CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204736Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	204,736	*Submission Date(s)*	9/27/2012, 12/7/2012, 2/11/2013, 2/15/2013
Brand Name	AcipHex Sprinkle®		
Generic Name	Rabeprazole		
Reviewer	Insook Kim, Ph.D.		
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OCP Division	Division of Clinical Pharmacology 3		
OND Division	Division of Gastroenterology and Inborn Errors Products		
Sponsor	Eisai		
Relevant IND(s)	33,985		
Submission Type; Code	Original	Priority	
Formulation; Strengths; Regimen	Delayed-release granules in capsule • For children weighing less than 15 kg, 5 mg once daily (b) (4) (with an option to increase to 10 mg after clinical reassessment) • For children ≥ 15 kg, 10 mg once daily (b) (4)		
Proposed Indication	Healing, Maintenance of Healing and Improvement of Symptoms in Pediatric Patients Aged 1 to 11 years with GERD		

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1 Executive Summary

This New Drug Application was submitted in response to the pediatric written request as well as in fulfillment of PREA requirement. In this submission, the sponsor is seeking the marketing approval of use of AcipHex® (Rabeprazole sodium) in pediatric patients 1-11 year of age with endoscopically-proven GERD for healing, maintenance of healing and improvement of symptoms. Supporting studies in patients < 11 years old were conducted with a new age-appropriate formulation i.e. delayed-release granules in softgel capsules. While approved for patients 12 years and above, the approved AcipHex® tablets were not studied in patients ≤11 years old. Studies in pediatric patients younger than 1 year old were also submitted; however, the indication is not proposed in patients less than 1 year old based on the failed efficacy trial in patients 1-11 months old in this program.

1.1 Recommendations

The office of Clinical Pharmacology has reviewed this application and found acceptable from a clinical pharmacology standpoint provided a mutual agreement on labeling languages is reached.

1.2 Post-Marketing Studies

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

This review will mainly discuss the studies in patients 1-11 year old. To support use of rabeprazole in pediatric patients 1-11 years old, one pharmacokinetic study in patients (Study 1002) and one efficacy and safety study (Study 3003) were submitted. The proposed product will not be indicated for patients younger than 1 year old and study results in patients < 1 year old were reviewed only for the labeling purpose. Studies in patients 12-17 year old were previously reviewed in support of the approval of AcipHex tablet in adolescents.
In this review, the proposed product will be referred as rabeprazole granules as rabeprazole was administered as granules after opening the capsules containing delayed-release granules. The administration of the whole capsule was not studied in this program.

Dose selection

The proposed dose of 5 mg for patients < 15 kg with an option of increase to 10 mg and 10 mg for patients ≥ 15 kg is acceptable from a clinical pharmacology standpoint (Table 1).

Table 1. Recommended dosage for patients 1-11 years old with GERD

Weight	Dosage	Treatment of GERD*
< 15 kg	5 mg once daily (with an option to increase to 10 mg after clinical reassessment)	Up to 12 weeks
≥ 15 kg	10 mg once daily	Up to 12 weeks

For patients ≥ 15 kg, the dose of 10 mg is recommended based on no apparent dose-response for healing of GERD between 10 mg and 20 mg. In addition, no concentration-response relationship is evident the healing of GERD.

For patients < 15 kg, the dose of 5 mg is also recommended based on no apparent exposure-response relationship for the healing of GERD between doses of 5 mg and 10 mg. We found the proposed dose of 5 mg acceptable as it is the lowest effective dose with an acceptable response rate. In addition, the proposed "option of dose increase to 10 mg after reassessment" is agreeable based on the limitations of the small sample size (n=16-17) for the definitive conclusion on the dose-response between 5 mg and 10 mg. On the other hand, the mean AUC after 5 mg dosing was estimated to be lower than the observed AUC at doses of 10 mg or 20 mg in adults while the systemic exposure at10 mg is within the AUC range observed in adults at the approved 20 mg.

The dose of rabeprazole for maintenance of healing will not be discussed in this review because of the on-going discussion on whether the continuous treatment for healed GERD is necessary in pediatric patients[1].

The proposed indication of healing and improvement of symptoms of endoscopically-proven GERD is under discussion. Detailed discussion on the indication is deferred to the clinical review by Dr. John Troiani.

Exposure (Dose)-Response Relationship

- ***Efficacy***

There was no clear exposure-response relationship for the healing rate[2] and there was no apparent relationship between rabeprazole systemic exposure, i.e. AUC and the probability of healing of GERD. The healing rate was over 70% regardless of the dose and was comparable between doses (Table 2). The small number of subjects in each dose cohort hampers meaningful statistical analysis between doses. Detailed review of efficacy is deferred to the clinical review Dr. John Troiani.

[1] Boccia et al. (2007) Maintenance therapy for erosive esophagitis in children after healing by omeprazole: Is it advisable? Am. J. Gastroenterol. 102: 1291-1297

[2] The healing of GERD was assessed after 12 week treatment with rabeprazole granules in patients 1-11 year old who had Hetzel-Dent score ≥ 1 and Histological Features of Reflux Esophagitis score greater than 0 at baseline. The healing rate is defined as having either Grade 0 on the Hetzel-Dent classification scale **or** Grade 0 on the Histological Features of Reflux Esophagitis scale.

Table 2. Endoscopic/Histologic Healing Rates During the 12-Week Double-Blind Treatment Phase

Body weight cohort	Patients < 15 kg		Patients ≥ 15 kg	
Dose	5mg	10 mg	10 mg	20 mg
Healing rate:% (n/N)	82 (14/17)	94 (15/16)	76 (29/38)	78 (29/37)

Safety:

There was no dose-dependent increase in treatment-emergent adverse events. The proportion of subjects with at least one TEAE was 74% (48/65) and 77% (48/62) in 0.5 mg/kg and 1 mg/kg target dose group, respectively (Table 3). On the other hand, the number of treatment-emergent serious adverse events was higher in 5 mg dose group. It is unclear why more patients experienced serious AE in the 5 mg dose group. Please see the clinical review for more details.

Pharmacokinetic/Biopharmaceutics Properties

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 between the to-be-marketed formulation as one 10 mg capsule and the phase 3 formulation as two 5 mg capsules was demonstrated (Table 4). In the study, rabeprazole granules were administered after sprinkled on applesauce under fasting condition and swallowed with 240 ml of water. The geometric mean ratio of Cmax and AUC for rabeprazole and its associated 90% CI met the bioequivalence criteria. The Office of Scientific Investigations 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. Please see the DSI review by Dr. Patel dated 3/1/2013 for more details.

Effect of a high fat meal on PK of rabeprazole

When a high fat meal was taken prior to the rabeprazole dosing, the absorption of rabeprazole was delayed and mean Cmax and AUC were decreased by 55% and 32%, respectively. On the contrary, the systemic exposure after administration of AcipHex® tablet, was not significantly altered under fed condition compared to fasting condition (AcipHex® Package Insert).

In the phase 3 trial in patients 1-11 years old, rabeprazole granules were allowed to be taken before or with meals; however, the meal intake in relation to rabeprazole dosing was not recorded. Based on the significant decrease in the systemic exposure by a high fat meal and the uncertainty in the lowest effective systemic exposure, the administration of rabeprazole granules prior to a meal e.g. 30 min is recommended.

Effect of food vehicles on PK of rabeprazole

There was no significant difference in pharmacokinetics of rabeprazole when rabeprazole granules were administered after sprinkled on apple sauce, yogurt or infant formula. While 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
The 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 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%. The extent of effects on the active metabolite of clopidogrel is similar to that by 80% pantoprazole by a cross-study comparison. The study report was submitted on 2/6/12 to IND 33,985 and the relevant labeling update is submitted to as to this submission (b) (4) For more details on the study results, please see the clinical pharmacology review by Dr. Kris Estes for IND 33,985 dated 12/7/12.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

This submission is to response to the Written Request, originally issued on December 31, 2001 and reissued in its final amended form on September 14, 2012. For adolescents 12 years and above, AcipHex® 20 mg Delayed-Release Tablets are also indicated for short-term treatment of symptomatic GERD.

Written Request Study
1. Pharmacokinetic (PK), Pharmacodynamic (PD) and safety study in neonates and pre-term infants with a corrected age less than 44 weeks
2. Efficacy and safety evaluation of pediatric patients 1 to 11 months of age
3. Pharmacokinetic, exposure/response, and safety study in pediatric patients 1 to 11 years of age
4. Pharmacokinetic and safety study in pediatric patients 12 to 16 years of age

On December 2012, the exclusivity was granted for the fulfillment of the terms in the Written Request.

This submission is also to fulfill the phase 4 commitments agreed upon the approvals of AcipHex® Delayed-Release Tablets for the treatment of erosive GERD (original NDA), symptomatic GERD (S-009) and *Helicobacter pylori* (S-013, approved 8 November 2002) in adults as below.

Post-Marketing Requirement
NDA 20-793: approved on August 19, 1999

- A study to assess the optimal dosage regimen in the pediatric population for the acute healing of GERD and for the maintenance of healing of GERD

NDA 20-793 S-009: approved on February 12, 2002

- Deferred PMR on the treatment of symptomatic GERD

In the United States (US), AcipHex® (rabeprazole) 20 mg Delayed-Release Tablets is approved in adults for following indications:

- short-term treatment of erosive or ulcerative gastroesophageal reflux disease (GERD)
- symptomatic GERD; maintenance of healing in subjects with GERD
- healing and symptomatic relief of duodenal ulcers
- long-term treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome
- eradication of *Helicobacter pylori* in combination with amoxicillin and clarithromycin

The 10 mg tablet was also approved along with the 20 mg tablet; however, the 10 mg tablet was withdrawn without being marketed for reasons unrelated to safety or effectiveness (FR Doc. 05-5975: March 28. 2005 (Volume 71, Number 58))[3]

2.1.2 What is the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

To support the use of rabeprazole in pediatric patients younger than 12 years of age, an age appropriate formulation i.e. a softgel capsule containing enteric-coated rabeprazole granules, was developed. In clinical trials in patients younger than 12 years old, the rabeprazole granules were administered after sprinkled on soft food (such as apple sauce or yogurt) or mixing with infant formula. The administration of whole capsule was not studied.

