small amount of soft food or mixed with a small amount of infant formula and then swallowed. The proposed expiration dating period of 24 months is supported by the long-term and accelerated stability data provided.

4.2 Clinical Microbiology

None.

4.3 Preclinical Pharmacology/Toxicology

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. Toxicokinetic analysis in this study included the unchanged drug (E3810), but not the thioether metabolite (PTBI), which is one of the primary metabolites in human plasma. Therefore, the Sponsor conducted a toxicokinetic bridging study in neonatal rats, using oral administration of 25 and 150 mg/kg/day E3810 on days 7 to 41 *post partum*. AUC values for PTBI exceeded that of E3810, with the exception of the low-dose group on *pp* day 7.

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.

4.4 Clinical Pharmacology

ACIPHEX Sprinkle Delayed-release capsules are in an enteric-coated capsule to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact.

4.4.1 Mechanism of Action

Rabeprazole is a substituted benzimidazole proton-pump inhibitor that suppresses gastric acid secretion by inhibiting gastric H^+/K^+ATPase at the secretory surface of the gastric parietal cell. Rabeprazole does not exhibit anticholinergic or histamine H_2-receptor antagonist properties. Because gastric H^+/K^+ATPase is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied *in vitro*, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

4.4.2 Pharmacodynamics

The pharmacodynamics have been extensively studied in adults—see label.

Neonates 0 to <1 month of age, Study 1005. The PD endpoint was % time with gastric pH<4 (PTGA4). Mean PTGA4 was 90%, which is consistent with levels defined for hypo- and achlorhydria. There does not appear to be a dose-response relationship for mean PTGA4, as follows:

- 1-mg dose: 90%
- 2-mg dose: 99%
- 3-mg dose: 81%

The PD effects of ACIPHEX are to:

- increase %-time with gastric pH>4 (65% in adults on Aciphex 20mg QD versus 2.8% on placebo)
- decrease 24-hour esophageal acid exposure (mean AUC acidity on ACIPHEX 20 mg QD was 341 on Day-1 and 77 on Day-8; versus placebo values of 926 and 862, respectively)
- increase serum gastrin
    - doubled in adults after 20mg QD for 4 weeks—35% of adult subjects developed serum gastrin levels above upper limit of normal).
- increase gastric ECL cell hyperplasia
    - incidence of ECL hyperplasia in adults (n=400) increases with time and dose (consistent with pharmacologic action of PPIs)
    - no patients developed adenomatoid, dysplastic, or neoplastic changes of ECL cells in the gastric mucosa; no patients developed carcinoid tumors (seen in rats)

Medical Reviewer Comment. ECL cell hyperplasia observed in animals and human adults is a risk of long-term treatment with any of the PPIs. In children with GERD for the labeled duration of 12 weeks in children or even longer, it should not be an issue.

4.4.3 Pharmacokinetics

Neonates 0 to <1 month of age. Based on population pharmacokinetic analysis, the median (range) for the apparent clearance (CL/F) was 1.05 L/h (0.0543-3.44 L/h) in neonates and 4.46 L/h (0.822-12.4 L/h) in patients 1-11 months of age following once daily administration of oral ACIPHEX Sprinkles.

Children 1-11 years of age. In patients with GERD aged 1 to 11 years, following once daily administration of rabeprazole granules at doses from 0.14 to 1 mg/kg, the median time to peak plasma concentration ranged 2-4 hours and the half-life was about 2.5 hour. No appreciable accumulation was noted following 5 days of dosing compared to exposure after a single dose.

Based on population pharmacokinetic analysis, over the body weight range from 7 to 77.3 kg, the apparent rabeprazole clearance increased from 8.0 to 13.5 L/hr, an

increase of 68.8%. The mean estimated total exposure i.e. AUC after a 10 mg dose of ACIPHEX Sprinkle Capsules in patients with GERD aged 1 to 11 years is comparable to a 10 mg dose of ACIPHEX Tablets in adolescents and adults.

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

The to-be-marketed granule formulation differs from the formulation used in the phase 3 trial in terms of the manufacturing site and the material grade of magnesium oxide. The bioequivalence was demonstrated between the to-be-marketed formulation as one 10 mg capsule and the phase 3 formulation as two 5 mg capsules. The geometric mean ratio of Cmax and AUC for rabeprazole and its associated 90% CI met the bioequivalence criteria. The Office of Scientific Investigations (OSI) inspected the clinical site and the bioanalytical site of the pivotal bioequivalence study (Study 1007). The OSI reviewer recommends that data from the analytical and clinical portions of study are acceptable for further agency review.

Effect of a high fat meal on PK of rabeprazole

When a high fat meal was taken prior to rabeprazole dosing, the absorption of rabeprazole was delayed, and mean Cmax and AUC of rabeprazole decreased by 55% and 32%, respectively. For the ACIPHEX tablet, systemic exposure was not significantly altered under the fed versus fasting condition. In the phase 3 trial in patients 1-11 years old, rabeprazole granules were allowed to be taken before or with meals, and the timing of meal intake relative to rabeprazole dosing was not recorded. Based on decreased systemic exposure with a fatty meal and the uncertainty in the lowest effective systemic exposure, administration of rabeprazole granules 30 minutes prior to a meal is recommended.

Effect of food vehicles on PK of rabeprazole

There was no significant difference in the pharmacokinetics of rabeprazole when sprinkles in apple sauce, yogurt or infant formula. Whereas this study was done with the phase 3 formulation, similar results are expected for the to-be-marketed formulation which is bioequivalent to the phase 3 formulation when administered after sprinkled on applesauce.

Effect of rabeprazole on PK of clopidogrel

A class labeling update was proposed for the drug interaction between rabeprazole and clopidogrel. The effect of concomitant rabeprazole on PK of clopidogrel was studied in healthy subjects with the ACIPHEX Tablet. When clopidogrel 75 mg was administered with rabeprazole 20 mg for 7 days (n=36), mean AUC of the active metabolite of clopidogrel was decreased by 12% (90% CI for mean ratio of 81.7 to 95%). In the same study, 20 mg omeprazole decreased the AUC of active metabolite of clopidogrel by 18%.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant's studies referenced in this clinical review are listed in Table 2.

Table 2 Table of referenced studies in this review

Study	Study Population	Primary and Secondary Endpoints	Design	Summary of Results
RABGRD1005 (Study 1005)	0 to <1 month of age	PK/PD in neonates (0 to <1 month old)	Multicenter, open-label, short-term (5-28days) of once daily rabeprazole (n=69): Phase 1: 1mg Phase 2: 2, 3mg (random assignment)	AUC ~3-fold higher in neonates than in 1-11 month age group. PD: mean (pooled dose groups) % of time with gastric pH>4 on rabeprazole Day 5: 90% [range 80% to 100%] (63% pre-rabeprazole) Safety: 1 death in a medically complex premature infant with multisystem pathology, adjudicated as not related to rabeprazole. Rate of anemia TEAEs (11%-20%-24% in 1mg-2mg-3mg dose groups)
RABGRD3004 (Study 3004)	1 to 11 months of age with suspected GERD, symptomatic GERD, or endoscopically proven GERD	Co-Primary—changes from baseline in both: a) frequency of regurgitation from baseline ; AND b) weight-for-age Z-score Secondary—regurgitant volume, I-GERQ-DD score and subscores	Randomized, multicenter, open-label followed by double-blind (DB), placebo-controlled trial in 344 enrolled patients; 268 responders to 1-3 weeks of open-label rabeprazole were then randomized into a 5-week DB period (placebo vs rabeprazole). Interim futility stopping was added but ended up being as already planned at end of trial.	Efficacy was not demonstrated. Other PPIs were also not able to demonstrate efficacy in same population in 1-11 month age group, which was the subject of an AC convened in Nov-2010. Safety: No deaths. TEAEs (PBO v 5mg v 10mg): 47% v 43% v 50%. GERD, vomiting, fever, URI, elevated serum gastrin.
RABGRD3003	1 year to 11 years of	Primary—Histologic	Randomized,	Healing rates (low, high

Study	Study Population	Primary and Secondary Endpoints	Design	Summary of Results
Part 1 (Study 3003 Part 1)	age with "endoscopically proven" GERD[1]	or endoscopic esophageal mucosal healing[2] at 12 weeks Secondary—pooled and individual symptom scores[3]	multicenter, double-blinded (no placebo) trial (n=127) of 2 dose levels by bodyweight: ≤15kg: 5 or 10 mg >15kg: 10 or 20mg	dose): <15kg: 82%(14/17), 94%(15/16) ≥15kg: 76% (29/38), 78%(29/37) Safety: no deaths; no new AEs not already reported in adults and adolescents
RABGRD3003 Part 2 (Study 3003 Part 2)	1 year to 11 years of age who passed primary endpoint in Part 1	Primary—Histologic or endoscopic esophageal healing[2] after 24 additional weeks (total 36 weeks of rabeprazole including Part 1) Secondary—pooled and individual symptom scores[3]	Double-blinded continuation of Part 1 on same dose as in Part 1	Healing rates (low, high dose): ≤15kg: 100%(8/8), 100%(6/6) >15kg: 89% (16/18), 85%(17/20) Safety: no deaths; no new AEs not already reported in adults and adolescents

1. "Endoscopically proven" is Applicant's term that is defined as an [endoscopic] Hetzel-Dent (HD) score≥1 AND biopsy with Histologic Features of Reflux Esophagitis (HFRE) grade>0. All enrolled patients must have had a history of at least one GERD symptom in the last 3 months prior to screening.
2. Definition of "healing" is HD=0 or HFRE=0. This is also the definition of success on the primary endpoint on an individual subject basis.
3. Total GERD Symptom and Severity Score and derived subscores. This is a pooled symptom score that is not accepted or validated at the time of this review for purposes of FDA approval.

5.2 Review Strategy

The strategy used in this review is to focus on the 1 to 11 year (1-11y) age group because that is the population for which the Applicant seeks approval. However, depending on the section of this review and relevance, the neonatal and infant age groups are sometimes presented.

The pediatric development program is divided into four age groups as follows:

- Adolescent (12-17y): APPROVED. Will not be reviewed.
- Pediatric (1-11y)—Study 3003 Parts 1 and 2
    - Will be reviewed

  - Applicant seeks indication for GERD in this age group. This review will detail safety and efficacy data from Study 3003 (Parts 1 and 2) in this age group.

- Infant (1-11 months)—Study 3004
  - Will be reviewed for clinical labeling issues (label sections 6 and 8)
  - The phase 3 trial for rabeprazole in this age group was not able to demonstrate safety and efficacy. Four other PPIs (in four similarly designed trials) also failed to demonstrate efficacy in infants, which was the subject of an Advisory Committee (Nov 2010). The consensus of the AC was that safety and efficacy have not been demonstrated in the 1-11m age group. The safety and efficacy results will be reviewed at a high level with regard to labeling requirements required for negative studies.
- Neonate (0 to <1 month)—Study 1005 (PK/PD)
  - Will be reviewed in safety section (label section 8)
  - No safety and efficacy clinical trial data were obtained or requested in this age group. A PD/PK study was performed and safety data were collected. This age group will be reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

See Table 2 for overview of studies.

Study 3003 Part 1. Double-blinded non-placebo trial in children with endoscopically proven GERD 1-11 years of age.

> 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 [Results of the 12-Week Treatment Phase]

Start and end dates: 30-Jan-2009 through 19-Aug-2010

Study 3003 Part 2. Double-blinded non-placebo extension of Part 1 for 24 additional weeks in children who responded to rabeprazole (healed) at the end of Part 1.

> 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 [Results of the 24-Week Maintenance Treatment Phase]

Start and end dates: 21-Apr-2009 through 25-Jan-2011

Study 3004. Double-blind placebo-controlled trial in infants 1-11 months of age with suspected, symptomatic, or endoscopically proven GERD. The data from this trial do not support efficacy, similar to the other PPIs in this age group and indication.

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Withdrawal Study to Evaluate the Safety and Efficacy of Delayed-Release Rabeprazole in 1- to 11-Month-Old Pediatric Subjects with Symptomatic/Erosive Gastroesophageal Reflux Disease (GERD)

Start and end dates: 04-Nov-2009 through 16-Nov-2011

Study 1005. PK/PD study in neonates 0 to <1 month of age or CGA<44 weeks.

A Pharmacokinetic, Pharmacodynamic and Short-term Safety Study of Single and Multiple Day Doses of Rabeprazole Sodium in Neonates and Pre-term Infants with a Corrected Age of Less than 44 Weeks with a Presumptive Diagnosis of GERD

Start and end dates: 21-Feb-2010 through 14-Jan-2012

6 Review of Efficacy

Efficacy Summary

Neonates. Efficacy and safety have not been demonstrated.

Infants. Efficacy and safety have not been demonstrated.

Children 1 year to 11 years of age. Efficacy and safety have been demonstrated for the treatment of GERD for up to 12 weeks.

6.1 Indication

The Applicant seeks the following indications in the 1-11y age group [ref: Label submitted on 10-Dec-2012]:

(b) (4)

Medical Reviewer Comment. A single indication of "Treatment of GERD" in the 1-11 year age group for up to 12 weeks is supported by these data, and this will be discussed later in this review. The proposed indications are not acceptable at this time, based on the following considerations:

1. *Indication 1.4.1—"* (b) (4) *„*

(b) (4)

(b) (4)

6.1.1 Methods

Efficacy data for the individual age groups of neonate, infant, and child are assessed separately.

6.1.2 Demographics

Infants 1-11 month olds. Study 3004. There were 344 patients enrolled in Study 3004. These patients were distributed by age as follows: 1 to <4months—49%, 4 to <8 months—37%, 8 to 11 months—14%.