During the formulation development, two interim formulations were used in clinical trials. The phase 1 formulation was a formulation used in the dedicated PK studies in patients. A relative BA study was conducted for the phase 1 formulation and the phase 3 formulation.

The phase 3 formulation was used in the safety and efficacy trial in patients 1-11 years old. The to-be-marketed formulation is different from the phase 3 formulation for the manufacturing site and the material grade of magnesium oxide, an inactive ingredient. A bioequivalence study was conducted to bridge the to-be-marketed formulation and the phase 3 formulation (Study 1007).

2.1.3 What are the mechanism(s) of action and the proposed therapeutic indication(s)?

Rabeprazole, the active pharmaceutical ingredient in AcipHex®, is a substituted benzimidazole molecule that is an inhibitor of H^+/K^+ ATPase, the proton pump responsible for the terminal step in gastric acid secretion.

[3] http://www fda.gov/ohrms/dockets/98fr/05-5975.htm

The proposed indication is the healing, maintenance of healing, and symptom improvement of GERD in subjects 1 to 11 years. The acceptability of indication as well as the use of rabeprazole for maintenance of healing of GERD is under discussion. Detailed discussion on the indication is deferred to the clinical review.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

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

Rabeprazole granules should be administered after sprinkled on a small amount of soft food before meals.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 3. List of the clinical trials

Study Number	Dose	Formulation	Study Description
Studies in Neonates Preterm infants with a corrected age of <44 weeks with a presumptive diagnosis of GERD			
RABGRD1005	Part 1: 1 mg Part 2: 2 or 3 mg Once daily for 5 days	Part 1: Phase 1 granules Part 2: Phase 3 granules	Phase 1, open-label, 2-part study to investigate the pharmacokinetics, pharmacodynamics (pH-metry, overall treatment effect), and safety of rabeprazole after single- and multiple-dose administration of rabeprazole granules.
Studies in Infants 1 to 11 Months Old With GERD			
RABGRD1003	Part 1: 0.14 or 0.5 mg/kg Part 2: 5 or 10 mg Once daily for 5 days	Part 1: Phase 1 granules Part 2: Phase 3 granules	Phase 1, open-label, 2-part study to investigate the pharmacokinetics, pharmacodynamics (pHmetry, Clinical Global Impression, palatability, GERD daily symptom diary), and safety of rabeprazole after singleand multiple-dose administration of rabeprazole granules.
RABGRD3004	5 and 10 mg	Phase 3 granules	Phase 3, open-label to double-blind, randomized multicenter, placebo-controlled parallel-group study to investigate the efficacy and safety of 2 dose levels (5 and 10 mg) of rabeprazole granules
Studies in Children 1 to 11 Years Old With GERD			
RABGRD1002	0.14, 0.5, or 1.0 mg/kg [a]	Phase 1 granules	Phase 1, open-label, two-part study to investigate the pharmacokinetics, pharmacodynamics (Clinical Global Impression), and safety of rabeprazole after single- and multiple-dose administration of rabeprazole granules at target weight-based dose levels.

RABGRD3003	0.5 or 1.0 mg/kg [b]	Phase 3 granules	Phase 3, double-blind, randomized, multicenter parallel-group study to investigate the efficacy and safety of two target dose levels (0.5 and 1.0 mg/kg) of rabeprazole granules.
Studies in Healthy Adults			
E3810-A001-015	10 mg	Tablet and Phase 1 granules	Relative bioavailability: **10 mg** tablet versus Phase 1 granule formulation
RABGRD1004	10 mg	Phase 3 granules	Relative bioavailability with different dosing vehicles
RABGRD1006	10 mg	Phase 1 and Phase 3 granules	Relative bioavailability: Phase 1 versus Phase 3 granule formulation; food effect for the Phase 3 granule formulation
RABGRD1007	10 mg	Phase 3 and to-be-marketed granules	Bioequivalence: food effect for the to-be-marketed granule formulation

GERD = gastroesophageal reflux disease, PD = pharmacodynamic(s), PK = pharmacokinetic(s).
a: Target dose levels, using increments of 1 mg.
b: Target dose levels, absolute doses of 5, 10, or 20 mg depending on dose group and body weight.

Primary efficacy endpoint

The primary efficacy endpoint in pediatric patients 1-11 year old was the healing of GERD (Study 3003).

The macroscopic/histologic healing of GERD was assessed at Week 12/End of 12-week double-blind treatment phase, where Week 12 had either a Grade 0 on the Hetzel-Dent classification scale (macroscopically normal esophageal mucosa) **or** Grade 0 on the Histological Features of Reflux Esophagitis scale (histologically normal esophageal mucosa).

The Hetzel-Dent classification was used for endoscopic grading, and scores ranged from Grade 0 = Normal esophageal mucosa, no abnormalities noted to Grade 4 = Deep ulcers anywhere in the esophagus or confluent erosion or ulceration of >50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa.

Histologic grading was done according to the Histological Features of Reflux Esophagitis scale and scores ranged from Grade 0 = None to Grade 5 = Mucosal erosions and/or ulcerations.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

When the healing of GERD was assessed after 12 week treatment with rabeprazole granules in patients 1-11 year old, there was no clear exposure-response relationship for the healing rate. At baseline, patients had to have a positive endoscopically proven GERD with a Hetzel-Dent (HD) classification, grade ≥1 and Histological Features of Reflux Esophagitis (HFRE) scale, grade >0 (Table 4). The healing rate was over 70% regardless of the dose and was comparable between doses when compared by the actual dose groups (Tables 5 and 6). The statistical power to demonstrate the dose-response was not considered in the study design.

Among 108 patients who had 12 week assessment results, the number of patients who had HFRE score of 1, 2, 3, 4, and 5 was 41, 16, 42, 4, and 5, respectively.

Table 4. Demographics of pediatric patients 1-11 years old in Study 3003

	Low Weight cohort (< 15 kg)		High-Weight cohort (≥ 15 kg)	
Target dose	0.5 mg/kg (n=21)	1 mg/kg (n=19)	0.5 mg/kg (n=44)	1 mg/kg (n=43)
Actual dose	5 mg	10 mg	10 mg	20 mg
Mean Age	2.4	1.9	7.6	7
Weight (kg) Mean (min, max)	12.4 (8, 15)	11.5 (7, 15)	32.7 (15, 76)	28.5 (15, 57)
Proportion of Hetzel-Dent Score at baseline				
1	12 (57%)	13 (68%)	25 (57%)	29 (67%)
2	6 (29%)	5 (26%)	16 (36%)	11 (26%)
3	1 (5%)	1 (5%)	2 (5%)	3 (7%)
4	2 (10%)	--	1 (2%)	--
Healing rate (%)				
	82	94	76	78

Table 5. Endoscopic/Histologic Healing Rates During the 12-Week Double-Blind Treatment Phase – (A) By Target Dose and (B) By Actual Dose - ITT Analysis Set

(A)

Target dose		0.5 mg/kg (N=55)	1 mg/kg (N=53)
Dose	< 15 kg	5mg	10 mg
	≥15 kg	10 mg	20 mg
Healing rate: n (%)		43 (78)	44 (83)

(B)

Body weight cohort	Patients < 15 kg		Patients ≥ 15 kg	
Dose	5mg	10 mg	10 mg	20 mg
Healing rate:% (n/N)	82 (14/17)	94 (15/16)	76 (29/38)	78 (29/37)

Table 6. Total GERD Symptom and Severity Score on the eCRF During the 12-Week Double-Blind Treatment Phase Change from Baseline – By Actual Dose - ITT Analysis Set

	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=21)	(N=19)	(N=44)	(N=43)
Baseline Mean (SD)	23.2	16.3	19.1	18.9
Week 12 (SD)	6.7 (8.80)	6.4 (6.27)	8.4 (7.75)	10.7 (9.47)
Change from Baseline to Week 12				
N	18	18	43	41
Mean (SD)	-13.6 (13.07)	-9.0 (11.17)	-10.6 (11.13)	-8.3 (9.20)
Median	-8.5	-4.5	-10.0	-8.0

Note: Total Gastroesophageal Reflux Disease Symptom and Severity Score was 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 electronic case report forms. The symptom scores were rated on severity during the week preceding the visit.
Note: Baseline was the last non-missing assessment prior to taking 12-week double-blind study drug.

The high healing rate is in part attributed to the definition of healing which allows the normalization (i.e. 0) of either HD or HFRE score. Out of 87 responders, 32 patients had score 0 for both scales while 55 patients had either non-normalized H-D score or HFRE score (Table 7). There was no apparent relationship between the non-zero scores and the dose in patients < 15 kg, while a definitive conclusion can not be made due to the small number of patients (Table 8)
Please see the clinical review by Dr. John Troiani for more details.

Table 7. The number of patients after 12 week treatment by Hetzel-Dent classification and Histological Features of Reflux Esophagitis scale*

		Histological Features of Reflux Esophagitis scale					
		0	1	2	3	4	5
Hetzel-Dent classification	0	32	12	13	20	1	-
	1	9	3	5	6	2	-
	2	-	1	1	1	-	-
	3	-	-	-	1	-	1
	4	-	-	-	-	-	-

*The responders were in shaded cells

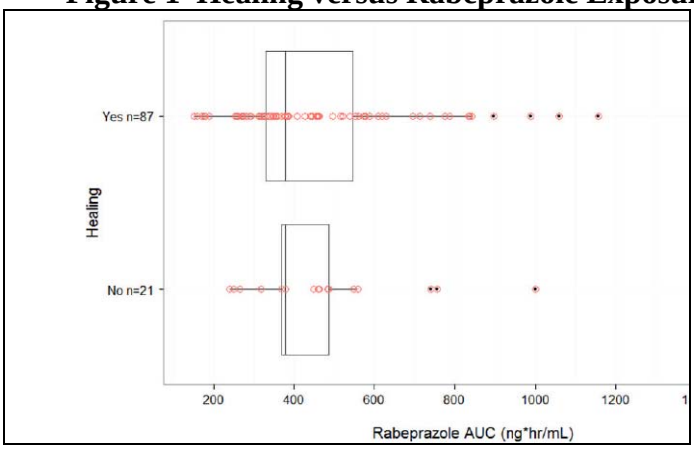
Table 8. The number of responders < 15 kg who had non-normalized H-D or Hetzel-Dent score by dose

Body weight	< 15 kg	
Dose	5 mg (n=14)	10 mg (n=15)
	Number of patients (HFRE score)	
H-D score		
0	0:n=4 1: n=1 2:n=3 3: n=4	0: n=4 1: n=3 2: n=1 3: n=5
1	0: n=2	0: n=2

No apparent concentration-response relationship for healing of GERD

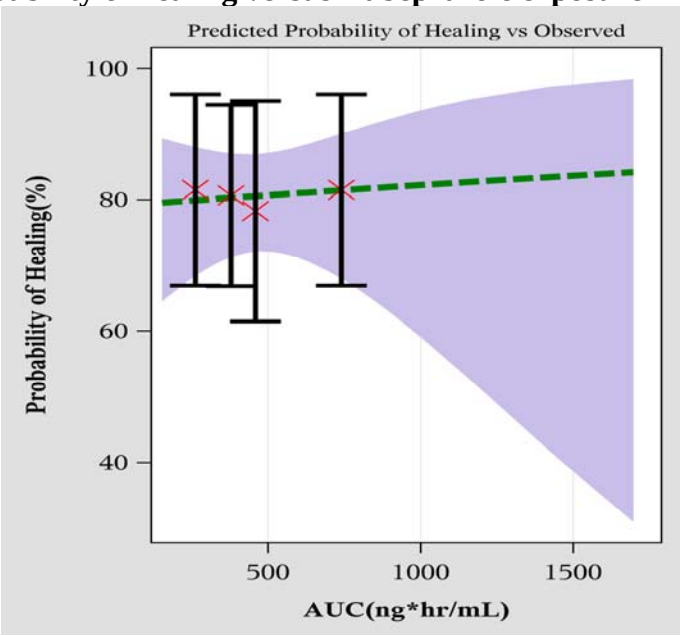
There was no apparent relationship between AUC of rabeprazole and the healing response. While the number of non-responders was significantly smaller than responders, the systemic exposure i.e. AUC was well overlap between responders and non-responders (Figure 1). While there was no apparent trend of response by H-D score at baseline

Figure 1 Healing versus Rabeprazole Exposure



Similarly, no evident relationship was observed between the probability of healing at week 12 and drug exposure (i.e., predicted AUCs at steady state) when analyzed by logistic regression (Figure 2).

Figure 2. The probability of healing versus Rabeprazole exposure



The mean and 95% CI of the observed probability versus the median of each quartile of AUCs is represented by black bars while dashed line and shade represent the model predicted mean and 95% interval of the probability of healing across different values of AUCs (P value=0.84).

For more details, please see the Pharmacometrics review in the Appendix.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

No apparent dose-dependent increase on adverse events was observed. The frequency of treatment-emergent AEs (TEAEs) was similar for the target and actual dose groups (range: 73% to 79%) (Table 9). For the entire study population, the most commonly reported TEAEs were cough in 14% of subjects, vomiting (14%), abdominal pain (12%), diarrhea (11%), pyrexia (10%), headache (9%), upper respiratory tract infection (8%), oropharyngeal pain (6%), and nasopharyngitis (5%). It was noted that more patients < 15 kg experienced serious adverse event after 5 mg dose than other dose groups (Table 10). The detailed review of adverse events is deferred to the clinical review by Dr. John Troiani.

Table 9: Summary of Treatment-Emergent Adverse Events in the 12-Week Double-Blind Treatment Phase - By Target Dose

	Rabeprazole Sodium Treatment by Target Dose		
Adverse Event Category	0.5 mg/kg (N=65) n (%)	1.0 mg/kg (N=62) n (%)	Total (N=127) n (%)
Number of Subjects With at Least One TEAE	48 (74)	48 (77)	96 (76)
Number of Subjects With at Least One Serious TEAE	5 (8)	1 (2)	6 (5)
Number of Subjects With at Least One TEAE Related to Study Medication	9 (14)	14 (23)	23 (18)
Number of Subjects With at Least One TEAE Leading to Discontinuation	1 (2)	2 (3)	3 (2)
Deaths	0	0	0

Table 10: Summary of Treatment-Emergent Adverse Events in the 12-Week Double-Blind Treatment Phase -By Actual Dose

Body weight	< 15 kg		≥ 15 kg	
Dose	5mg	10 mg	10 mg	20 mg
Number of subjects	N=21	N=19	N=44	N=43
With TEAE; n (%)	16 (76)	15 (79)	32 (73)	33 (77)
With SAE; n (%)	4 (19)	1 (5)	1(2)	0

Modified from Table 12.4. in CSR 3003

2.2.4.3 How were the doses for the phase 3 trial selected?

In this development program, the dose-response relationship of rabeprazole granules was explored in pediatric patients 1-11 years of age in the efficacy and safety trial. Two doses studied in the phase 3 trial i.e. 0.5 mg/kg and 1 mg/kg were selected based on the pharmacokinetics of rabeprazole in 1-11 years old patients with GERD and mean AUC associated with the effective doses in adult patients with erosive and ulcerative GERD. The weight-based target doses were administered as two fixed doses stratified by the body weight (Table 11)

Table 11. Doses studied in the efficacy and safety study in patients 1-11 years old

Weight	Once Daily Dosage
< 15 kg	5 mg (> 0.3 mg/kg) or 10 mg (> 0.6 mg/kg)
≥ 15 kg	10 mg (≤ 0.6 mg/kg) or 20 mg (≤ 0.3 mg/kg)

The target AUC range, 400 -800 ng·h/ml was chosen based on mean AUC observed at 10 mg and 20 mg daily dosing in adults. The dose of 20 mg is approved for various indications in adults and for treatment of symptomatic GERD in adolescents. On the other hand, the dose of 10 mg is not an approved dose but showed statistically significant effects compared to placebo in adult patients for acid suppression, a healing of erosive or ulcerative GERD in a phase 2 trial and for long-term maintenance of healing of erosive ulcerative GERD (Table 12).

Table 12. The AUC acidity (A), the response rate of healing (B) and a long-term maintenance (C) by dose in healthy subjects (A) or adult patients (B-C)(From AcipHex Pacakge Insert)

(A)

AUC ACIDITY (MMOL'HR/L)
ACIPHEX VERSUS PLACEBO ON DAY 7
OF ONCE DAILY DOSING (MEAN±SD)

AUC interval (hrs)	Treatment			
	10 mg RBP (N=24)	20 mg RBP (N=24)	40 mg RBP (N=24)	Placebo (N=24)
08:00 – 13:00	19.6±21.5*	12.9±23*	7.6±14.7*	91.1±39.7
13:00 – 19:00	5.6±9.7*	8.3±29.8*	1.3±5.2*	95.5±48.7
19:00 – 22:00	0.1±0.1*	0.1±0.06*	0.0±0.02*	11.9±12.5
22:00 – 08:00	129.2±84*	109.6±67.2*	76.9±58.4*	479.9±165
AUC 0-24 hours	155.5±90.6*	130.9±81*	85.8±64.3*	678.5±216

*(p<0.001 versus placebo)

(B)

HEALING OF EROSIVE OR ULCERATIVE
GASTROESOPHAGEAL REFLUX DISEASE (GERD)
PERCENTAGE OF PATIENTS HEALED

Week	10 mg ACIPHEX QD N=27	20 mg ACIPHEX QD N=25	40 mg ACIPHEX QD N=26	Placebo N=25
4	63%*	56%*	54%*	0%
8	93%*	84%*	85%*	12%

*(p<0.001 versus placebo)

(C)

TABLE 12

PERCENT OF PATIENTS IN ENDOSCOPIC REMISSION

	ACIPHEX 10 mg	ACIPHEX 20 mg	Placebo
Study 1	N=66	N=67	N=70
Week 4	83%*	96%*	44%
Week 13	79%*	93%*	39%
Week 26	77%*	93%*	31%
Week 39	76%*	91%*	30%
Week 52	73%*	90%*	29%
Study 2	N=93	N=93	N=99
Week 4	89%*	94%*	40%
Week 13	86%*	91%*	33%
Week 26	85%*	89%*	30%
Week 39	84%*	88%*	29%
Week 52	77%*	86%*	29%

2.2.4.4 How is the proposed dose for pediatric patients aged 1 to 11 years with GERD supported by population PK modeling and simulation?

The pharmacokinetic modeling and simulation predicts that at the proposed dose, 5 mg for patients < 15 kg and 10 mg for patients ≥ 15 kg, median AUC in patients 1 to 11 year of age would be about 256 ng*h/ml and 456 ng*h/ml, respectively (Table 13). At 10 mg dose, mean AUC in patients < 15 kg is predicted to be slightly higher, 514 ng*h/ml with higher variability than in patients ≥ 15 kg. As such in patients < 15 kg, the systemic exposure following 5 mg dose is expected to be lower than that in adults after the approved dose i.e. 20 mg as well as the unapproved 10 mg. On the other hand, the systemic exposure following 10 mg dose is expected to be lower than the approved dose i.e. 20 mg in adults.

For more details, please see the Pharmacometrics review in the Appendix.