Mean time from initial diagnosis of GERD was 57 days (SD 64, range 1 to 335). Of 344 patients, 12 patients had endoscopy; and the average time since this endoscopy prior to enrollment was 20 days (1 to 65, range). Failure to thrive/poor weight gain was present in 25% (86/344) of enrollees. During the open-label phase, 63% (218/344) of patients took at least one concomitant medication--colecalciferol (11%) and vitD (6%).

1-11 year olds. Study 3003 Part 1. Table 3 shows the demographics of Study 3003 Part 1.

Table 3 Demographics: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
Parameter	(N=21) n (%)	(N=19) n (%)	(N=44) n (%)	(N=43) n (%)
Age Group, n (%)				
1 to 5 Years	21 (100)	19 (100)	15 (34)	14 (33)
6 to 11 Years	0	0	29 (66)	29 (67)
Age, Years				
Mean (SD)	2.4 (1.24)	1.9 (1.08)	7.6 (2.91)	7.0 (2.66)
Median	2.0	2.0	8.0	7.0
Range	(1; 5)	(1; 5)	(2; 11)	(1; 11)
Sex, n (%)				
Female	12 (57)	8 (42)	19 (43)	17 (40)
Male	9 (43)	11 (58)	25 (57)	26 (60)
Race, n (%)				
White	16 (76)	13 (68)	38 (86)	32 (74)
Black or African American	1 (5)	3 (16)	2 (5)	7 (16)
Asian	2 (10)	1 (5)	0	0
Other*	2 (10)	2 (11)	4 (9)	4 (9)
Ethnicity, n (%)				
Hispanic or Latino	1 (5)	0	4 (9)	7 (16)
Not Hispanic or Latino	18 (86)	17 (89)	38 (86)	32 (74)
Unknown/Not Provided	2 (10)	2 (11)	2 (5)	4 (9)
Screening Weight, kg				
Mean (SD)	12.4 (1.86)	11.5 (2.26)	32.7 (15.20)	28.5 (11.85)
Median	12.7	11.9	29.5	25.4
Range	(8; 15)	(7; 15)	(15; 76)	(15; 57)
Screening Height, cm				
Mean (SD)	90.9 (7.34)	87.6 (8.83)	129.4 (20.51)	124.6 (18.19)
Median	92.5	87.0	134.0	125.5
Range	(75; 102)	(72; 104)	(93; 165)	(89; 169)
Screening BMI, kg/m^2				
Mean (SD)	15.1 (2.30)	15.0 (1.62)	18.7 (4.28)	17.7 (3.26)
Median	15.5	14.9	17.6	17.0
Range	(11; 20)	(12; 17)	(13; 32)	(13; 27)

* Other races included mixed, Mexican, North African, Caucasian, etc. Since no 'American Indian', 'Alaskan Native', 'Native Hawaiian', or 'Other Pacific Islanders' were enrolled in the study, those categories are not listed in the demographics table.

[ref: CSR Study 3003 Part 1, Table 11.1, p. 69]

Medical Reviewer Comment. Demographics appear to be approximately balanced between dose groups within each weight cohort, considering the relatively small sample sizes and random variation.

Regarding prior medication, 80% (101/127) of patients had taken at least 1 medication prior to enrollment. The most common prior medications were lansoprazole, macrogol,

ranitidine, and salbutamol, each of which was used in 14% of patients. There were 22% (28/127) of patients who used antacids.

During the treatment period, 87% of patients used concomitant medications including paracetamol (24%), ibuprofen (19%), calcium carbonate (17%), and salbutamol (16%), and others whose rates of use were less than 15%. Rescue medications were reported in 40% of patients during Part 1, the most common being calcium carbonate (17%) and Aludrox (13%).

Prohibited medications were used by 6% (8/127) patients at some point in Part 1. Prohibited medications included sucralfate or motility modifiers such as baclofen, EES, and metoclopramide, digoxin/digitalis, ketoconazole, caffeine, theophylline, PPIs, H2-blockers. These drugs were used for a short period of time (1 to 4 days) prior to or on initiation day of study drug.

1-11 year olds. Study 3003 Part 2. Table 4 shows the demographics of Study 3003 Part 2.

Table 4 Demographics: Study 3003 Part 2

	Rabeprazole Sodium Treatment by Actual Dose			
	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
Parameter	(N=9) n (%)	(N=8) n (%)	(N=24) n (%)	(N=23) n (%)
Age Group, n (%)				
1 to 5 Years	9 (100%)	8 (100%)	9 (38%)	6 (26%)
6 to 11 Years	0	0	15 (63%)	17 (74%)
Age, Years				
Mean (SD)	2.4 (1.24)	1.5 (0.53)	7.7 (2.74)	7.2 (2.66)
Median	2.0	1.5	9.0	8.0
Range	(1; 5)	(1; 2)	(3; 11)	(1; 11)
Sex, n (%)				
Female	5 (56%)	4 (50%)	8 (33%)	10 (43%)
Male	4 (44%)	4 (50%)	16 (67%)	13 (57%)
Race, n (%)				
White	6 (67%)	6 (75%)	22 (92%)	17 (74%)
Black or African American	0	1 (13%)	1 (4%)	4 (17%)
Asian	2 (22%)	1 (13%)	0	0
Other*	1 (11%)	0	1 (4%)	2 (9%)
Ethnicity, n (%)				
Hispanic or Latino	1 (11%)	0	1 (4%)	2 (9%)
Not Hispanic or Latino	8 (89%)	7 (88%)	21 (88%)	19 (83%)
Unknown/Not Provided	0	1 (13%)	2 (8%)	2 (9%)
Screening Weight, kg				
Mean (SD)	11.9 (2.52)	10.5 (2.13)	33.8 (15.57)	31.0 (13.17)
Median	11.8	10.2	31.3	28.0
Range	(8; 15)	(7; 14)	(15; 76)	(15; 54)
Screening Height, cm				
Mean (SD)	92.1 (7.61)	83.7 (6.77)	130.0 (18.57)	127.3 (19.52)
Median	94.0	83.8	136.0	128.5
Range	(75; 101)	(75; 97)	(99; 154)	(89; 169)
Screening BMI, kg/m^2				
Mean (SD)	14.0 (2.11)	14.8 (1.65)	19.0(4.86)	18.3 (3.43)
Median	13.4	15.0	17.5	17.3
Range	(11; 17)	(12; 17)	(14; 32)	(14; 25)

*Other races included mixed, Mexican, North African, Caucasian, etc. Since no 'American Indian', 'Alaskan Native', 'Native Hawaiian', or 'Other Pacific Islanders' were enrolled in the study, those categories are not listed in the demographics table.

[ref: CSR Study 3003 Part 2, Table 11.2, p. 57]

Medical Reviewer Comment. Demographics appear to be approximately balanced between dose groups within each weight cohort, considering the relatively small sample sizes and random variation.

6.1.3 Subject Disposition

Subject disposition is now summarized.

1-11 year olds. Study 3003, Part 1, by dose group: see Table 5.

Table 5 Subject disposition by dose group: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Target Dose		
Disposition Status Primary Reason	0.5 mg/kg (N=65) n (%)	1.0 mg/kg (N=62) n (%)	Total (N=127) n (%)
Completed	55 (85)	53 (85)	108 (85)
Withdrawn	10 (15)	9 (15)	19 (15)
Adverse Event	1 (2)	2 (3)	3 (2)
Protocol Violation	0	1 (2)	1 (1)
Other	0	2 (3)	2 (2)
Physician Decision	1 (2)	0	1 (1)
Lost to Follow-Up	2 (3)	2 (3)	4 (3)
Subject Withdrew Consent	6 (9)	2 (3)	8 (6)
Continuing in the Long-Term Phase	34 (52%)	31 (50%)	65 (51%)

Cross Reference: Attachment DSUB03A

[ref: Clinical Study Report for study 3003, Part 1, Table 10.1, p.62]

1-11 year olds. Study 3003, Part 1, dose-weight group: see Table 6.

Table 6 Subject disposition by dose-weight group: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
Disposition Status Primary Reason	(N=21) n (%)	(N=19) n (%)	(N=44) n (%)	(N=43) n (%)
Completed	17 (81)	16 (84)	38 (86)	37 (86)
Withdrawn	4 (19)	3 (16)	6 (14)	6 (14)
Adverse Event	1 (5)	1 (5)	0	1 (2)
Lost to Follow-Up	1 (5)	0	1 (2)	2 (5)
Physician Decision	0	0	1 (2)	0
Protocol Violation	0	0	0	1 (2)
Subject Withdrew Consent	2 (10)	1 (5)	4 (9)	1 (2)
Other	0	1 (5)	0	1 (2)
Continuing into the 24-week Double-Blind Maintenance Treatment Phase	10 (48)	8 (42)	24 (55)	23 (53)

Note: Actual dose was determined by baseline weight category and randomized dose. For subjects randomized to 0.5 mg/kg, if baseline weight < 15 kg, the actual dose was 5 mg and if baseline weight was ≥ 15 kg the actual dose was 10 mg (denoted 10 mg [0.5 mg/kg]). For subjects randomized to 1.0 mg/kg, if baseline weight < 15 kg, the actual dose was 10 mg (denoted 10 mg [1.0 mg/kg]) and if baseline weight was ≥ 15 kg the actual dose was 20 mg.
Cross Reference: Attachment DSUB03AT

[ref: Clinical Study Report for study 3003, Part 1, Table 10.2, p.63]

In Table 5, the most common reason for not completing the study was withdrawal of consent (6%). Reasons for withdrawal of consent were unreported for these patients, except for one patient (6533002), a 1 year old white female with a complex medical history reported below.

In Table 5 and Table 6, the Applicant reported that 3 patients were discontinued for an AE as follows, and that none had an SAE:

- 1433009 (0.5 mg/kg target dose; 5 mg actual dose)—2 year old white male with onset on Day 6 of moderate diarrhea and severe exacerbation of vomiting. Investigator considered the vomiting “doubtfully related” and the diarrhea “possibly related” to rabeprazole. Diarrhea resolved after 7 days and the vomiting was ongoing at time of discontinuation.
- 1433001 (1.0 mg/kg target dose; 10 mg actual dose, low-weight cohort)—2 year old white male with onset on Day 2 of mild intermittent diarrhea considered “probably related” to rabeprazole. Resolved in 2 days.
- 5023001 (1.0 mg/kg target dose; 20 mg actual dose)—10 year old white male with onset on Day 2 of severe nausea and on Day 3 of severe abdominal pain exacerbation. Both events were considered “possibly related” to rabeprazole. Both AEs resolved.

The Applicant classified one patient (6533002) as withdrawal of consent. However, it is possible that consent might have been withdrawn because of an SAE of bronchopneumonia that the investigator considered "possibly related" to rabeprazole, as follows:

- Patient 6533002 (0.5 mg/kg target dose; 5 mg actual dose, low-weight cohort). This patient was a 1-year-old white female with a complex medical history involving recurrent infections and 2 episodes of pneumonia. Baseline evaluation had HD=2 and HFRE=3. During Study 3003 she continued to have "severe signs and symptoms of GERD 5 to 6 times daily". The day prior to study drug initiation, the patient had began developing a gastroenteritis. After about 6 weeks of rabeprazole, she was diagnosed with croup and bronchopneumonia. Her mother withdrew consent, and the patient received her last dose of study drug at the beginning of Week-8. The investigator considered SAE of bronchopneumonia as possibly related to the study drug.

Medical Reviewer Comment. Even though this withdrawal was classified as withdrawal of consent by the Applicant, it seems most likely that consent was withdrawn because of the SAE of bronchopneumonia. With this patient classified as an AE withdrawal, the numbers in Table 5 change slightly to an overall AE withdrawal rate of 4/127 (3%) from the originally reported 3/127 (2%).

In the "other" reasons category for discontinuation were 2 patients--one patient who was reclassified to have a histologic score of 0 rather than the original score of 1, and the other patient whose mother refused further study procedures (blood draws, endoscopy, and other procedures).

Medical Reviewer Comment. These study disposition figures do not suggest an issue with the conduct of this trial.

1-11 year olds. Study 3003 Part 2. Disposition by dose group is shown in Table 7.

Table 7 Subject disposition by dose group: Study 3003 Part 2

	Rabeprazole Sodium Treatment by Target Dose		
Disposition Status Primary Reason	0.5 mg/kg (N=33) n (%)	1.0 mg/kg (N=31) n (%)	Total (N=64) n (%)
Completed	26 (79%)	24 (77%)	50 (78%)
Withdrawn	7 (21%)	7 (23%)	14 (22%)
Adverse Event	0	1 (3%)	1 (2%)
Death	0	0	0
Lost to Follow-up	0	0	0
Non-Compliance With Study Drug	1 (3%)	1 (3%)	2 (3%)
Physician Decision	0	0	0
Protocol Violation	0	0	0
Study Terminated by Sponsor	0	0	0
Subject Withdrew Consent	1 (3%)	3 (10%)	4 (6%)
Other	5 (15%)	2 (6%)	7 (11%)

Key: n = size of sub sample; N=total sample size
Cross Reference: Attachment DSUB03B

[ref: CSR for Study 3003 Part 2, Table 10.1, p. 49]

Broken out by weight and dose, the disposition figures are shown in Table 8.