Table 13. Model-Predicted Average AUC at Steady State from the Final Rabeprazole PK Model in the Subjects in the Population Analysis

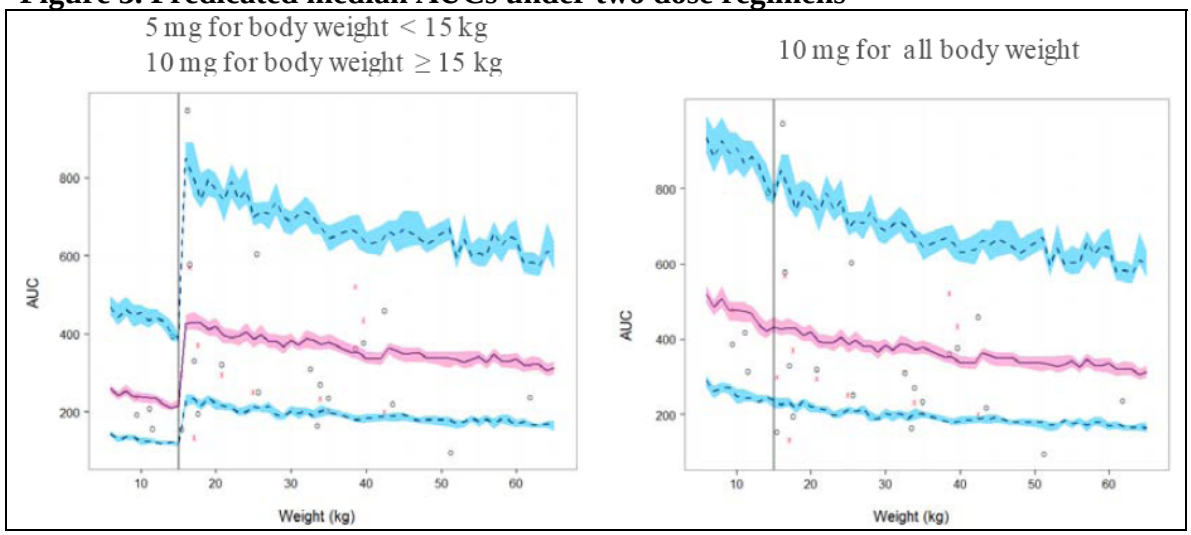
Age Group	Model Predicted Average AUC		
	5 mg	10 mg	20 mg
1-11 years	235 (n=11)	473 (n=62)	864 (n=20)
< 15 kg	249 (n=9)	514 (n=18)	--
≥ 15 kg	174 (n=2)	456 (n=44)	864 (n=20)
≤ 5 years	209 (n=7)	482(n=27)	436 (n=1)
> 5 years	280 (n=4)	466 (n=35)	886 (n=19)
12-16 years	--	233 (n=13)	596 (n=12)
≥ 17 years	--	345 (n=165)	1388 (n=28)

Subjects administered with the exact doses of 5, 10 and 20 mg were included.

Table 4 in population PK report

Reviewer's comments: The observed mean AUCt at steady-state after multiple doses of 20 mg AcipHex Tablet was 731±501 ng·h/ml (n=12; Study 119) in patients 12-17 years old with GERD and mean AUCt after single dose AcipHex Tablet 20 mg was 828±378 ng·h/ml in healthy adult subjects (n=88; Study 009).

Figure 3. Predicated median AUCs under two dose regimens



Sources: Sponsor's Rabeprazole: Population PK Analysis page 90

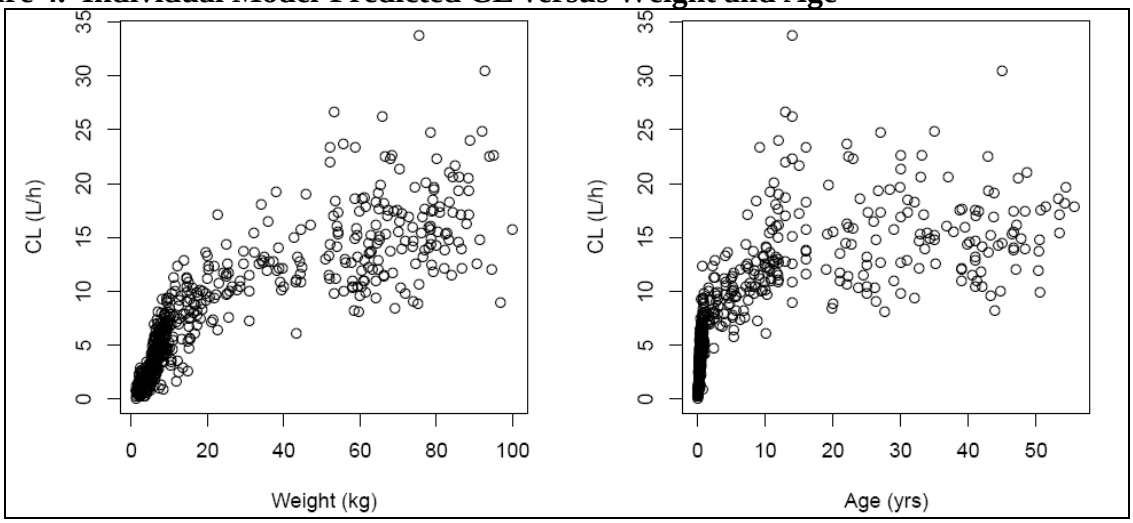
The solid line is the median of the simulated AUC and the dashed line indicates the 95% prediction interval. The outer blue shaded ribbons are the 95% confidence intervals on the prediction intervals, and the inner red shaded ribbon is the 95% confidence interval on the median simulated data. The symbols are the AUCs derived from NCA assuming linear kinetics. Circles indicate Day 1 and crosses indicate Day 5 for RABGRD1002. A vertical reference line at 15 kg is presented.

2.3 Intrinsic factors

2.3.1 Pediatric patients with GERD

Population PK analysis suggested that age- and body-weight dependent PK changes were profound in patients < 1 year old of age but less profound in patients 1-11 years old (Figure 4). For more details, please see the Pharmacometrics review in the Appendix.

Figure 4. Individual Model-Predicted CL versus Weight and Age



Sources: Sponsor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 98

Pediatric patients 1-11 year of age

Population PK analysis estimated that over the body weight range in pediatric subjects aged 1 to 11 years in the present database, the typical rabeprazole clearance and thioether metabolite clearance increases from 8.0 to 13.5 L/hr and from 10 to 28.6 L/hr, respectively.

Based on non-compartmental PK analysis in children 1 to 11 years of age receiving the Phase 1 formulation, rabeprazole systemic exposure increased in a dose-dependent manner as the dose the dose increased from 0.14, 0.5, and 1.0 mg/kg. According to the wide range of body weight, the actual dose ranges widely from 2 to 9 mg, 5 to 26 mg, and 12 to 43 mg, for target doses 0.14, 0.5, and 1.0 mg/kg, respectively.

The median time to reach Cmax following drug administration of rabeprazole was 2 hours (after single dosing and at steady state) and the mean half-life of rabeprazole was approximately 1 to 2 hours (Table 14). There was a broad overlap in Cmax and AUC values across the range of age and body weight.

At steady state AUCt of rabeprazole for the target dose groups of 0.5 mg/kg (actual dose range: 0.48 to 0.54 mg/kg) or 1.0 mg/kg (actual dose range: 0.93 to 1.07 mg/kg), i.e., 419 and 869 ng·h/mL (mean values). The mean parent versus thioether metabolite ratio for AUCi was 0.70 after single dose and 0.87 after multiple doses (AUC0–t) (Table 15).

Reviewer's comments: The phase 1 formulation was administered as a suspension in water with inert strawberry-flavored vehicle granules (Study 1004). The vehicle granules are different from the granule formulation used for rabeprazle. The ratio of mean Cmax and AUC between the phase 3 formulations administered sprinkled on applesauce and the phase 1 formulation administered as suspension was 94% and 99 %, respectively in healthy subjects.

Table 14. PK parameters of rabeprazole after single-dose and once daily dosing for 5 days

Dose Group	Parameter	Units	Day 1			Day 5		
			n	Mean	SD	n	Mean	SD
0.14 mg/kg	C_{max}	ng/mL	7	59.2	46.2	8	50.7	34.5
	t_{max}[a]	h	7	2.00	1.00 – 6.00	8	2.00	1.00 – 4.00
	AUC_{last}	h.ng/mL	3	169	98.4	4	142	57.6
	AUC_{all}	h.ng/mL	3	181	101	4	157	50.4
	AUC_{∞}	h.ng/mL	1	261[c]	-	2	224, 185[c]	-
	$t_{1/2}$	h	1	1.3[c]	-	2	1.2, 1.4[c]	-
	AR_{AUCall}[b]	-	-	-	-	3	1.23	0.69
0.5 mg/kg	C_{max}	ng/mL	10	184	102	10	200	149
	t_{max}[a]	h	10	2.00	1.00 – 5.98	10	1.53	1.00 – 2.08
	AUC_{last}	h.ng/mL	9	309	78.2	9	419	234
	AUC_{all}	h.ng/mL	9	337	94.1	9	429	232
	AUC_{∞}	h.ng/mL	5	346	77.9	6	490	263
	$t_{1/2}$	h	5	1.3	0.4	6	1.1	0.4
	AR_{AUCall}[b]	-	-	-	-	7	1.16	0.49
1 mg/kg	C_{max}	ng/mL	7	204	106	9	439	298
	t_{max}[a]	h	7	2.00	1.00 – 4.00	9	2.00	0.68 – 4.00
	AUC_{last}	h.ng/mL	7	694	519	9	869	579
	AUC_{all}	h.ng/mL	7	716	505	9	884	579
	AUC_{∞}	h.ng/mL	6	785	526	7	936	600
	$t_{1/2}$	h	6	1.9	1.0	7	1.2	0.6
	AR_{AUCall}[b]	-	-	-	-	7	1.39	0.83

[a] median (range)
[b] AR_{AUCall} calculated as the ratio of AUC_{all} values on Day 5 versus Day 1 for each subject
[c] individual values provided
Note: PK parameters could not be estimated for subjects with rabeprazole concentrations below the limit of quantification at multiple timepoints over the 12-hour interval. Details are provided in the appropriate PK attachments.

Table 15. PK parameters of thioether after single-dose and once daily dosing for 5 days

Dose Group	Parameter	Units	Day 1			Day 5		
			n	Mean	SD	n	Mean	SD
0.14 mg/kg	C_{max}	ng/mL	8	38.6	25.6	8	40.8	20.3
	t_{max}[a]	h	8	4.00	2.00 – 12.00	8	2.99	1.97 – 12.00
	AUC_{last}	h.ng/m	6	164	122	7	207	112
	AUC_{all}	h.ng/mL	6	171	119	7	212	110
	AUC_{∞}	h.ng/mL	5	227	143	-	-	-
	$t_{1/2}$	h	5	2.9	1.4	5	2.7	0.7
	AR_{AUCall}[b]	-	-	-	-	5	1.32	0.39
0.5 mg/kg	C_{max}	ng/mL	10	131	163	10	136	48.5
	t_{max}[a]	h	10	4.00	1.00 – 8.00	10	2.00	2.00 – 6.00
	AUC_{last}	h.ng/mL	10	467	349	10	626	298
	AUC_{all}	h.ng/mL	10	589	677	10	635	293
	AUC_{∞}	h.ng/mL	7	495	157	-	-	-
	$t_{1/2}$	h	7	2.6	0.7	10	2.4	0.8
	AR_{AUCall}[b]	-	-	-	-	9	1.54	0.81
1 mg/kg	C_{max}	ng/mL	7	207	113	9	228	109
	t_{max}[a]	h	7	4.00	2.03 – 6.00	9	3.85	1.70 – 6.00
	AUC_{last}	h.ng/mL	7	1114	733	9	1047	524
	AUC_{all}	h.ng/mL	7	1120	725	9	1053	518
	AUC_{∞}	h.ng/mL	5	1538	643	-	-	-
	$t_{1/2}$	h	5	2.4	0.7	8	2.2	0.7
	AR_{AUCall}[b]	-	-	-	-	7	1.35	0.97

[a] median (range)
[b] AR_{AUCall} calculated as the ratio of AUC_{all} values on Day 5 versus Day 1 for each subject
Note: PK parameters could not be estimated for subjects with thioether metabolite concentrations below the limit of quantification at multiple timepoints over the 12-hour interval. Details are provided in the appropriate PK attachments.

Patients 1 month old to less than 1 year old

Population PK analysis estimated that mean apparent clearance in patients 1-11 months old is 4.5 L/h with a range from 0.8 to 12 L/h.

Patients < 1 month old

Mean apparent clearance in neonates (<1 month) is predicted to be about 10% of that of aged 1-11 month and 25% of that of aged 1-11 years. In addition, the clearance in neonates is highly variable with % CV of 60% and has a wide range from 0.0543 to 3.44 L/h, which can be reasonably attributed to the fast growth, enzyme and organ maturation in new borns (Table 16). Please see the Pharmacometrics review for more details.

Table 16 Mean (S.D.) PK parameters of rabeprazole by Age

Parameter/Metric	Neonates* (n=69)	1-11 MO (n=261)	1-11 yrs (n=119)	Adolescents (n=26)	Adults (n=122)
CL (L/h)	1.23 ± 0.745	4.51 ± 1.96	10.8 ± 3.27	17.7 ± 5.95	15.3 ± 4.05
	1.05	4.46	10.4	16.6	15.1
	(0.0543-3.44)	(0.822-12.4)	(4.27-23.4)	(8.94-33.8)	(8.14-30.5)
V_c (L)	1.36 ± 0.518	3.73 ± 1.09	9.53 ± 2.35	13.7 ± 1.47	15 ± 1.53
	1.27	3.73	9.32	13.6	14.9
	(0.212-2.77)	(1.39-6.92)	(4.55-15.6)	(11.1-17.9)	(11.4-22.8)
Half-Life (h)	0.926 ± 0.36	0.647 ± 0.295	0.635 ± 0.155	0.595 ± 0.217	0.715 ± 0.17
	0.828	0.581	0.617	0.563	0.693
	(0.503-2.71)	(0.318-3.75)	(0.378-1.43)	(0.292-1.39)	(0.427-1.21)

Results are presented (by row) as mean ± standard deviation, median and (range). MO=months old. *Includes neonates and pre-term infants with a corrected age of less than 44 weeks recruited in study RABGRD1005.

2.3.2. What is the effect of rabeprazole on intragastric and intraesophageal pH in neonates or pre-term infants with a corrected age of less than 44 weeks?

The effects of rabeprazole on intragastric and intraesophageal pH were studied in neonates in 31 neonates with a presumptive diagnosis of GERD, who were inpatients and required a feeding-tube. In this study rabeprazole granules were administered through nasogastric or orogastric tube after suspending in water with inert vehicle materials (prepared from vehicle tablet). In this study a different formulation from the phase 3 formulation or the to-be-marketed formulation i.e. phase 1 formulation was used.

The intraesophageal and intragastric pH assessment was done using a 24-hour dual channel pH-meter at baseline (Day -1; prior to the first dose of rabeprazole), after a single dose (Day 1), and after 5 daily doses. The assessments on Day 1 and Day 5 started within 1 hour of dosing with rabeprazole. Each pH assessment continued for 22 to 24 hours.

The treatment with rabeprazole resulted in intragastric acid suppressant in doses from1 mg to 3 mg daily in neonatal and preterm infants. The effect was shown with dose of 1 mg and with a single day treatment (Tables 17 and 18; Figure 5). However, increasing the doses to 2 mg and 3 mg did not result in statistically significant increases in acid suppression and more prolonged periods of hypochlorhydria. There was no clear dose effect on each of days of treatment (Day 1 and Day 5).

Table 17. Mean intragastric pH over time

	Mean intragastric pH over time (min, max)		
	1 mg [1]	2 mg [2]	3 mg [2]
Day -1	4.8 (3.1,6.4)	4.6 (2.7, 6.3)	4.2 (2.7, 6.3)
Day 1	6.0 (3.6, 7.0)	6.4 (5.1, 7.4)	5.6 (3.4, 7.3)
Day 5	6.0 (3.6, 7.4)	7.0 (6.2, 7.6)	5.9 (3.4, 7.7)

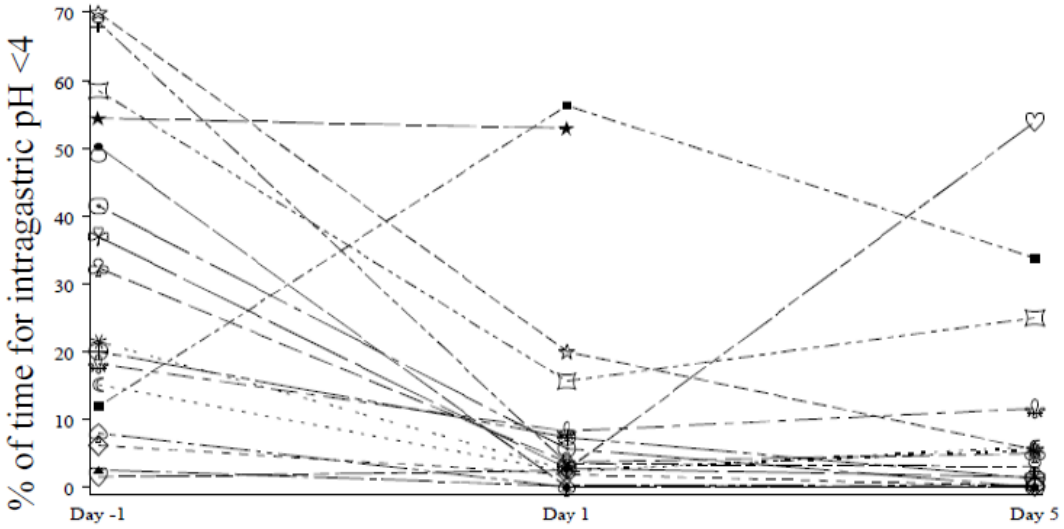
[1]n=16-18, [2]n=7-8,

Table 18. Mean % time for intragastric pH > 4 and for intraesophageal pH < 4

	Mean % time for intragastric pH > 4 (min, max)			Mean % time for intraesophageal pH < 4 (min, max)		
Dose	1 mg	2 mg	3 mg	1 mg	2 mg	3 mg
Day -1	67 (29, 98)	63 (33,98)	54 (28, 96)	4.2 (0, 17)	7.0 (0, 26)	18.2 (0, 62)
Day 1	88 (42, 100)	94 (80, 100)	78 (43, 99)	3.7 (0, 45)	1.0 (0, 2.7)	3.8 (0.01, 10)
Day 5	90 (45, 100)	99 (98, 100)	81 (30, 100)	2.5 (0, 17)	2.4 (0, 8.7)	2.1 (0.04, 20)

Reviewer's comments: It is noted that mean intragastric pH at the baseline was greater than 4 in all dose groups and some patients had intragastric pH>4 during the most of the time at baseline. The % of time for intragastric pH < 4 at baseline varied widely (Figure 5). While the possibility of misplacement of the pH probe can not be completely ruled out for prolonged high pH in some patients, patients with prolonged high intragastric pH should not be a candidate for the acid-reducing therapy. This further supports the difficulty of identifying neonate patients for acid-reducing therapy.

Figure 5. Individual % of time for intragastric pH < 4 in neonates after 1 mg dosing

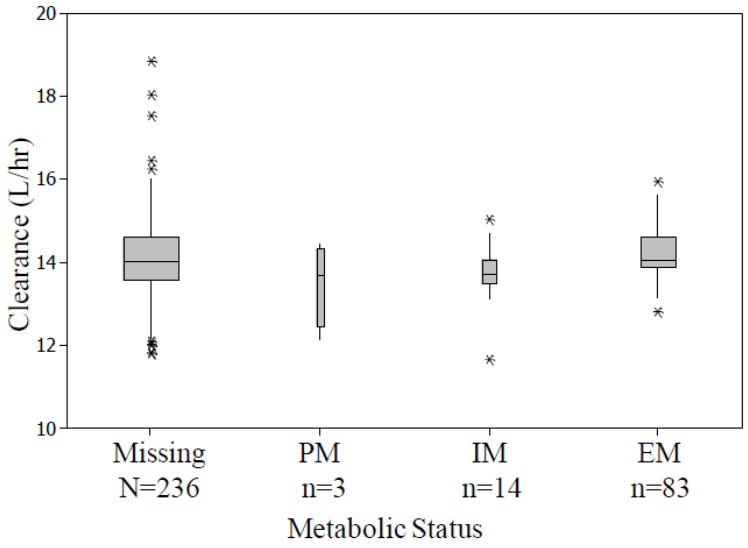


2.3.3. What pharmacogenetics information is there in the application and is it important or not?

Optional DNA collection was performed for 3 studies: E3810-A001-119 (adolescents), RABGRD1006 (adults), and RABGRD3003 (1-11 years old). CYP2C19 genotyping was performed for the *2 and *3 alleles in 100 subjects. Phenotype determination was made based on genotype and the 100 subjects were classified as follows: 3 poor metabolizers, 14 intermediate metabolizers, and 83 extensive metabolizers. Mean clearance values were similar among all three phenotype groups (Figure 6). The lack of significant impact of CYP2C19 metabolizer status on the clearance of rabeprazole is consistent with what is described in the current labeling and, as such, no labeling update is recommended at this time. Please see the pharmacogenomics review by Dr. Jeffrey Kraft in the Appendix.