Table 8 Subject disposition by weight-dose group: Study 3003 Part 2

	Rabeprazole Sodium Treatment by Actual Dose			
	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
Disposition Status Primary Reason	(N=9) n (%)	(N=8) n (%)	(N=24) n (%)	(N=23) n (%)
Completed	8 (89%)	6 (75%)	18 (75%)	18 (78%)
Withdrawn	1(11%)	2 (25%)	6 (25%)	5 (22%)
Adverse Event	0	0	0	1 (4%)
Death	0	0	0	0
Lost to Follow-Up	0	0	0	0
Non-Compliance With Study Drug	0	0	1 (4%)	1 (4%)
Physician Decision	0	0	0	0
Protocol Violation	0	0	0	0
Study Terminated by Sponsor	0	0	0	0
Subject Withdrew Consent	0	2 (25%)	1 (4%)	1 (4%)
Other	1 (11%)	0	4 (17%)	2 (9%)

Key: n = size of sub sample; N=total sample size
Cross Reference: Attachment DSUB03BT

[ref: CSR for Study 3003 Part 2, Table 10.2, p. 50]

The most common reason for discontinuation in Study 3003 Part 2 was “Other” (9%), followed by withdrawal of consent (6%). The “Other” category included study termination, scheduling problems (especially endoscopy), not showing up for scheduled visits, and parents not wanting study procedures (especially endoscopy). Four patients had parental withdrawal of consent. Two patients were withdrawn for non-compliance with study drug administration.

Medical Reviewer Comment. These study disposition figures do not suggest an issue with the conduct of this trial.

Infants 1-11 month olds. Study 3004. Subject disposition is summarized in Table 9.

Table 9 Subject disposition: Study 3004, open-label phase

Disposition Status Primary Reason	Rabeprazole Sodium 10 mg (N=344)
Completed	**267 (77.6)**
Withdrawn	**77 (22.4)**
Adverse Event	4 (1.2)
Did Not Meet CGI Criteria	37 (10.8)
Lost to Follow-Up	1 (0.3)
Non-Compliance with Study Drug	2 (0.6)
Physician Decision	4 (1.2)
Protocol Deviation	3 (0.9)
Withdrawal of Consent	20 (5.8)
Other	6 (1.7)

Note(s): Percentages are based on the number of subjects in the relevant analysis set.
Completed: As indicated on the eCRF
Key: CGI = Clinical Global Impression

[ref: CSR Study 3004, Table 10-1, p. 56]

There were 4 patients discontinued for an AE, and only 1 of these was considered in any way related to rabeprazole (constipation of "doubtful relationship"). Other reasons for study discontinuation were error, protocol deviation, and lack of efficacy.

Table 10 shows subject disposition for the double-blind treatment phase of Study 3004.

Table 10 Subject disposition: Study 3004 double-blind phase

Disposition Status Primary Reason	Placebo (N=90)	Rabeprazole Sodium 5 mg (N=90)	Rabeprazole Sodium 10 mg (N=88)	Rabeprazole Sodium Total (N=178)
Completed	**76 (84.4)**	**77 (85.6)**	**78 (88.6)**	**155 (87.1)**
Withdrawn	**14 (15.6)**	**13 (14.4)**	**10 (11.4)**	**23 (12.9)**
Adverse Event	6 (6.7)	2 (2.2)	3 (3.4)	5 (2.8)
Lost to Follow-Up	0 (0.0)	0 (0.0)	2 (2.3)	2 (1.1)
Non-Compliance with Study Drug	0 (0.0)	2 (2.2)	0 (0.0)	2 (1.1)
Withdrawal of Consent	7 (7.8)	5 (5.6)	2 (2.3)	7 (3.9)
Other	1 (1.1)	4 (4.4)	3 (3.4)	7 (3.9)

Note(s): Percentages are based on the number of subjects in the relevant analysis set.
Completed: As indicated on the eCRF.
Subject 4074013: Subject was randomized to placebo but withdrew consent prior to receiving any DB study drug
Key: DB = double-blind; eCRF = electronic Case Report Form

[ref: CSR Study 3004, Table 10-2, p. 57]

The data in Table 10 do not suggest a dose-response relationship between adverse events and study discontinuations because the placebo group has the highest rate (6.7%). There were 5 patients on rabeprazole who discontinued because of AEs, which included worsening of GERD symptoms of varying degree from mild to severe that were ongoing at the time of discontinuation. "Other" reasons for discontinuation in the

rabeprazole group were lack of efficacy and in one case non-compliance with study procedures (E-diary, visit schedule, and study drug administration).

Medical Reviewer Comment. These study discontinuation figures do not suggest an issue with the conduct of this trial.

6.1.4 Analysis of Primary Endpoint(s)

1-11 year olds. Study 3003 Parts 1 and 2. The primary efficacy endpoint for Study 3003 was assessed after 12 weeks (Part 1) and 24 additional weeks (Part 2) of rabeprazole. Success on the primary endpoint on a per-subject basis at a given timepoint (12 or 36 weeks) was defined based on endoscopy and biopsy findings at 12 weeks for Part 1 and at 36 weeks for Part 2 of this trial, as follows:

- Hetzel-Dent (HD) Score=0 **or** Histologic Features of Reflux Esophagitis (HFRE) score=0. The Hetzel-Dent scoring system[1] [ref: as described in Applicant's protocol] is shown in Table 11.

1 Originally described in Hetzel DT, Dent J, Reed WD, Narielvala FM et al. Healing and relapse of severe peptic esophagitis after treatment with omeprazole. Gastroenterology 1988;95:903-912.

Table 11 Hetzel-Dent (HD) scoring system

Grade	Endoscopic findings
Grade 0	Macroscopically normal esophageal mucosa, no abnormalities noted
Grade 1	No macroscopic erosions visible but erythema, hyperemia, and/or friability may be present
Grade 2	Superficial erosion(s) or ulcer(s) involving <10% of the mucosa of the distal 5 cm of esophageal squamous mucosa
Grade 3	Superficial erosion(s) or ulcer(s) involving 10% to 50% of the mucosal surface of the distal 5 cm of esophageal squamous mucosa
Grade 4	Deep ulcers anywhere in the esophagus or confluent erosion or ulceration of >50% of the mucosal surface of the distal 5 cm of esophageal squamous mucosa

The Histologic Features of Reflux Esophagitis (HFRE) scoring system [ref: as described in Applicant's protocol] is shown in Table 12.

Table 12 Histologic Features of Reflux Esophagitis (HFRE) scoring system

Grade	Histologic findings
Grade 0	None
Grade 1	Basal zone hyperplasia (>20% of the epithelial thickness) and elongation of the papillae (if their height is >50% of the total epithelial thickness)
Grade 2	Grade 1 + in growth of vessels in the papillae
Grade 3	Grade 2 + 1 to 19 eosinophils and/or neutrophils on the most involved highpower field
Grade 4	Grade 3 + >20 eosinophils and/or neutrophils on the most involved highpower field
Grade 5	Mucosal erosions and/or ulceration

The protocol describes the procedure with endoscopy as follows:

> "Scheduled endoscopies and biopsies were conducted when possible by the same endoscopists and read by the same pathologist. The protocol specified that biopsies were to be taken as follows [ref: Study 3003 Protocol, p. 105]:
>
> - 1 from midesophagus
> - 2 from approximately 1 inch above the G-E junction (preferably from the area of the erosion)
> - 1 from antrum (If indicated, additional biopsies could be taken from body of stomach)
> - 1 from duodenum"

The primary endpoint results for Study 3003 Part 1 were calculated using the intent-to-treat (ITT) population (randomized plus at least one efficacy assessment, n=108), and are shown in Table 13.

Table 13 Primary efficacy endpoint results: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
Visit	(N=21) n (%)	(N=19) n (%)	(N=44) n (%)	(N=43) n (%)
Week 12/End of 12-week Double-Blind Phase Healing Rate				
N	17	16	38	37
n (%)	14 (82)	15 (94)	29 (76)	29 (78)

[ref : CSR Study 3003 Part 1, Table 11.4, p. 77]

In Table 13, in the low-weight (≤15kg) cohort, the healing rates were 82% (14/17) and 94% (15/16) for the low- and high-dose groups, respectively; for the high-weight cohort (>15kg), the healing rates were 76% and 78%.

Medical Reviewer Comment. In the high-weight cohort, although the sample sizes are small, there appears to be no incremental benefit of a higher dose than a lower dose. Although this was not a placebo-controlled trial, 81% is a clinically significant healing rate on endoscopy. For the low-weight cohort, the healing rates of 82% and 94% are also clinically significant and an incremental benefit is suggested, although the sample sizes are small. In this case, the preferable starting dose for the low-weight cohort is 5mg and if the low-weight patient has inadequate response, it would be reasonable to try 10mg.

Broken out by weight-dose groups and presence of baseline EE (HD>1) or NE (HD=1), the healing rates were as in Table 14.

Table 14 Primary efficacy results by EE: Study 3003 Part 1

Endoscopic Classification of GERD at Baseline	Healing Rate at 12 weeks			
	Bodyweight <15 kg		Bodyweight ≥15 kg	
	5 mg dose	10 mg dose	10 mg dose	20 mg dose
Erosive (EE)*	88% (7/8)	83% (5/6)	71% (12/17)	100% (11/11)
Non-erosive (NE)*	78% (7/9)	100% (10/10)	81% (17/21)	69% (18/26)

* Hetzel-Dent score ≥2
** Hetzel-Dent score = 1

Medical Reviewer Comment. The data in Table 14 suggest high healing rates in all subgroups (69% to 100%). With these small sample sizes, there appears to be no appreciable differences in healing rate between EE and NE. In this context, it is likely that the apparent dose-response relationship with healing for NE in the low-weight cohort and for EE in the high-weight cohort are random.

Some patients (n=9) achieved healing on biopsy (HFRE=0) in the presence of inflammation on endoscopy (HD>0). These patients were classified as having healed for purposes of the primary endpoint. Excluding patients who achieved healing only on histology but not endoscopy ("histologic-only healing"), the primary endpoint results become as shown in Table 15 (cells that changed are shown in bold red font).

Table 15 Primary efficacy endpoint results, histologic-only healing excluded: Study 3003 Part 1

Esophageal Lesion Pre-treatment	Bodyweight	Healing Rate at 12 weeks	
		0.5 mg/kg dose	1.0 mg/kg dose
Erosive	<15 kg	**75% (6/ 8)**	83% (5/ 6)
	≥15 kg	**65% (11/17)**	**73% (8/11)**
Non-erosive	<15 kg	**67% (6/ 9)**	**80% (8/10)**
	≥15 kg	81% (17/21)	**65% (17/26)**
Total	<15 kg	**71% (12/17)**	**81% (13/16)**
	≥15 kg	**74% (28/38)**	**68% (25/37)**
Overall	All bodyweights	**73% (40/55)**	**72% (38/53)**
Grand Total	All bodyweights	**72% (78/108)**	

Medical Reviewer Comment. As shown in Table 15, excluding patients with normal esophageal mucosal histology but abnormal appearance on endoscopy does not significantly impact the healing rates including these patients; and does not alter my efficacy assessment. Healing rates are still in excess of 65%.

For Part 2, the primary endpoint results at 36 weeks are shown in Table 16, which shows that 90% (47/52) of 12-week responders (healed) remained healed at 36 weeks.

Table 16 Primary efficacy endpoint results: Study 3003 Part 2

Esophageal Lesion Pre-treatment	Bodyweight	Healing Rate at 36 weeks	
		0.5 mg/kg dose	1.0 mg/kg dose
Erosive	<15 kg	100% (5/5)	100% (3/3)
	≥15 kg	88% (7/8)	75% (6/8)
Non-erosive	<15 kg	100% (3/3)	100% (3/3)
	≥15 kg	90% (9/10)	92% (11/12)
Total	<15 kg	100% (8/ 8)	100% (6/ 6)
	≥15 kg	89% (16/18)	85% (17/20)
Overall	All bodyweights	92% (24/26)	88% (23/26)
Grand Total	All bodyweights	90% (47/52)	

Broken out by individual dose-weight group and EE, the results are as in Table 17.

Table 17 Primary efficacy results by EE: Study 3003 Part 2

Endoscopic Classification of GERD at Baseline	Healing Rate at 36 weeks			
	Bodyweight <15 kg		Bodyweight ≥15 kg	
	5 mg dose	10 mg dose	10 mg dose	20 mg dose
Erosive (EE)*	100% (5/5)	100% (3/3)	88% (7/8)	75% (6/8)
Non-erosive (NE)*	100% (3/3)	100% (3/3)	90% (9/10)	92% (11/12)

* Hetzel-Dent score ≥2
** Hetzel-Dent score = 1

Medical Reviewer Comment. (b) (4)

(b) (4)

2 Gabriella Boccia, M.D.,1 Francesco Manguso, M.D., Ph.D,2 Erasmo Miele, M.D., Roberta Buonavolont`a, M.D.,1 and Annamaria Staiano, M.D. Maintenace therapy for erosive esophagitis in children after healing by omeprazole: is it advisable?. Am J of Gastroenterol 2007;102:1291-1297.

3 Orenstein SR. Pediatric erosive esophagitis maintenance: finally, some level 1 evidence!. Am J Gastroenterol 2007;102:1298-1300.

Infants 1-11 month olds. Study 3004. The primary efficacy endpoint hypothesis test was not statistically significant (p=(b) (4)).

The primary endpoint was a composite endpoint with two components:

- Change from baseline in frequency of average daily frequency of regurgitation

AND

- Change from baseline in weight-for-age Z-score

Each component had to be statistically significant in order for the primary endpoint to be statistically significant. Rabeprazole groups (5mg and 10mg) were pooled for the primary efficacy hypothesis test.

The co-primary efficacy endpoint results for the frequency of regurgitation component are shown in Table 18, the lower right cell of which shows that the primary endpoint test of rabeprazole versus placebo was not statistically significant (p=(b) (4)). Therefore testing did not proceed to the weight-for-age Z-score component.

Table 18 Co-primary endpoint results--frequency of regurgitation: Study 3004

	Placebo (N=89)	Rabeprazole Sodium 5 mg (N=90)	Rabeprazole Sodium 10 mg (N=88)	Rabeprazole Sodium Total (N=178)
DB Baseline				
N				
Mean (SD)				
Median				
Min/Max				
DB Endpoint/DB BOCF				
N				
Mean (SD)				
Median				
Min/Max				
Change from DB Baseline to DB Endpoint/DB BOCF				
N				
Mean (SD)				
Median				
Min/Max				
Rabeprazole Sodium vs Placebo:				
Diff in LS Means				
95% Confidence Interval				
p-Value				

(b) (4)

Note(s): ANCOVA: Analysis of Covariance with Treatment as fixed effect, Region and Age as stratification factors and Change from OL Baseline to OL Endpoint as covariate to test the hypothesis of no difference in change in daily average frequency of regurgitation from DB Baseline to DB Endpoint between rabeprazole sodium and placebo.
OL Baseline: Calculated as the average of the available results from the first three days of OL Treatment Period.
OL Endpoint: Calculated as the average of the available results from the last three days of the OL Treatment Period.
DB Baseline: Calculated as the average of the available results from the last three days of the OL Treatment Period.
DB Endpoint: Calculated as the average of the available results from the last three days of the DB Treatment Period.
DB BOCF: If DB Endpoint is missing the DB Baseline observation is carried forward.
Production\Tables\DEFF01AA.sas, (b) (4) 731398,SAS V9.2,Windows_NT) 22MAR2012 13:21

[ref: CSR Study 3004, Table 11-3, p. 68]

The weight-for-age Z-score component results are shown in Table 19. The weight-for-age Z-score component hypothesis test results were not statistically significant (p= (b) (4), lower right cell).

Table 19 Co-primary endpoint results: weight-for-age Z-score: Study 3004

	Placebo (N=89)	Rabeprazole Sodium 5 mg (N=90)	Rabeprazole Sodium 10 mg (N=88)	Rabeprazole Sodium Total (N=178)
DB Baseline				
N				(b) (4)
Mean (SD)				
Median				
Min/Max				
DB Endpoint/DB BOCF				
N				
Mean (SD)				
Median				
Min/Max				
Change from DB Baseline to DB Endpoint/DB BOCF				
N				(b) (4)
Mean (SD)				
Median				
Min/Max				
Diff in LS Means				
95% Confidence Interval				
p-Value				

Note(s): ANCOVA: Analysis of Covariance with Treatment as fixed effect, Region and Age as stratification factors and DB Baseline as covariate to test the hypothesis of no difference in change in Weight-for-Age Z-Score from DB Baseline to DB Endpoint between Rabeprazole Sodium and Placebo.
DB Baseline: Defined as the last available result before or on the last administration of OL study drug.
DB Endpoint: Defined as the last available result after the first administration of DB study drug.
DB BOCF: If DB Endpoint is missing the DB Baseline observation is carried forward.
Production\Tables\ DEFF02AA.sas, (b) (4) 731398,SAS V9.2,Windows_NT) 27MAR2012 11:09

[ref: CSR Study 3004, Table 11-4, p. 69-70]

Medical Reviewer Comment. None of the PPIs for use in infant GERD have been approved because all of their primary endpoints in their pivotal trials failed to achieve statistical significance. This was the subject of an AC meeting on Nov 05, 2010.

6.1.5 Analysis of Secondary Endpoints(s)

Infants 1-11 month olds. Study 3004. There was no evidence of superiority of rabeprazole over placebo for any of the secondary endpoints. Secondary endpoints included volume of regurgitation, various subscores of the I-GERQ-DD, and global impression and satisfaction scores. However, because the primary efficacy hypothesis test did not achieve statistical significance, testing did not proceed to any of the secondary endpoints.

1-11 year olds. Study 3003 Parts 1 and 2. Secondary endpoints included percent and absolute changes in the GERD Symptom Relief Score and subscales, global treatment satisfaction scores, changes in HD and HFRE scores, antacid use (frequency and amount), and percentage of subjects with esophageal pH≥4.

Although the secondary endpoints did not play a significant role in the FDA assessment of efficacy, the Applicant's GERD Symptom and Severity Score is shown in Figure 1 for completeness.

Figure 1 Weekly average GERD Symptom and Severity (ITT): Study 3003 Part 1

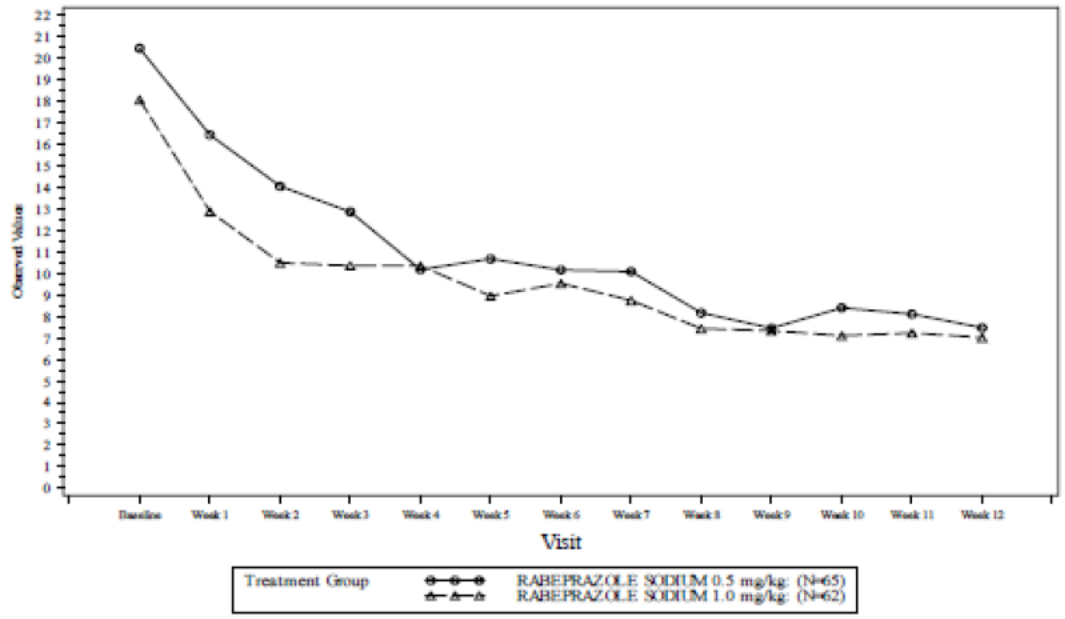


Table Reference: DEFF05CA
Source: [redacted] (b) (4) 23-JAN-2011 13:50

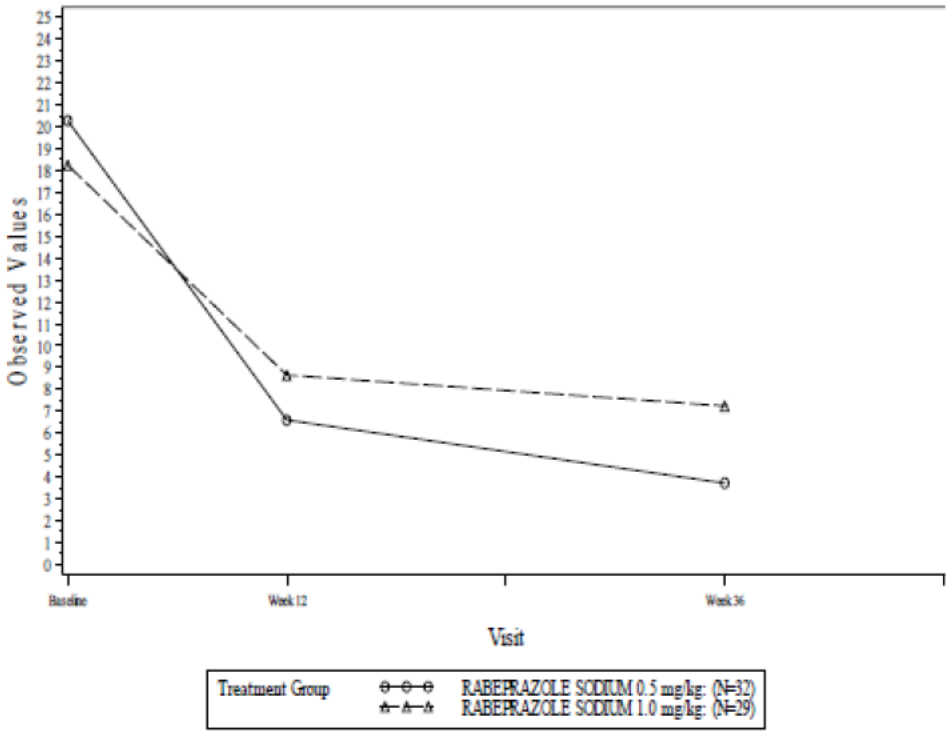
Cross-reference: Attachment FEFF01AA

[ref: CSR Study 3003 Part 1, Figure 1, p. 77]

For the secondary endpoint of antacid use through Week-12, there was a 19% decline between baseline and 12 weeks in the number of patients who used concomitant antacids (23% for the 0.5mg/kg/day group and 15% for the 1.0 mg/kg/day group).

Medical Reviewer Comment. The GERD Symptom and Severity Score is a composite score involving 12 GERD symptoms, which has not been validated for general use by FDA in determining efficacy in the pediatric age group. But we do know that GERD presents as various combinations of the symptoms comprising the Applicant's survey instrument. Despite the lack of validation as a primary efficacy endpoint and the lack of a concurrent control group, the symptom score trend in Figure 1 suggests a decrease in symptoms over time in both groups.

Figure 2 Weekly average GERD Symptom and Severity (ITT): Study 3003 Part 2



Note: Total GERD Symptom and Severity Score is the sum of the scores for the 12 individual symptoms (heartburn, dysphagia, belch/burping, regurgitation, vomiting, hoarseness, coughing, choking, fullness during eating, anorexia, nausea, and abdominal pain) measured and recorded on the eCRF. The symptom scores are rated on severity during the week preceding the visit.

Table Reference: DEFF05BA
Source: [S:\SAS\JPRD\AcipHexEJA3076?_Unblinded_Run\BIOSTATISTICS\PRODUCTION\FIGURES\CSR2] (b) (4) 8JUN2011 13:08

Cross Reference: Attachment DEFF05BA

[ref: CSR Study 3003 Part 2, Figure 1, p. 62]

Medical Reviewer Comment. Figure 2 does not suggest a further decrease in mean symptom score between weeks 12 and 36, under the caveat that this survey instrument is not validated for purposes of FDA assessment of efficacy. .

6.1.6 Other Endpoints

Infants 1-11 month olds. Study 3004. Other endpoints included weekly I-GERQ-R subscores (questions on breather difficulty and color change), length-for-age Z-score, clinical response, global impression and treatment satisfaction scores, wheezing, and aspiration.

Medical Reviewer Comment. These endpoints were not used in the assessment of efficacy.

1-11 year olds. Study 3003 Parts 1 and 2. None.

6.1.7 Subpopulations

Infants 1-11 month olds. Study 3004. Subpopulations were not used in the assessment of efficacy or safety.

1-11 year olds. Study 3003 Parts 1 and 2. See Section 6.1.4 (Analysis of Primary Endpoint(s)) for subpopulations of erosive (EE) and non-erosive (NE) GERD.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

1-11 year olds. Study 3003 Parts 1 and 2. For patients <15 kg, the dose of 5 mg is 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 to 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 at 10 mg is within the AUC range observed in adults at the approved 20 mg.

Four biopharmaceutic studies were conducted in healthy adults in support of the development of the age-appropriate formulation:

1. E3810-A001-015 (Module 2.7.1/Section 2.7.1.2.1): to assess the relative bioavailability of the Phase 1 granule formulation (2x5 mg) versus the tablet (1x10 mg)

2. RABGRD1006 (Module 2.7.1/Section 2.7.1.2.2): to assess the relative bioavailability of the Phase 3 granule formulation (4x2.5 mg) versus the Phase 1 granule formulation (2x5 mg), and food effect on the Phase 3 granule formulation

3. RABGRD1007 (Module 2.7.1/Section 2.7.1.2.3): to assess the bioequivalence of the to-be-marketed granule formulation (1x10 mg) and the Phase 3 granule formulation (2x5 mg), and food effect for the to-be-marketed granule formulation

4. RABGRD1004 (Module 2.7.1/Section 2.7.1.2.4): to assess the relative bioavailability of the Phase 3 granule formulation (2x5 mg) with different dosing vehicles.

Each of these studies involved administration of single doses of 10 mg of rabeprazole as a granule formulation. With the exception of small amounts of soft food (i.e., 1 or 2

tablespoons) or infant formula (5 mL) used as a dosing vehicle in some studies, rabeprazole was administered in the morning under fasting conditions (unless otherwise specified).

Infants 1-11 month olds. Study 3004. Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

1-11 year olds. Study 3003 Parts 1 and 2. The short-term trial (Part 1, 12 weeks of rabeprazole) was followed by an extension trial (Part 2, 24 additional weeks of rabeprazole). To be eligible for the long-term trial, patients had to have achieved the primary efficacy endpoint (HD=0 or HFRE=0) in Part 1 and consented to Part 2. In Part 2, each patient continued for 24 additional weeks on the same dose of rabeprazole he/she took in Part 1.