Figure 6. Effect of CYP2C19 genotypes on the apparent clearance

Figure 1: Effect of Predicted CYP2C19 Phenotype on Clearance of Rabeprazole, for the Combined Database, Including Children, Adolescents and Adults



The solid line in the box is the median value, the lower and upper edges of the box are the 25th and 75th percentiles, respectively, and the lower and upper whiskers are the 2.5th and 97.5th percentiles. Outliers are designated as asterisk symbol.

2.5 General Biopharmaceutics

2.5.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed granule formulation differs from the formulation used in the phase 3 trial in terms of the manufacturing site. The bioequivalence between the to-be-marketed formulation as one 10 mg capsule and the phase 3 formulation as two 5 mg capsules was demonstrated (Table 18). In the study, rabeprazole granules were administered as sprinkled on applesauce under

fasting condition and swallowed with 240 ml of water. The pharmacokinetics of thioether metabolite was not significant different between the to-be-marketed formulation and the phase 3 formulation (Table 19).

Table 18. Mean PK parameters and statistical analysis of rabeprazole

PK Parameter	Treatment A TBM N=78	Treatment B Phase 3 formulation N=78	Treatment C TBM N=76	Point estimate (90% CI) of LS geometric means ratio	
				Treatment A vs B	Treatment C vs A
	fasting	fasting	fed		
C_{max} (ng/mL)	157±64.0 (40.7-331)	168±76.6 (43.3-447)	73.3±34.8 (9.44-201)	94.72 (86.014~104.27)[e]	45.03 (40.91~49.58)[e]
t_{max*} (h)	2.50 (1.00-6.50)	2.50 (1.50-5.00)	4.50 (0.50-6.50)		
AUC_{last} (ng.h/mL)	353±169 (99.3-845)	373±192 (101-1137)	246±124 (15.4-576)	95.80 (89.37~102.70)[e]	67.60 (63.05~72.46)[e]
AUC∞ (ng.h/mL)	378±173 (103-862)[a]	388±198 (107-1159)[b]	266±123 (68.3-621)[c]	96.41 (90.44~102.77)[f]	72.73 (68.22~77.53)[f]
$t_{1/2}$ (h)	1.33±0.645 (0.48-3.85)[a]	1.22±0.54 (0.47-2.65)[b]	1.69±0.80 (0.59-3.77)[d]		

Arithmetic mean ± S.D(range), *median
a: N=34, b: N=31

Table 19. Summary of PK parameters and statistical analysis of thioether metabolite.

PK Parameter	Treatment A N=78	Treatment B N=78	Treatment C N=76	Point estimate (90% CI) of LS geometric means ratio	
				Treatment A vs B	Treatment C vs A
t_{lag} (h)	1.00 (0.50-4.00)	1.00 (0.50-2.50)	1.50 (0.50-4.00)		
C_{max} (ng/mL)	60.7±26.5 (22.2-153)	58.5±23.0 (19.6-139)	69.9±31.9 (16.6-170)	102.70 (96.72~109.06)[d]	113.79 (107.16~120.83)[d]
t_{max} (h)	4.50 (3.00-7.50)	4.50 (2.50-8.00)	5.50 (3.00-10.00)		
AUC_{last} (ng h/mL)	374±213 (86.8-1137)	361±200 (91.0-1096)	463±244 (70.6-1179)	103.12 (97.32~109.26)[d]	125.34 (118.29~132.81)[d]
AUC∞ (ng h/mL)	415±239 (102-1321)[a]	414±225 (124-1308)[b]	511±269 (106-1332)[c]	102.97 (97.28~108.99)[e]	124.62 (117.74~131.90)[e]
$t_{1/2}$ (h)	3.01±0.64 (1.63-4.49)[a]	3.11±0.64 (2.12-4.94)	2.98±0.86 (1.72-6.05)		

Arithmetic mean ± S.D(range), *median
a: N=77, b: N=74, c: N=73, d: N=76. e: N=68
Treatment A: To-be-marketed formulation under fasting condition
Treatment B: Phase 3 formulation under fasting condition
Treatment C: To-be-marketed formulation under fed condition

Relative bioavailability between the approved tablet and the proposed capsule product

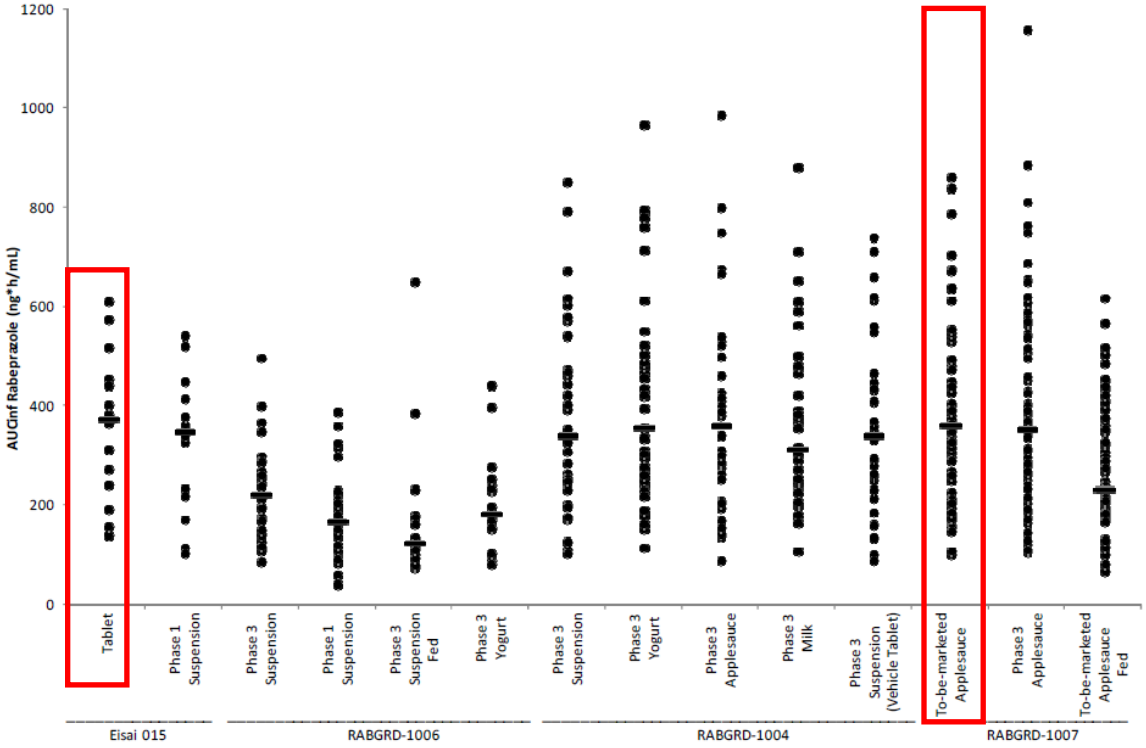
Relative bioavailability between the to-be-marketed formulation or the phase 3 formulation and the marketed rabeprazole 20 mg tablet was not studied in this development program. The

sponsor evaluated the relative BA between the 10 mg rabeprazole tablet and the phase 1 formulation used in dedicated PK studies in pediatric patients. During the development program, the granule formulation changed from the phase 1 formulation which showed higher systemic exposure compared to the 10 mg tablet to the phase 3 formulation which was used in the phase 3 trial in patients 1-11 years old of age.

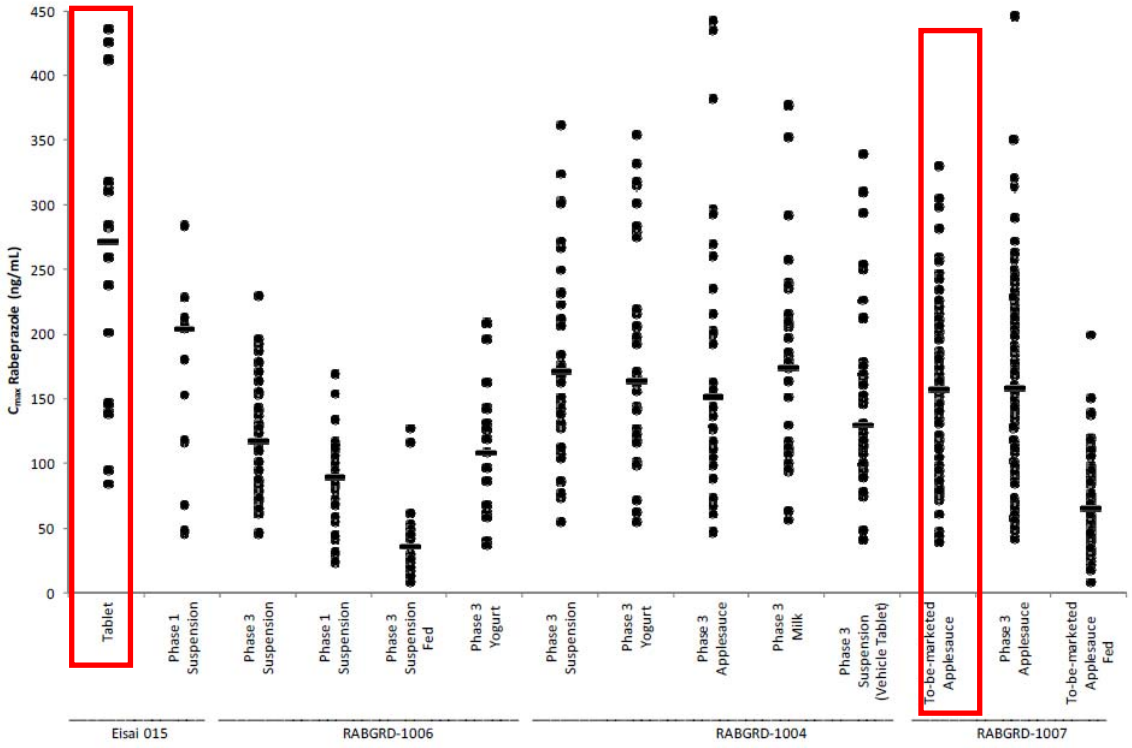
When the systemic exposure was compared across relative bioavailability studies conducted in healthy adult subjects, the mean and range of AUC and Cmax were generally consistent between studies using phase 3 formulation i.e. Studies 1004 and 1007 while a study comparing phase 1 and phase 3 formulations resulted in overall lower systemic exposure i.e. Study 1006 (Figures 7). The cross-study comparison suggested that AUC of rabeprazole would be comparable between the 10 mg tablet and the granules while the granules would have a lower mean Cmax than 10 mg tablet. This suggests no additional safety issue for the granules compared to the 10 mg tablet; however, a definitive conclusion can not be drawn based on this multiple cross study comparison.