Medical Reviewer Comment. Regarding persistence of efficacy, Part 2 was essentially a continuation of therapy for an additional 24 weeks in patients who had already healed after 12 weeks. However, the absence of a concurrent placebo control group prevents us from concluding persistence of efficacy, durability of healing, or maintenance of healing for reasons presented earlier under Table 17 in Section 6.1.4 Analysis of Primary Endpoint(s).

Infants 1-11 month olds. Study 3004. Not applicable. This was a short-term study (up to 5 weeks) that did not demonstrate efficacy.

6.1.10 Additional Efficacy Issues/Analyses

There are no additional efficacy issues or analyses. See Section 6.1.4 Analysis of Primary Endpoint(s).

7 Review of Safety

Safety Summary

Children 1-11 year olds. Based on the data submitted in this Application, the use of ACIPHEX for treatment of GERD in this age group for up to 12 weeks appears to be relatively safe when weighted against the benefit of healing of the esophagus in GERD.

Adolescents 12-16 years of age. Approved. Safety profile similar to adults.

Infants 1-11 month olds. Efficacy was not demonstrated for symptomatic or suspected GERD in this age group, so that use of ACIPHEX or any other PPI does not favor benefit.

Neonates 0-<1 month old. Studies were not conducted to assess safety and efficacy in this age group.

7.1 Methods

Safety data for Study 3003 Parts 1 and 2 are now presented. Safety data in adolescents are not presented here because rabeprazole is already approved in this age group.

Safety data in infants and neonates are presented but not discussed in terms of risk-benefit since use of rabeprazole in these age groups is not approved or being sought for approval.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from studies 3003, 3004, and 1005 are now presented. See Table 2 for summaries of these studies.

7.1.2 Categorization of Adverse Events

Adverse events in these studies were classified using the MedDRA system.

For uncontrolled Study 3003, treatment-emergent adverse events (TEAEs), abbreviated "AEs" in this review, are further qualified as to relationship to treatment (rabeprazole). In trials without a concurrent control group, to determine which AEs are adverse drugs reactions (ADRs) requires attributing relationship of the AE to study drug.

Medical Reviewer Comment. For controlled Study 3004, AEs occurring at a higher rate in the treatment than placebo group are potential candidates for being classified as ADRs. However, for uncontrolled studies such as Study 3003, the classification of an adverse effect as being an ADR relies on investigator adjudication of relatedness to study drug and therefore already-known ("expected") side effects. Both AEs and ADRs are presented for Study 3003. The advantage of a concurrent placebo-controlled trial is that unexpected ADRs can be detected through differential rates of expression in placebo and control groups.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

There is one study per age group, and data are not pooled across age groups because of differences in disease characteristics at different ages and verbal abilities.

7.2 Adequacy of Safety Assessments

Safety assessments were adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The target population in this review is the 1-11 year age group. Safety data will also be presented for the infant and neonatal age groups. Therefore, the already labeled adolescent data will not be presented.

Infants 1-11 month olds. Study 3004. During the open-label period, there were 344 patients exposed to rabeprazole (mean 17.1 days) for a total rabeprazole exposure of 16.1 patient-years (pt-yr) in the open-label phase of Study 3004 *[ref: Applicant's ISS, Table 12, p. 50-51]*.

Of the 344 patients enrolled in the open-label phase, 267 patients continued into the double-blinded phase. Of these 267 patients, 178 patients were exposed to rabeprazole (and 89 patients to placebo). For the 178 rabeprazole-exposed patients during the double-blind period alone, mean exposure was 32.7 days (SD=8 days) for a total of 15.9 pt-yr [range 1 to 48 days] of rabeprazole exposure in the double-blind phase.

Therefore, total rabeprazole exposure in Study 3004 was 32 pt-yr (=16.1+15.9) with individual total patient exposures in Study 3004 ranging from 12 to 68 days.

1-11 year olds. Study 3003 Part 1. In Study 3003 Part 1, 127 patients were exposed to at least 1 dose of rabeprazole (Table 20). Total rabeprazole exposure in Study 3003 Part 1 was 28.7 pt-yr with individual patient exposures ranging from 6 to 119 days.

Table 20 Exposure to rabeprazole: Study 3003 Part 1

	Rabeprazole Treatment for Low-Weight Cohort: 6.0-14.9 kg		Rabeprazole Treatment for High-Weight Cohort: >15.0 kg	
(Target dose)	0.5 mg/kg	1.0 mg/kg	0.5 mg/kg	1.0 mg/kg
(Actual dose) Duration of Exposure	5 mg (N=21)	10 mg (N=19)	10 mg (N=44)	20 mg (N=43)
Category, n (%)				
1 to 28 days	1 (5)	2 (11)	0	2 (5)
29 to 56 days	1 (5)	0	5 (11)	3 (7)
57 to 84 days	7 (33)	11 (58)	13 (30)	22 (51)
>84 days	12 (57)	6 (32)	26 (59)	16 (37)
Mean (SD), days	81.7 (19.33)	77.0 (23.61)	80.7 (16.28)	79.5 (20.32)
Median, days	86.0	83.0	85.0	84.0
Range, days	11; 98	6; 99	29; 99	16; 119[a]

Note: Actual dose determined by baseline body weight category and randomized dose. For subjects randomized to the target dose of 0.5 mg/kg, if baseline body weight was <15 kg the actual dose was 5 mg and if baseline body weight was ≥15 kg the actual dose was 10 mg. For subjects randomized to the target dose of 1.0 mg/kg, if baseline body weight was <15 kg the actual dose was 10 mg and if baseline body weight was ≥15 kg the actual dose was 20 mg.

Note: Exposure is calculated as the difference between last exposure date for the phase and the first exposure date for the phase plus 1 day.

[a] One subject (Subject 1243006) was exposed to study drug for 119 days.

Cross Reference: Module 5.3.5.1/RABGRD3003 CSR Part 1 DSUB08AT

[ref: Applicant's ISS, Table 13, p. 52]

1-11 year olds. Study 3003 Part 2. In Study 3003 Part 2, a total of 64 patients were exposed to at least one dose of rabeprazole (Table 21). Rabeprazole exposure during Study 3003 Part 2 was 28.1 patient-years with individual patient exposures ranging from 38 to 189 days.

Table 21 Exposure to rabeprazole: Study 3003 Part 2

Parameter	Rabeprazole Sodium Treatment by Target Dose		
	0.5 mg/kg (N=33)	1.0 mg/kg (N=31)	Total (N=64)
Mean duration of exposure (days)			
Category, n (%)			
1-28 days	0	0	0
29-56 days	1 (3%)	2 (6%)	3 (5%)
57-84 days	1 (3%)	0	1 (2%)
85-112 days	0	1 (3%)	1 (2%)
113-140 days	0	1 (3%)	1 (2%)
141-168 days	20 (61%)	10 (32%)	30 (47%)
>168 days*	11 (33%)	17 (55%)	28 (44%)
Mean (SD)	161.2 (27.96)	160.2 (32.57)	160.7 (30.04)
Median	168.0	169.0	168.0
Range	(38; 178)	(51; 189)	(38; 189)

Note: Exposure was calculated as the difference between last exposure date for the phase and the first exposure date for the phase plus 1 day.

*The maximum scheduled duration for Part 2 was up to 175 days (168 ±7days). A total of 6 subjects exceeded this duration by 1 to 14 days due to scheduling delays (subject # 1523001 by 1 day, subjects # 6533003 & 6553003 by 3 days, subject # 2523001 by 9 days, subject # 1433008 by 11 days and subject # 6563002 by 14 days.

Key: n = size of sub sample; N=total sample size, SD = standard deviation

Cross Reference: Attachment DSUB08B

[ref: Applicant's CSR, Table 12.1, p. 82]

Therefore, total rabeprazole exposure in Study 3003 Parts 1 and 2 was 56.8 pt-yr (=28.7+28.1).

Neonates 0-<1 month old, Study 1005 (PK/PD). Rabeprazole exposure during Study 1005 was 1.6 pt-yr (n=69 patients, mean 8.7 days, range 1 to 28 days.

Other studies:

- E3810-A001-202 (Phase 3, adolescents)—already labeled. There were 111 patients who received at least one dose of rabeprazole (10 or 20 mg).
- Study 1002 (Phase 1). Doses were 0.14mg/kg (n=8 patients), 0.5mg/kg (n=11), and 1mg/kg (n=9). All patients received once daily dosing for 5 consecutive days, for a total of 0.4 pt-yr of rabeprazole exposure.
- Study 1003 (Phase 1). Eight subjects were each exposed to 10 to 14 doses of rabeprazole. In this study a serious breach report was filed, which is now summarized. At completion of this study, the Applicant identified a dose-mislabeling event that resulted in half the patients getting placebo rather than rabeprazole. This event was identified when half the patients were noted to have levels of 0 for rabeprazole. The error was traced by the Applicant to a human

labeling error at the Janssen warehouse in Sep-2009, when a box of placebo was incorrectly labeled as active. Upon commencement of 1003, the contents of this box had been dispersed to the seven sites in 1003. The Sponsor promptly notified FDA and other non-US regulatory agencies about the error. This error did not affect other clinical trials in this development program.

Neglecting the "other studies" (above), the total rabeprazole exposure in the above listed studies (not including adolescents and adults) is approximately **120 patient-years**.

Medical Reviewer Comment. To get a rough idea of how many patients on a 3-month course of rabeprazole might be represented in the patient-years of exposure reported for the <12 year age group, I make the following assumptions:

- *Each patient takes rabeprazole for 3 months (12 weeks, 0.25 years)*
- *Total pediatric (0-11 years) safety exposure evaluation is 120 patient-years*

Dividing 120 pt-yrs by 0.25 yrs/pt gives a figure of 480 patients each on rabeprazole for 3 months. This is acceptable exposure for safety evaluation in this Application.

7.2.2 Explorations for Dose-Response

Infants 1-11 month olds. Study 3004. PPI therapy in symptomatic GERD (sGERD) in infants will not be approved at this time as discussed earlier related to the AC of Nov-2010. Nonetheless the major dose-response safety findings of Study 3004 have been reviewed and are now presented.

There were no deaths in Study 3004.

The following table is a summary of the AEs observed in the double-blind phase of Study 3004 (Table 22). Approximately half of all subjects experienced at least one AE in Study 3004.

Table 22 Rate of AEs: Study 3004, double-blind phase

	Placebo (N=89) n (%)	Rabeprazole Sodium 5 mg (N=90) n (%)	Rabeprazole Sodium 10 mg (N=88) n (%)	Rabeprazole Sodium Total (N=178) n (%)
Number of subjects with at least one TEAE	42 (47.2)	39 (43.3)	44 (50.0)	83 (46.6)
Number of TE deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of subjects with at least one TESAE	2 (2.2)	6 (6.7)	2 (2.3)	8 (4.5)
Number of subjects with at least one TEAE leading to discontinuation of study drug	7 (7.9)	2 (2.2)	3 (3.4)	5 (2.8)
Number of subjects with at least one severe TEAE	1 (1.1)	2 (2.2)	3 (3.4)	5 (2.8)
Number of subjects with at least one related TEAE	1 (1.1)	8 (8.9)	11 (12.5)	19 (10.7)

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.

[ref: CSR for Study 3004, Table 12-4, p. 82]

Although there is no suggestion of a dose-response relationship for AEs (first line in Table 22 shows rates of 47%-43%-50% for placebo-5mg-10mg), data in the last line suggest a possible dose-response relationship for adverse drug reactions (ADRs, as defined by "related TEAE") with rates of 1.1%-8.9%-12.5% for placebo-5mg-10mg.

Table 23 summarizes data from Study 3004 double-blind phase on the most common AEs (at least 5% in any treatment group).

Table 23 AEs in at least 5% of patients in any treatment group: Study 3004, double-blind phase

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.
Adverse events are coded using MedDRA Version 12.0.

[ref: CSR, Study 3004, Table 12-5, p. 83]

In Table 23, the only AE that occurred in at least 5% of patients in any treatment group, and exhibited a possible dose-response relationship based on increasing rate with higher rabeprazole doses [ref: CSR for Study 3004, Table 12-5], was 'serum gastrin increased' (0%-2%-8% in placebo-5mg-10mg). The degree of increase (in ng/L) from

baseline in serum gastrin was -13.2/91.5/163.7 in placebo/5mg/10mg dose groups. For serum iron, there was no dose-response relationship.

Medical Reviewer Comment. Increase in serum gastrin is expected with acid suppression as from a PPI or H2-blocker. However, its clinical importance in patients on 12 weeks of PPI therapy is not known at this time. In fact, gastrin was not discussed at all at the Nov 2010 Advisory Committee meeting on the safety and efficacy of PPIs in infant GERD [ref: AC Meeting Minutes, 05-Nov-2010]. Gastrin is made in the stomach, pancreas, and duodenum. It stimulates gastric motility and acid secretion, as well as secretion of pepsinogen, zymogen, and pepsin that have a role in protein digestion. Additionally gastrin might play a role in relaxation of the lower esophageal sphincter, which could potentially increase the volume of refluxate.

For SAEs in the double-blind phase, there was no apparent dose-response relationship, although the sample sizes are relatively small: the rate of SAEs was 2.2%-6.7%-2.3% in placebo-5mg-10mg dose groups. The single most common SAE was urinary tract infection (UTI), which occurred in the 5mg group in 2 patients (one 3-month old male and one 4-month old female, both adjudicated as not related to study drug and hence not ADRs). Otherwise for SAEs in the double-blind phase, the most common System Organ Class was "Infections and infestations" (0%-4.4%-1.1% in placebo-5mg-10mg dose groups). The most common SAE infection other than UTI was a case of upper respiratory infection and a case of gastroenteritis.