Figure 7. Mean and individual AUC (A) and Cmax (B) of rabeprazole in healthy adults among different studies

(A)



(B)



2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals?

Concomitant high fat meal delayed the absorption of rabeprazole and decreased mean Cmax and AUC by 55% and 33%, respectively. while increased mean Cmax and AUC of the thioether metabolite by 13% and 25%, respectively. In the phase 3 study, the rabeprazole granules were sprinkled onto a small amount of soft food (pureed fruit or yogurt). If the amount of sprinkles was too large for a single spoonful of soft food, it was to be given with several spoonfuls of food. The investigator instructed the subject's parent(s)/guardian/legal representative that the granules could be sprinkled on yogurt or any type of pureed fruit as part of the subject's morning meal or just with a small amount of yogurt or pureed fruit alone.

***Reviewer's comments*:** Although rabeprazole was shown to be effective at AUC lower than observed in adults, the efficacy data was obtained with the limited number of patients. The variability of systemic exposure is expected to be higher in pediatric patients than in adults. Rabeprazole granules were instructed to be taken before or with meals in the phase 3 trial; however, the meal intake in relation to the dosing was not recorded.
Therefore, administration of rabeprazole granules before a meal in the morning is recommended to avoid significant decrease in the systemic exposure to rabeprazole. This is because the observed and the predicted AUC at the proposed dose is close to the lower end of the systemic

exposure observed in adults while the lowest effective concentration is not established in pediatric patients.

2.5.4. What are the effects of the type of soft food on which rabeprazole granules were sprinkled on PK of rabeprazole?

The rabeprazole granules are to be taken as sprinkled on soft food such as applesauce, fruit juice and infant formula. The administration of whole capsule containing granules was not studied in this development program.

Effects of different administration medium were studied in healthy adult subjects using two 5 mg capsules (Study 1004). Ten mg dose of rabeprazole consisted of two 5-mg strength capsules. Study drug was administered orally with 160 mL of noncarbonated water. After the capsules were opened, the granules were either added to a vehicle suspension (Treatments A and E), sprinkled on soft food (Treatments B and C) or mixed with milk (Treatment D).
Type of soft food i.e. applesauce, plain yogurt, or infant milk, which rabeprazole granules sprinkled on did not affect the pharmacokinetics of rabeprazole and its thioether metabolite. The PK parameters after administration as suspension were not significantly different from that after administration sprinkled on soft food (Table 20 and Figure 8).

Reviewer's comments: The suspension of rabeprazole granules were studied in neonates for whom the granules were added to a suspension of inert vehicles in water prior to administration via NG or OG tube. The formulation of inert vehicles in either granule or tablet form were different from the rabeprazole granules. However, the suspension is not pursued further for this application. Although this study was conducted with the phase 3 formulation, similar results are expected for the to-be-marketed formulation which was shown to be bioequivalent with the phase 3 formulation when administered sprinkled on applesauce.

Table 20. Mean (S.D.) PK parameters for rabeprazole after single dose administration sprinkled on different soft food

PK Parameter	Suspension	Soft food that rabeprazole granules sprinkled on			Geometric mean ratio (90% CI)		
	A N = 35	B: plain yogurt N = 35	C: Applesauce N = 34	D: Infant formula N = 35	D/B N= 33	B/C N= 33	D/C N= 33
C_{max} (ng/mL)	185±80.0	183±81.1	182±103	171±75.9	97.98 (87.6-103.0)	105.79 (97.5-114.8)	100.49 (92.6-109.0)
t_{max} (h)*	3.00 (1.50-5.00)	2.50 (1.5-5.0)	2.50 (1.5-4.5)	2.50 (1.5-4.5)			
$t_{1/2}$ (h)	1.33±0.78[a]	1.39±0.767	1.27±0.616	1.27/0.587[a]			
AUC_{last} (ng h/mL)	370±185	396±201	375±205	360±174	91.77 (86.9-96.9)	107.62 (102.0-113.6)	98.76 (93.6-104.3)
AUC∞ (ng h/mL)	378±192[a]	409±207	387±209	365±177[a]	92.7 (88.0-98.0)	106.57 (101.1-112.3)	98.79 (93.7-104.1)

Modified from Tables 4 and 5 in CSR 1004
Arithmetic mean ± S.D, *median(range), [a] N=34, [b] N=31
A: Granules were suspended in water with inert vehicle granules different from rabeprazole granules
B: Granules were sprinkled on plain yoghurt (1 tablespoon).
C : Granules were sprinkled on applesauce (1 tablespoon).
D : Granules were mixed with infant milk (5 mL).

Figure 8. Mean Rabeprazole Plasma Concentration-Time Profiles

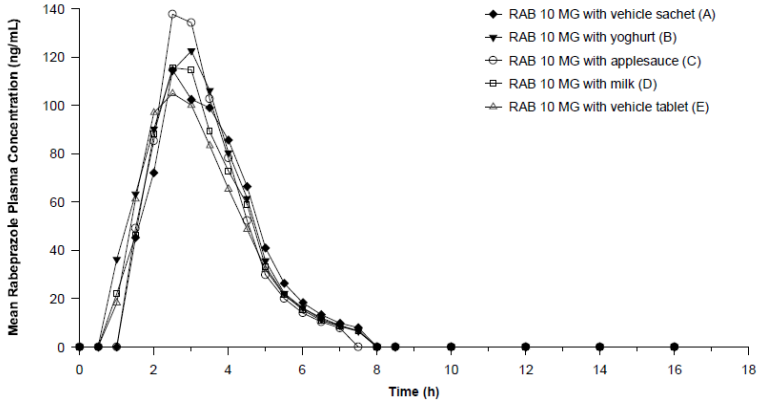


Figure 1 in CSR 1004

In vitro food compatibility study

In addition to the soft food tested in in vivo PK study, other foods including fruit juice, different brand infant formula, and commercial pureed infant food, were tested for compatibility with rabeprazole granules in vitro. In vitro food compatibility studies conducted to demonstrate the integrity of the enteric coating film when rabeprazole granules are exposed to different dosing vehicles showed that the acid resistance was not impacted for up to 30 minutes after mixing the granules with soft food (i.e., commercially available infant formulas, fruit juices, and soft food products generally given to children – all with a pH ranging from 3.5 to 7.2 (Table 21). For more details, please see CMC review.

Table 21. In vitro food compatibility

Test	Acceptance Criteria	Food	Mixing Time (minutes)	Test Time Point (months)	
				Initial	12
Food Compatibility	Recovery at 2 hours (using apparatus 2, 75 rpm): Not less than 90%	A	15	96-102 [a]	96 – 99 [b]
		B	15	95-101	97 – 100
		C	15	100-103	97 – 101
		D	15	96-102 [a]	98 – 99 [b]
		E	15	101-102	98 – 99
		F	30	99-101	98 – 99
		G	30	99-101	98 – 99
		H	30	99-102	99 – 101
		I	30	100-102 [a]	98 – 100 [b]

A: Infant formula (a: Sensitive® R.S. instant formula, b: Sensitive®)
B: Infant formula (Neosure®)
C: Infant formula (Alimentum® Hypoallergenic)
D: Infant formula (a: Enfamil® Prosorbee, b: Similac® Isomil Soy)
E: Vegetable based soft food (Gerber® Spring Vegetable with Brown Rice)
F: Fruit based soft food (Gerber® Banana Raspberry Oatmeal)
G: Yogurt based soft food (Gerber® Yogurt Blend Simply Banana)
H: Juice based meal (Gerber® Apple Juice from Concentrate)
I: Others (a: Compare to Pedialyte® Oral Electrolyte Maintenance Powder, b: Compare to Pedialyte® Oral Electrolyte Solution (fruit))

2.6 Analytical Section

2.6.1 How are rabeprazole and its major thioether metabolite identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The parent and thioether metabolite compounds were analyzed using an adequately validated liquid chromatography-mass spectrometry (LC-MS/MS) assay with acceptable accuracy and precision. Omeprazole was used as an internal standard. The lower limit of quantification (LLOQ) was 5 ng/mL for both analytes. The thioether metabolite does not have anti-acid secretion effects.

2.6.2. How the PK sampling from vein or capillary affect the PK results?

In patients 1-11 years, PK samples were collected from vein. On the other hand, in patients younger than 1 year old, sparse PK samplings from vein or capillary were allowed. To support the blood sampling from capillaries, plasma concentrations of rabeprazole and its metabolite thioether concentrations were compared after venous and capillary blood samplings from adult volunteers in Study 1004.

Mean rabeprazole concentration-time profiles following venous and capillary blood sampling, including dry blood spots method, are presented on a linear scale in Figures 9.

At almost all time points, rabeprazole plasma concentrations after venous and capillary sampling were similar. However, rabeprazole blood concentrations measured from dry blood spots were (Figure 10). Intersubject variability of plasma concentrations from capillary sampling and blood concentrations from dry blood spots was moderate to high (45% to 170% and 48% to 153%, respectively).