Medical Reviewer Comment. The relationship of UTI to rabeprazole is not immediately obvious. However, one might postulate that a state of hypo- or achlorhydria could change the gut microbiome, which in turn could change the perineal flora that normally help protect against UTI (especially in females).

1-11 year olds. Study 3003 Part 1. In this trial, there was no concurrent control group with which to assess a dose-response relationship. However, there were two dose levels to which patients were randomized. Table 24 summarizes rates of AEs and ADRs (middle row, "TEAE related to study medication").

Table 24 Rate of AEs: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
Adverse Event Category	(N=21) n (%)	(N=19) n (%)	(N=44) n (%)	(N=43) n (%)
Number of Subjects With at Least One TEAE	16 (76)	15 (79)	32 (73)	33 (77)
Number of Subjects With at Least One Treatment-emergent SAE	4 (19)	1 (5)	1 (2)	0
Number of Subjects With at Least One TEAE Related to Study Medication	3 (14)	2 (11)	6 (14)	12 (28)
Number of Subjects With at Least One TEAE Leading to Discontinuation	1 (5)	1 (5)	0	1 (2)
Deaths	0	0	0	0

Note: Actual dose was determined by baseline weight category and randomized dose. For subjects randomized to 0.5 mg/kg, if baseline weight < 15 kg, the actual dose was 5 mg and if baseline weight was ≥ 15 kg the actual dose was 10 mg (denoted 10 mg [0.5 mg/kg]). For subjects randomized to 1.0 mg/kg, if baseline weight < 15 kg, the actual dose was 10 mg (denoted 10 mg [1.0 mg/kg]) and if baseline weight was ≥ 15 kg the actual dose was 20 mg
Note: Treatment-emergent adverse events were defined as events that started on or after the date of first short-term study drug through the end of the therapeutic reach which was 15 days (non-serious adverse events) or 30 days (serious adverse events) after last short-term study drug administration for subjects who did not enter the long-term phase and the first dose of long-term study drug for those who entered the long-term phase. Adverse events with missing start dates were considered treatment-emergent.
Key: TEAE = Treament-emergent adverse events, SAE = serious adverse events
Cross Reference: Attachment DAE01AT

[ref: CSR Study 3003 Part 1, Table 12.4, p.124]

In Table 24, the rate of AEs within each weight cohort are slightly higher for the higher dose level, although the numbers are small. Within the high-weight cohort for ADRs (3rd row of numbers), the ADR rate is 14% and 28% for the low- and high-dose groups, respectively.

AEs reported in Study 3003 Part 1 are listed in Table 25.

Table 25 AEs reported in at least 5% of patients in any group: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
System Organ Class Preferred Term	(N=21) n (%)	(N=19) n (%)	(N=44) n (%)	(N=43) n (%)
Blood and lymphatic system disorders	1 (5)	0	1 (2)	1 (2)
Anaemia	1 (5)	0	0	0
Ear and labyrinth disorders	0	1 (5)	1 (2)	3 (7)
Ear pain	0	1 (5)	0	2 (5)
Eye disorders	0	1 (5)	0	2 (5)
Conjunctivitis	0	1 (5)	0	1 (2)
Gastrointestinal disorders	3 (14)	5 (26)	17 (39)	20 (47)
Abdominal pain	0	0	7 (16)	8 (19)
Abdominal pain upper	0	0	2 (5)	1 (2)
Diarrhoea	3 (14)	4 (21)	4 (9)	3 (7)
Flatulence	0	0	0	2 (5)
Nausea	0	0	0	3 (7)
Vomiting	2 (10)	2 (11)	6 (14)	8 (19)
General disorders and administration site conditions	4 (19)	2 (11)	5 (11)	5 (12)
Fatigue	0	1 (5)	0	0
Pyrexia	4 (19)	1 (5)	4 (9)	4 (9)
Immune system disorders	0	1 (5)	0	0
Hypersensitivity	0	1 (5)	0	0
Infections and infestations	11 (52)	8 (42)	15 (34)	14 (33)
Acute tonsillitis	0	1 (5)	0	0
Bronchitis	1 (5)	0	1 (2)	2 (5)
Bronchopneumonia	1 (5)	0	0	0
Conjunctivitis infective	0	1 (5)	0	0
Croup infectious	1 (5)	0	0	0
Ear infection	0	0	0	2 (5)
Gastroenteritis	0	1 (5)	0	1 (2)
Influenza	0	0	0	2 (5)
Lower respiratory tract infection viral	1 (5)	0	0	0
Nasopharyngitis	0	1 (5)	3 (7)	2 (5)
Otitis media	2 (10)	0	1 (2)	0
Pharyngitis	1 (5)	0	2 (5)	1 (2)
Pneumonia	1 (5)	0	0	2 (5)
Rhinitis	3 (14)	1 (5)	0	0
Sinusitis	1 (5)	1 (5)	1 (2)	2 (5)
Upper respiratory tract infection	2 (10)	3 (16)	4 (9)	1 (2)
Urinary tract infection	1 (5)	0	1 (2)	1 (2)
Viral infection	0	1 (5)	1 (2)	1 (2)
Viral upper respiratory tract infection	1 (5)	0	0	0
Injury, poisoning and procedural complications	2 (10)	0	3 (7)	1 (2)
Fall	1 (5)	0	1 (2)	0
Humerus fracture	1 (5)	0	0	0
Skin laceration	1 (5)	0	0	0
Investigations	1 (5)	2 (11)	0	0
Blood alkaline phosphatase increased	0	1 (5)	0	0
Blood creatine phosphokinase increased	1 (5)	0	0	0
Body temperature increased	0	1 (5)	0	0
Metabolism and nutrition disorders	1 (5)	1 (5)	2 (5)	0
Decreased appetite	1 (5)	1 (5)	1 (2)	0
Dehydration	1 (5)	0	0	0
Musculoskeletal and connective tissue disorders	0	1 (5)	0	2 (5)
Back pain	0	1 (5)	0	0
Pain in extremity	0	1 (5)	0	0
Nervous system disorders	0	1 (5)	5 (11)	9 (21)
Headache	0	0	4 (9)	7 (16)
Lethargy	0	1 (5)	0	0

Psychiatric disorders	1 (5)	1 (5)	1 (2)	1 (2)
Mental disorder	1 (5)	0	0	0
Sleep disorder	0	1 (5)	0	0
Respiratory, thoracic and mediastinal disorders	4 (19)	5 (26)	12 (27)	14 (33)
Adenoidal hypertrophy	1 (5)	0	0	0
Asthma	0	0	0	2 (5)
Cough	3 (14)	4 (21)	6 (14)	5 (12)
Dyspnoea	1 (5)	0	0	0
Nasal congestion	0	0	4 (9)	1 (2)
Oropharyngeal pain	0	1 (5)	2 (5)	5 (12)
Productive cough	1 (5)	0	0	0
Skin and subcutaneous tissue disorders	1 (5)	0	0	3 (7)
Rash pruritic	1 (5)	0	0	0
Surgical and medical procedures	1 (5)	0	0	0
Suture insertion	1 (5)	0	0	0

Note: Adverse events were coded using Medical Dictionary for Regulatory Activities version 12.0.

[ref: CSR Study 3003 Part 1, Table 12.6, p. 128-130]

In Table 25 there is a suggestion of a possible dose-response relationships as follows, although the sample sizes are relatively small:

- Low-weight cohort (low-dose vs high-dose)
  - Diarrhea: 14% (3/21) vs 21% (4/19)
  - Cough: 14% (3/21) vs 21% (4/19)
- High-weight cohort (low-dose vs high-dose)
  - Headache: 9% (4/44) vs 16% (7/43)
  - Oropharyngeal pain: 5% (2/44) vs 12% (12/43)

Medical Reviewer Comment. These are small sample sizes and minor side effects, considering the potential benefit of PPI therapy in this population. As a consequence of the small sample sizes, just one or two more cases in either group would change the rate (%) figures.

The relationship between rabeprazole and headache is unclear, although headache is probably more common in children with GERD on a behavioral basis. For oropharyngeal pain, one might postulate that the sprinkles somehow irritate the pharynx in certain states perhaps when the patient has a pharyngitis. In any event, these are not clinically important side effects compared to the potential benefit of rabeprazole in treating GERD. Diarrhea can be related to rabeprazole on the basis of the distal consequences of acid reduction. The relationship to cough is uncertain although it has been reported in association with GERD in general.

Table 26 shows the rate of ADRs.

Table 26 ADRs: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
System Organ Class Preferred Term	(N=21) n (%)	(N=19) n (%)	(N=44) n (%)	(N=43) n (%)
Number of Subjects with ≥ 1 Related TEAE	3 (14)	2 (11)	6 (14)	12 (28)
Gastrointestinal disorders	1 (5)	2 (11)	2 (5)	9 (21)
Abdominal pain	0	0	1 (2)	5 (12)
Diarrhoea	1 (5)	2 (11)	2 (5)	1 (2)
Eructation	0	0	0	1 (2)
Flatulence	0	0	0	1 (2)
Nausea	0	0	0	2 (5)
Vomiting	0	0	0	4 (9)
Infections and infestations	1 (5)	0	0	0
Bronchopneumonia	1 (5)	0	0	0
Investigations	1 (5)	0	0	0
Blood creatine phosphokinase increased	1 (5)	0	0	0
Metabolism and nutrition disorders	0	0	1 (2)	0
Hypercholesterolaemia	0	0	1 (2)	0
Musculoskeletal and connective tissue disorders	0	1 (5)	0	0
Back pain	0	1 (5)	0	0
Nervous system disorders	0	0	3 (7)	5 (12)
Dysgeusia	0	0	1 (2)	1 (2)
Headache	0	0	2 (5)	4 (9)
Respiratory, thoracic and mediastinal disorders	0	0	1 (2)	2 (5)
Cough	0	0	0	2 (5)
Increased upper airway secretion	0	0	1 (2)	0
Skin and subcutaneous tissue disorders	0	0	0	1 (2)
Pruritus	0	0	0	1 (2)

[ref: CSR Study 3003 Part 1, Table 12.7, p. 132]

From the data in Table 26, the low-weight cohort has very few ADRs, small group sizes, and ADRs are scattered as single cases except for diarrhea (5%-11%). For the high-weight cohort, which has a larger sample size, there appears to be a possible dose-response relationship for the following ADRs (10mg-20mg)—abdominal pain (2%-12%), vomiting (0%-9%), nausea (0%-5%), headache (5%-9%), and cough (0%-5%).

Medical Reviewer Comment. In Table 26 the ADRs with a marginal rate (over all four dose-weight groups) of at least 5% are abdominal pain, diarrhea, and headache; so these ADRs will appear in the label. Although the investigators considered these to be related to rabeprazole, there can be error in this adjudication. In comparison with the potential benefit of a course of rabeprazole therapy for GERD, these side effects do not represent unacceptable risk.

There was no dose-response relationship for SAEs as a group (8% (8/65) for low-dose and 2% (2/62) for high-dose) or individually.

1-11 year olds. Study 3003 Part 2. In this trial, there was no concurrent control group with which to assess a dose-response relationship. However, there were two dose levels to which patients were randomized.

There were no deaths in Study 3003 Part 2.

Table 27 summarizes rates of AEs and ADRs (row "TEAE related to study medication").

Table 27 Rate of AEs: Study 3003 Part 2

	Rabeprazole Sodium Treatment by Actual Dose			
	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
	(N=9)	(N=8)	(N=24)	(N=23)
Adverse Event Category	n (%)	n (%)	n (%)	n (%)
Number of Subjects With at Least One Treatment-Emergent AE	4 (44%)	4 (50%)	15 (63%)	17 (74%)
Number of Subjects With at Least One Treatment-Emergent Serious AE	1 (11%)	2 (25%)	1 (4%)	1 (4%)
Number of Subjects With at Least One Treatment-Emergent AE Related to Study Medication	1 (11%)	0	0	1 (4%)
Number of Subjects With at Least One Severe Treatment-Emergent AE	0	2 (25%)	1 (4%)	0
Number of Subjects With at Least One Treatment-Emergent AE Leading to Discontinuation	0	0	0	1 (4%)
Deaths	0	0	0	0

[ref: CSR Study 3003 part 2, Table 12.4, p. 85]

In Table 27, the rate of AEs within each weight cohort is slightly higher for the higher dose. There are very few ADRs (2 patients, Row 3) and there does not appear to be a dose-response relationship.

Medical Reviewer Comment. The sample sizes are small and there were few ADRs.

Table 28 AEs reported in at least 5% of patients in any group: Study 3003 Part 2

	Rabeprazole Sodium Treatment by Actual Dose			
	Low-Weight Cohort: 6.0-14.9 kg		High-Weight Cohort: ≥15 kg	
(Target Dose)	0.5 mg/kg	0.5 mg/kg	1.0 mg/kg	1.0 mg/kg
(Actual Dose)	5 mg	10 mg	10 mg	20 mg
System Organ Class Preferred Term	(N=9) n (%)	(N=8) n (%)	(N=24) n (%)	(N=23) n (%)
Blood and lymphatic system disorders	0	1 (13%)	0	0
Lymphadenitis	0	1 (13%)	0	0
Gastrointestinal disorders	1 (11%)	1 (13%)	4 (17%)	9 (39%)
Abdominal pain	1 (11%)	0	2 (8%)	2 (9%)
Constipation	1 (11%)	0	0	1 (4%)
Diarrhoea	0	1 (13%)	1 (4%)	2 (9%)
Dyspepsia	0	0	0	2 (9%)
Vomiting	1 (11%)	0	3 (13%)	3 (13%)
General disorders and administration site conditions	0	1 (13%)	0	2 (9%)
Pyrexia	0	1 (13%)	0	2 (9%)
Infections and infestations	2 (22%)	3 (38%)	11 (46%)	8 (35%)
Bronchitis	1 (11%)	0	0	0
Bronchopneumonia	0	1 (13%)	0	0
Gastroenteritis rotavirus	0	1 (13%)	0	0
Nasopharyngitis	0	0	2 (8%)	1 (4%)
Otitis media	0	0	2 (8%)	0
Pharyngitis	1 (11%)	0	0	1 (4%)
Pharyngitis streptococcal	0	0	2 (8%)	1 (4%)
Rash pustular	0	1 (13%)	0	0
Rhinitis	0	0	2 (8%)	0
Sinusitis	0	0	2 (8%)	1 (4%)
Upper respiratory tract infection	1 (11%)	0	3 (13%)	4 (17%)
Viral infection	0	1 (13%)	1 (4%)	0
Injury, poisoning and procedural complications	2 (22%)	0	1 (4%)	3 (13%)
Head injury	1 (11%)	0	0	0
Procedural vomiting	1 (11%)	0	0	0
Investigations	1 (11%)	0	1 (4%)	1 (4%)
Beta 2 microglobulin urine increased	1 (11%)	0	0	0
Metabolism and nutrition disorders	1 (11%)	0	0	0
Acidosis	1 (11%)	0	0	0
Iron deficiency	1 (11%)	0	0	0
Psychiatric disorders	1 (11%)	0	0	2 (9%)
Sleep disorder	1 (11%)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (11%)	0	3 (13%)	4 (17%)
Cough	1 (11%)	0	1 (4%)	0
Oropharyngeal pain	0	0	0	2 (9%)
Skin and subcutaneous tissue disorders	1 (11%)	0	1 (4%)	2 (9%)
Prurigo	1 (11%)	0	0	0

[ref: CSR Study 3003 Part 2, Table 12.6, p. 88-89]

In Table 28 there samples sizes are relatively small, and there are no clear dose-response patterns for individual ADRs.

Neonates 0-<1 month old, Study 1005 (PK/PD). This 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. There does not appear to be a dose-response relationship for mean PTGA4:

- 1-mg dose: 90%
- 2-mg dose: 99%
- 3-mg dose: 81%

Medical Reviewer Comment. A large and highly variable degree of acid suppression (90%) was observed in Study 1005, even considering that neonates are typically more acid-suppressed than adults. And in Study 1005, baseline mean PTGA4 was 63%, which is the level of acid suppression in adults on a PPI.

Safety was also assessed in Study 1005. There was one death in Study 1005, and it occurred at the 3-mg dose level, in a premature infant with multisystem complications of prematurity including lung disease, pseudomonas sepsis, cerebral atrophy, and necrotizing enterocolitis.

Medical Reviewer Comment. In medically complex cases, it is often difficult if not impossible to attribute a single fatality to a drug, especially for small sample sizes and no non-active concurrent control group.

A dose-response relationship for the rate of AEs (as percentage of patients experiencing at least one AE) is suggested in these data with rates of 42%, 48%, and 64% in the 1-, 2-, and 3-mg dose groups, respectively. The most common AEs for the 1-, 2-, and 3-mg dose groups were as follows:

- Anemia: 2/19 (11%), 5/25 (20%), 6/26 (24%)
- Dyspepsia: 0, 0, 1/25 (4%)
- NEC: 0, 0, 1/25 (4%)

In the laboratory data, most values did not change before and after rabeprazole, except for hemoglobin:

- albumin: minimal increases in all dose groups
- total protein: not done
- ionized calcium: minimal increases in all dose groups
- chloride: minimal increases in all dose groups
- hemoglobin (in g/dL): -0.51, -0.65, -0.87 (all small decreases)

Medical Reviewer Comment. It is interesting that both anemia (and AE) and decrease in hemoglobin (a scheduled laboratory assessment) suggest a dose-response relationship, although the sample sizes are too small to conclude a real relationship to achlorhydria.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or in vitro testing.

7.2.4 Routine Clinical Testing

Routine clinical testing—see Section 7.4.2 Laboratory Evaluations.

7.2.5 Metabolic, Clearance, and Interaction Workup

ACIPHEX is already approved and has been studied extensively.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

All of the PPIs have a similar safety profile.

7.3 Major Safety Results

7.3.1 Deaths

One death occurred in the pediatric development program for ages birth to 11 years. The death occurred in Study 1005 (PK/PD) in a premature neonatal patient with a complex medical history, and was not felt to be related to ACIPHEX.

7.3.2 Nonfatal Serious Adverse Events

Neonates 0-<1 month old, Study 1005 (PK/PD). There were 7 patients with non-fatal SAEs reported in Study 1005 including SAEs in the patient who expired prior to death, as follows. All of these SAEs were adjudicated as not related to study drug, and hence not ADRs.

- 1mg dose group (n=19): 2/19 (10.5%)
  - Apnea/bradycardia—discontinued from trial
- 2mg dose group (n=25): 1/25 (4.0%)
  - Apnea—discontinued from trial. Study drug had already stopped 10 days prior to this event.
- 3mg dose group (n=25): 3/25 (12.0%)
  - Presumed sepsis—discontinued from trial
  - 2 Retinopathy of prematurity

Infants 1-11 month olds. Study 3004. Counts and rates of serious adverse events (SAEs) in the double-blinded phase of Study 3004 are shown in Table 29.

Table 29 SAEs in double-blinded phase: 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 TESAE	2 (2.2)	6 (6.7)	2 (2.3)	8 (4.5)
Ear and Labyrinth Disorders	**1 (1.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Hypoacusis	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration Site Conditions	**0 (0.0)**	**1 (1.1)**	**0 (0.0)**	**1 (0.6)**
Pyrexia	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)
Infections and infestations	**0 (0.0)**	**4 (4.4)**	**1 (1.1)**	**5 (2.8)**
Bronchiolitis	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.6)
Gastroenteritis	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)
Upper respiratory tract infection	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)
Urinary tract infection	0 (0.0)	2 (2.2)	0 (0.0)	2 (1.1)
Investigations	**0 (0.0)**	**0 (0.0)**	**1 (1.1)**	**1 (0.6)**
Beta 2 microglobulin increased	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.6)
Metabolism and nutrition disorders	**1 (1.1)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Failure to thrive	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	**0 (0.0)**	**1 (1.1)**	**0 (0.0)**	**1 (0.6)**
Agitation	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**1 (1.1)**	**0 (0.0)**	**1 (0.6)**
Stridor	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.6)

[ref: CSR Study 3004, Table 12-7, p. 86]

Overall, the rate of SAEs in the double-blinded portion of Study 3004 was 4.5% compared to 2.2% for placebo. However, by individual dose group, there appears to be no dose-response relationship based on rates in the placebo (2.2%), 5mg (6.7%), and

10mg (2.3%) groups. The single most frequent SAE was urinary tract infection, which was reported for 2 subjects (1.1%), both of whom were in the 5mg group (one male and one female) There were no SAE urinary tract infections reported for the placebo group.

Medical Reviewer Comment. Urinary tract infection is not an expected side effect of PPIs, and given the small sample sizes, probably represents a spurious finding. However, one might postulate that a state of hypo- or achlorhydria could change the gut microbiome, thereby changing the perineal flora that normally help protect against UTI (especially in females) and increasing the propensity for UTI.

1-11 year olds. Study 3003 Part 1. Seven SAEs were reported in 6 patients: 5 patients in the low-dose group (4 on 5mg in low-weight cohort and 1 on 10mg in high-weight cohort) and 1 patient in the high-dose low-weight cohort. None of these SAEs resulted in discontinuation. Table 30 summarizes the nonfatal SAEs from Study 3003 Part 1.

Table 30 Nonfatal SAEs: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
System Organ Class	(N=21)	(N=19)	(N=44)	(N=43)
Preferred Term	n (%)	n (%)	n (%)	n (%)
Number of Subjects With at Least One Treatment-Emergent SAE	4 (19)	1 (5)	1 (2)	0
Infections and infestations	3 (14)	1 (5)	1 (2)	0
Bronchitis	1 (5)	0	0	0
Bronchopneumonia	1 (5)	0	0	0
Gastroenteritis	0	1 (5)	0	0
Gastrointestinal infection	0	0	1 (2)	0
Pneumonia	1 (5)	0	0	0
Injury, poisoning and procedural complications	1 (5)	0	0	0
Humerus fracture	1 (5)	0	0	0
Metabolism and nutrition disorders	1 (5)	0	0	0
Dehydration	1 (5)	0	0	0

Note: Adverse events were coded using Medical Dictionary for Regulatory Activities version 12.0.

[ref: CSR Study 3003 Part 1, Table 12.9, p. 135]

No dose-response relationship is suggested in these data based on the rates shown in Table 30. No SAEs of pneumonia or bronchopneumonia were reported in the high dose group. Two patients in the low-weight low-dose cohort were reported with SAEs of pneumonia or bronchopneumonia. In the low-weight low-dose cohort, the pneumonia case was reported as doubtfully related to rabeprazole, and the bronchopneumonia case was reported as possibly related to rabeprazole.

Medical Reviewer Comment. Given the complexity of these SAE cases, it is difficult if not impossible to assess relatedness to rabeprazole with any certainty.

1-11 year olds. Study 3003 Part 2. Five patients were reported to have nonfatal SAEs in Study 3003 Part 2, as shown in Table 31. All of these cases were considered to be 'not related' to rabeprazole.

Table 31 Nonfatal SAEs: Study 3003 Part 2

	Rabeprazole Sodium Treatment by Actual Dose			
	LowWeight 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
System Organ Class Preferred Term	(N=9) n (%)	(N=8) n (%)	(N=24) n (%)	(N=23) n (%)
Number of Subjects With at Least One Treatment-Emergent SAE	1 (11%)	2 (25%)	1 (4%)	1 (4%)
Blood and lymphatic system disorder	0	1 (13%)	0	0
Lymphadenitis	0	1 (13%)	0	0
Infections and infestations	0	1 (13%)	0	0
Bronchopneumonia	0	1 (13%)	0	0
Injury, poisoning and procedural complications	1 (11%)	0	0	0
Head injury	1 (11%)	0	0	0
Nervous system disorder	0	0	1 (4%)	0
Partial seizures with secondary generalization	0	0	1 (4%)	0
Psychiatric disorder	0	0	0	1 (4%)
Conversion disorder	0	0	0	1 (4%)

Note: Adverse events were coded using MedDRA version 12.0.

[ref: CSR Study 3003 Part 2, Table 12.8, p. 93]

7.3.3 Dropouts and/or Discontinuations

Neonates 0-<1 month old, Study 1005 (PK/PD). Four patients had AEs that led to premature discontinuation from the trial. They included apnea/bradycardia and presumed sepsis.

Infants 1-11 month olds. Study 3004. In the double-blinded portion of Study 3004, the following numbers of patients were discontinued from the trial for an adverse event, and all but one of these cases was from worsening of GERD:

- Placebo: 7.8% (7/89)
  - Worsening of GERD: 6.7% (7/89)
  - Increased beta-2 microglobulin: 1.1% (1/89)

- 5mg dose: 2.2% (2/90)
    - Worsening of GERD: 2.2% (2/90)
- 10mg dose: 3.4% (3/88)
    - Worsening of GERD: 3.4% (3/88)

Medical Reviewer Comment. The higher rate of discontinuation in the placebo group does not suggest discontinuation from adverse reactions to rabeprazole. In fact, most discontinuations in Study 3004 were for worsening of GERD. It is conceivable that the worsening of GERD symptoms resulted from random variation within the trial, lack of effect, or possibly hypochlorhydria with resultant hypergastrinemia that caused lower esophageal sphincter tone and increased volume of refluxate. Again it is unclear whether any these patients, or indeed the majority of patients in trial 3004, truly had GERD, based on the inclusion criterion of "suspected GERD, symptomatic GERD, or endoscopically or histologically proven GERD" as discussed at the Nov-2010 AC meeting.

1-11 year olds. Study 3003 Part 1. There were 2 patients (5%) in the low-weight cohort (one at low-dose and one at high-dose) discontinued for an AE in this trial, and one patient (2%) in the high-dose high-weight group, as shown in Table 24. Reasons for discontinuation were exacerbation of vomiting, diarrhea, nausea, and abdominal pain, and all were considered possibly or probably related to study drug.

1-11 year olds. Study 3003 Part 2. There was one patient discontinuation (4%) for an AE in this extension study, as shown in Table 27. It occurred in the high-dose high-weight group.

7.3.4 Significant Adverse Events

See Sections 7.3.2 and 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Neonates 0-<1 month old, Study 1005 (PK/PD). See Section 7.2.2 Explorations for Dose-Response. None of the SAEs were adjudicated as related to rabeprazole.

Infants 1-11 month olds. Study 3004. See Table 23 (AEs). AEs that occurred in at least 5% of any treatment group and with a higher rate than placebo included (placebo-rabeprazole)—pyrexia (2%-7%) and increased serum gastrin (0%-5%).

1-11 year olds. Study 3003 Part 1. See Section 7.2.2 Explorations for Dose-Response: Table 25 (AEs) and Table 26 (ADRs).

SAEs reported in Study 3003 Part 1 are listed in Table 32.

Table 32 SAEs: Study 3003 Part 1

	Rabeprazole Sodium Treatment by Actual Dose			
	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
System Organ Class Preferred Term	(N=21) n (%)	(N=19) n (%)	(N=44) n (%)	(N=43) n (%)
Number of Subjects With at Least One Treatment-Emergent SAE	4 (19)	1 (5)	1 (2)	0
Infections and infestations	3 (14)	1 (5)	1 (2)	0
Bronchitis	1 (5)	0	0	0
Bronchopneumonia	1 (5)	0	0	0
Gastroenteritis	0	1 (5)	0	0
Gastrointestinal infection	0	0	1 (2)	0
Pneumonia	1 (5)	0	0	0
Injury, poisoning and procedural complications	1 (5)	0	0	0
Humerus fracture	1 (5)	0	0	0
Metabolism and nutrition disorders	1 (5)	0	0	0
Dehydration	1 (5)	0	0	0

[ref: CSR Study 3003 Part 1, Table 12.10, p. 136]

The only SAE that was considered as having any relationship to rabeprazole was a case of bronchopneumonia, which occurred in a 1-year old patient with a complex medical history. The investigator considered the relationship to study drug as 'possible', and the event was reported resolved in approximately 10 days.

1-11 year olds. Study 3003 Part 2. There were only 2 patients with ADRs reported in this study. The patient in the high-weight cohort had an AE of vomiting, and the patient

in the low-weight cohort had an AE of acidosis and increased urine beta-2-microglobulin. The case of increased beta-2-microglobulin resulted in study discontinuation by the investigator.

SAEs reported in Study 3003 Part 2, none of which were adjudicated by investigators as being related to rabeprazole, are listed in Table 33.

Table 33 SAEs: Study 3003 Part 2

	Rabeprazole Sodium Treatment by Actual Dose			
	LowWeight 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
System Organ Class Preferred Term	(N=9) n (%)	(N=8) n (%)	(N=24) n (%)	(N=23) n (%)
Number of Subjects With at Least One Treatment-Emergent SAE	1 (11%)	2 (25%)	1 (4%)	1 (4%)
Blood and lymphatic system disorder	0	1 (13%)	0	0
Lymphadenitis	0	1 (13%)	0	0
Infections and infestations	0	1 (13%)	0	0
Bronchopneumonia	0	1 (13%)	0	0
Injury, poisoning and procedural complications	1 (11%)	0	0	0
Head injury	1 (11%)	0	0	0
Nervous system disorder	0	0	1 (4%)	0
Partial seizures with secondary generalization	0	0	1 (4%)	0
Psychiatric disorder	0	0	0	1 (4%)
Conversion disorder	0	0	0	1 (4%)

[ref: CSR Study 3003 Part 2, Table 12.8, p. 93]

The partial seizure SAE was reported in a 5 year old male approximately 6 months after the first dose of rabeprazole in Part 1 (3 months after first dose in Part 2). The event was reported to have resolved the next day, and did not result in discontinuation from the trial. The investigator did not consider it related to study drug. The patient reportedly did not exhibit any abnormalities in vital signs or physical examination.

Medical Reviewer Comment. The normal physical exam and vital signs likely reflect the delay between the reported event and the examination by the investigator.

The conversion disorder was reported in a 9 year old female approximately 5 months after the first dose of rabeprazole in Part 1 (2 months after first dose in Part 2). The event was reported to have resolved the next day, and no medication was administered. The investigator did not consider it related to study drug.

Medical Reviewer Comment. A single occurrence of conversion does not make the diagnosis of 'conversion 'disorder'. So this sounds like a conversion episode with or without a conversion disorder.

7.4.2 Laboratory Findings

Neonates 0-<1 month of age. See Section 7.2.2 Explorations for Dose-Response, where a possible dose-response relationship to hemoglobin concentration was described.

Infants 1-11 month olds. Study 3004. Serum chemistry, hematology, and urine data were assessed. For serum gastrin, there appears to be a dose-response relationship (See Section 7.2.2). For serum iron, the mean change was a decrease in serum iron level in all dose groups. Change in serum iron (negative number indicates decrease from baseline to end of study) was as follows: placebo (-2.245 micromol/L), 5mg dose group (-1.74 micromol/L), and 10mg dose group (-0.342 micromol/L).

Medical Reviewer Comment. With clinically significant achlorhydria, iron absorption would be expected to decrease. In this case, however, it decreased the least with the highest dose level (10mg). These data do not support an association between decrease in iron and achlorhydria.

In the open-label phase, clinically significant AEs included an episode of increased urine beta-2-microglobulin that led to study discontinuation and was not associated with elevation of serum creatinine, BUN, abnormal urinary sediment, or signs of renal disease; and increased serum gastrin levels.

In the double-blind phase, there were 15 patients with AEs related to clinical laboratory findings including increased serum creatine phosphokinase, serum creatinine, serum gastrin, blood urea nitrogen/creatinine ratio, platelet count, serum ferritin, white blood cell count, and urine creatinine levels. None of these led to discontinuation of rabeprazole.

1-11 year olds. Study 3003 Part 1. The most prominent change was in gastrin levels. There was a shift to higher gastrin levels in both dose groups as follows:

- In the low-dose group at Baseline, no patients had low gastrin levels, 89% had normal levels, and 12% had high levels. At Week-12, 2% had low levels, 66% had normal levels, and 33% had high levels. Mean gastrin was 58 ng/L at Baseline and 96 ng/L at Week-12.
- In the high-dose group at Baseline, 2% of patients had low gastrin, 88% had normal gastrin, and 10% had high gastrin. At Week-12, no patients had low levels, 66% had normal levels, and 34% had high levels. Mean gastrin was 51 ng/L at Baseline and 115 ng/L at Week-12.

Medical Reviewer Comment. The levels of gastrin seem to be dose-related and this is expected based on the mechanism of action of rabeprazole. However, their clinical significance is not known at this time and for short courses of PPI therapy.

There were 4 AEs related to clinical laboratory findings—anemia, creatine phosphokinase increased, alkaline phosphatase increased, and hypercholesterolemia. No action was taken with study drug in response to these AEs.

There was a slight decrease in mean magnesium levels as follows:

- Low-dose group: 0.89 mmol/L to 0.86 mmol/L.
- High-dose group: 0.88 mmol/L to 0.87 mmol/L.

Medical Reviewer Comment. Hypomagnesemia has recently been reported in post-market reports involving long-term use of PPIs.

1-11 year olds. Study 3003 Part 2. Three patients had AEs related to clinical laboratory findings including increased urine beta-2-microglobulin, decreased blood iron, and decrease serum ferritin. No action was taken with study medication due to these AEs.

For gastrin, changes were as follows:

- Low-dose group: 15% of patients went from normal to high between Baseline and 36 weeks. For these patients, mean gastrin increased from Baseline to 36 weeks from 93 ng/L to 114 ng/L.
- High-dose group: 32% of patients went from normal to high between Baseline and 36 weeks. For these patients, mean gastrin increased from Baseline to 36 weeks from 85 ng/L to 113 ng/L.

For glucose, changes were as follows:

- Low-dose group: 10% of patients went from normal to high between Baseline and 36 weeks. For these patients, mean glucose increased from Baseline to 36 weeks from 4.7 mmol/L to 4.8 mmol/L.
- High-dose group: 11% of patients went from normal to high between Baseline and 36 weeks. For these patients, mean glucose increased from Baseline to 36 weeks from 4.6 mmol/L to 4.8 mmol/L.

Medical Reviewer Comment. Changes serum gastrin are attributable to acid suppression. Increases in mean serum glucose do not appear clinically significant.

7.4.3 Vital Signs

Infants 1-11 month olds. Study 3004. There were no clinically meaningful changes in mean vital sign parameters within- or between-groups (heart rate changes of -2 to +4 BPM not dose-related, systolic BP changes of -3 to 1 mmHg not dose-related, diastolic changes of approximately 0 in all groups, respiratory changes of -2 to 1 not dose-related, temperature changes of approximately 0 in all groups) during the double-blind phase.

1-11 year olds. Study 3003 Part 1. There were no clinically meaningful changes in vital sign data.

1-11 year olds. Study 3003 Part 2. There were no clinically meaningful changes in vital sign data.

7.4.4 Electrocardiograms (ECGs)

Infants 1-11 month olds. Study 3004. Scheduled ECGs were not done.

1-11 year olds. Study 3003 Part 1. Scheduled ECGs were not done.

1-11 year olds. Study 3003 Part 2. Scheduled ECGs were not done.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials.

7.4.6 Immunogenicity

There are no immunogenicity concerns with this approved medication.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Section 7.2.2 Explorations for Dose-Response.

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs could not be assessed due to the short duration of these trials and small numbers of patients.

7.5.3 Drug-Demographic Interactions

There does not appear to be drug-demographic interactions based on these data.

7.5.4 Drug-Disease Interactions

Drug-disease interaction was not studied in controlled fashion. There appears to be no relationship between comorbid disease other than GERD and rabeprazole, and the sample sizes are too small to detect such interactions if they were present.

7.5.5 Drug-Drug Interactions

Drug-drug interactions have already been reported in the labeling for ACIPHEX, and include increased INR and prothrombin times with warfarin; inhibition of cyclosporine metabolism; inhibition of gastric secretion that can interfere with drugs where gastric pH is an important determinant of bioavailability (ie, ketoconazole, iron salts, digoxin); and reduced plasma levels of atazanavir [ref: ACIPHEX label].

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenicity has been studied in animal models, where gastric mucosal hyperplasia has been observed. See current ACIPHEX label for details.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies with ACIPHEX in pregnant females. No evidence of teratogenicity was seen in animal reproduction studies at exposures 8-13 times human exposures at the recommended adult dose for GERD in adults [ref: ACIPHEX label].

7.6.3 Pediatrics and Assessment of Effects on Growth

The PREA requirement has been met.

The effects of ACIPHEX on growth in pediatric patients has not been studied in controlled fashion. However, in Study 3004 in infants, weight-for-age Z-score was a coprimary endpoint for which the mean change in the pooled rabeprazole groups was 0.14 (Table 19).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The potential for overdose always exists in pediatric populations, whether accidental or deliberate. ACIPHEX is not addicting. There is evidence that following discontinuation of any of the PPIs, there could be rebound hyperacidity and hypergastrinemia consequent to parietal cell mass in response to prolonged PPI exposure.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

There is already extensive postmarket data for ACIPHEX DR tablets in adults and adolescents, which appears in the label.

9 Appendices

9.1 Literature Review/References

See footnotes.

9.2 Labeling Recommendations

(b) (4)

Medical Reviewer Comment. *The Boccia study cited earlier suggested that no therapy was just as good as PPI therapy subsequent to achievement of short-term healing in EE. And because sGERD is a milder form of EE, it is assumed that the same should hold for sGERD.*

The following label recommendations are made by the Clinical Reviewer:

1. Grant indication of "Treatment of GERD" for up to 12 weeks
2. Approve 2 dose levels (5mg, 10mg) for (b) (4) indication (b) (4)

3. Approve a single dose level for the high-weight cohort in the 1-11 year age group (b) (4)

   (b) (4)

4. Place information in the label, as the Applicant has proposed, about the inability to demonstrate efficacy in Study 3004 (infants 1-11 months of age)
   a. FDAAA 505(G)(2) requires information on negative or inconclusive studies be placed in the label (section 8.4)
   b. The phase 3 efficacy/safety trial was not able to demonstrate efficacy, similar to 4 other PPIs
   c. We agree with the Applicant's placing information about this study in Section 8.4 Pediatric Use>Pediatric Patients Aged 1 to 11 months but not in Section 6 Adverse Reactions or in Section 14 Clinical Studies.
5. For the neonatal (<1 month of age) PK/PD study, may place a statement in the label about higher exposures in neonates than infants. Place another statement indicating that safety and efficacy studies were not done in the neonatal age group rather than simply stating (b) (4)
   a. FDAAA 505(G)(2) requires information on negative or inconclusive studies be placed in the label
   b. No study of safety and efficacy was done in the neonatal age group
   c. Considerations about placing or not placing information on the neonatal study in the label
      i. FDA does not want to condone, explicitly or implicitly, use of Aciphex in neonates by placing information in the label.

         Medical Reviewer Comment. Placing information about neonates in the label could potentially be interpreted by prescribers as condoning use in neonates. On the other hand, not placing neonatal information in the label could suggest that no study was ever done in neonates, which is not the case (Study 1005 was a PK/PD in neonates). And not reporting such a study in the label could potentially be in violation of FDAAA 505(G)(2).

         So, although there are no negative or inconclusive results on safety and efficacy in neonates, the Division concluded after consultation with PeRC (29-Jan-2013) that neonatal data should be placed in the label. However, the data should be similar to that described in

NEXIUM label—drug clearance values (lower in neonates) and the statement should include that safety and efficacy have not been "established". This issue will be further discussed during labeling negotiations with the Applicant.

d. The language FDA proposes at this time and will be further reviewed in labeling discussions is the following:

> "Neonates 0 to 1 month of age: Following administration of oral ACIPHEX, the median (range) for the apparent clearance (CL/F) was 1.05 L/h (0.0543-3.44 L/h) in neonates and 4.46 L/h (0.822-12.4 L/h) in patients 1-11 months of age.
>
> Safety and efficacy of ACIPHEX have not been studied in patients less than 1 month of age. Based on the results of the Phase 3 efficacy study, rabeprazole was not shown to be effective, and should not be used to treat symptomatic GERD in infants (1-11 months of age)."

9.3 Advisory Committee Meeting

No Advisory Committee was convened to discuss this sNDA.

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

/s/

JOHN S TROIANI
03/11/2013

RUYI HE
03/11/2013