Figure 9. Mean Rabeprazole (A) and Thioether metabolite (B) Plasma Concentration-Time Profiles Following Venous and Capillary Sampling

(A)

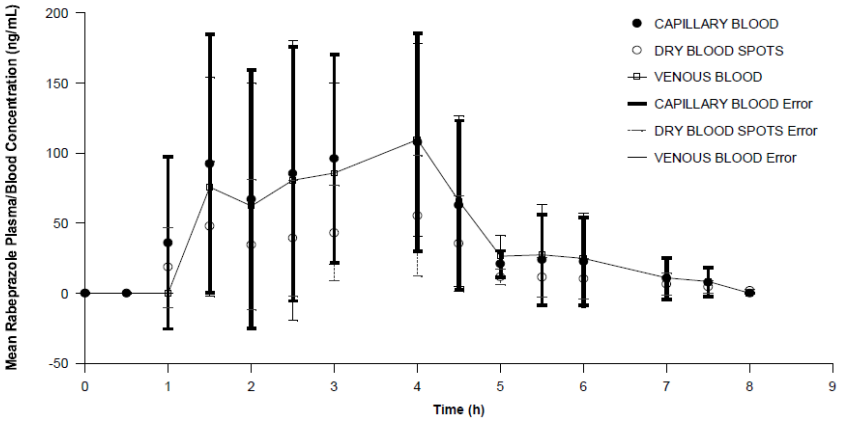


Figure 3 in CRS 1004

(B)

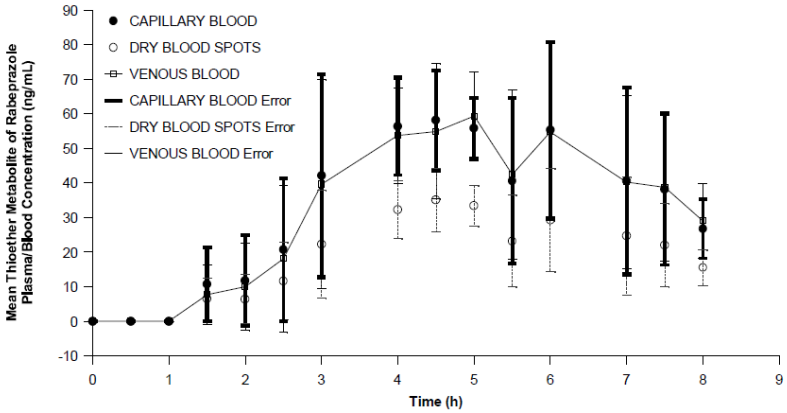
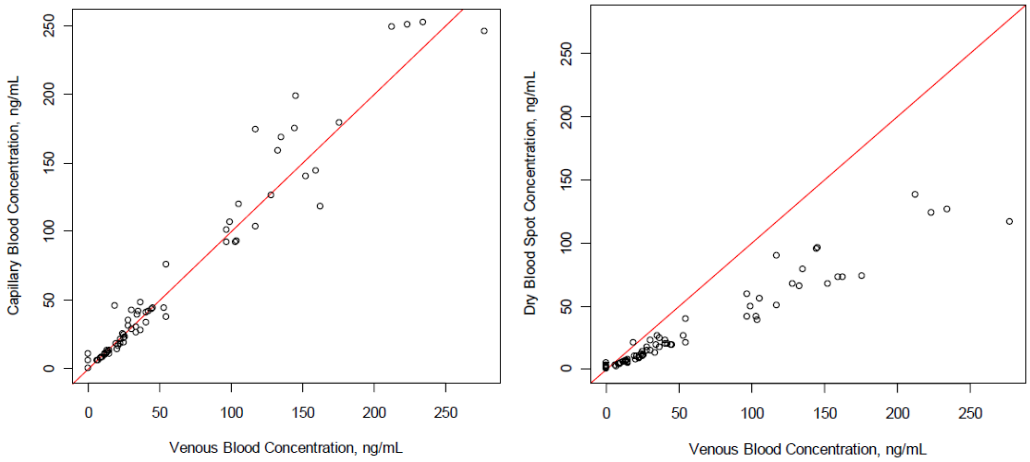


Figure 6 in CSR 1004

Figure 10. Comparison of rabeprazole concentration obtained by blood sampling methods



2.6.2 Which metabolites have been selected for analysis and why?

Rabeprazole thioether metabolite is a non-enzymatic product of rabeprazole and was selected for analysis based on its relative systemic exposure greater than 25% of rabeprazole. The thioether metabolite is inactive and presumed to be formed before and/or after oral absorption.

2.6.3 What is the range of the standard curve and the accuracy, and precision of the bioanalytical assay methods?

The range of the standard curve was from 5 ng/ml to 1000 ng/ml for rabeprazole and the thioether metabolite. The LLOQ and ULOQ are 5 ng/ml and 1000 ng/ml, respectively for both analytes.

Table 22. Precision and accuracy of bioanalytical assay method for rabeprazole and thioether metabolite

Analyte	Assay Range (ng/ml)	Intraday Precision (%CV)	Intraday Accuracy (%Diff)	Interday Precision (%CV)	Interday Accuracy (%Diff)
Rabeprazole	5 to 1000	3.9 to 8.8%	-3.1 to 5.7%	6.5 to 7.8%	-0.3 to 7.9%
Thioether metabolite	5 to 1000	1.6 to 10.3%	-9.8 to 3.3%	4.6 to 7.2%	-1.5 to 1.4%

3 Major Labeling Recommendations

Detailed labeling revisions on the Pharmacokinetic parameters will be conveyed to the sponsor during the labeling negotiations.

1) We recommend the apparent clearance in patients < 1 year old be included in section 8.4 (b) (4).

2) We recommend following revisions to the proposed update for Drug Interactions with clopidogrel

7.**8 Clopidogrel**

Concomitant administration of rabeprazole and clopidogrel in healthy subjects had no clinically meaningful effect on exposure to the active metabolite of clopidogrel (b) (4) [*see PHARMACOKINTETICS section* (12.3)]. No dose adjustment of clopidogrel is necessary when administered with an approved dose of ACIPHEX.

12.3 Pharmacokinetics

Drug-drug interactions

(b) (4)

4 Appendices

4.1 Pharmacometric Review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Is the proposed dose appropriate for pediatric patients aged 1 to 11 years for the healing of GERD?

Yes, the proposed dose in pediatric patients aged 1 to 11 years is appropriate. The sponsor proposes a dose of 5 or 10 mg QD in pediatric patients less than 15 kg and 10 mg for pediatric patients > 15 kg. The proposed dose is supported by the following : (1) efficacy profile is acceptable based on the clinical trial (2) safety profile is also acceptable given that the exposure in pediatric patients are unlikely to be higher than that observed in adults following approved dose of 20 mg QD. (3) No evident exposure-response (E-R) relationship for efficacy and safety identified based on the data from the Phase 3 trial in pediatrics.

- Efficacy Results:

The proposed dose and corresponding healing rate is listed in Table 1. Overall, the observed healing rate by 5 or 10 mg QD dose in pediatric patients aged 1 to 11 years is greater than 80% and appears to be comparable with that in adults. The healing rate in adults following 10 mg or 20 mg dose ranged from 73 to 96%

Table 1. Proposed dose regimen and corresponding healing rate for pediatric patients aged 1 to 11 years for the healing of GERD

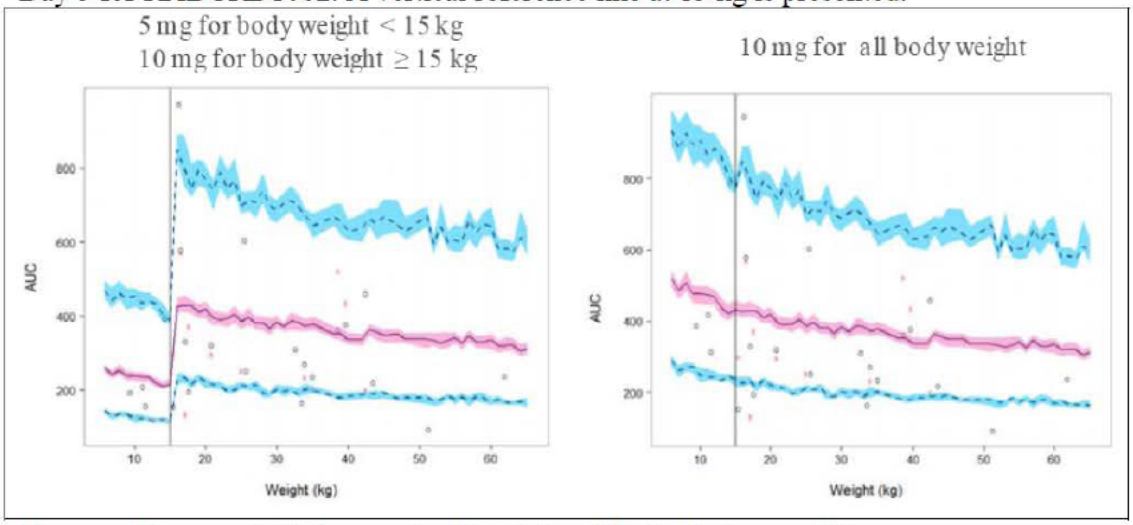
Weight	Dose (QD): Healing Response Rates (12 weeks)
<15 kg	**5 mg : 82% (14/17)** **10 mg: 94% (15/16)**
≥15 kg	**10 mg: 76% (29/38)**

- Exposure comparison between pediatric and adults

The simulation results based on population PK model for aged 1 to 11 years also support the proposed dose. The target AUCs are 400 and 800 ng*h/mL that are associated with the effective exposure levels in adults receiving 10 and 20 mg daily dose, respectively. As shown in Figure 1 (right panel), doses of 10/20 mg are likely achieve exposures close to the target AUC values of 400/800 ng*h/mL regardless of body weight. The 5 mg daily dose is proposed as initial dose for subjects with body weight < 15 kg, which may not be

sufficient to achieve the target exposure level of 400 ng*h/mL as shown in the figure below (Figure 1 (left panel)). However, the efficacy for subjects with body weight < 15 kg by 5 mg QD dose is acceptable and comparable to adults. The dose of 10 mg will be available as an option for subjects with body weight < 15 kg. More importantly, the predicted 95% upper bound of exposure at 10 mg (i.e., worst scenario) is comparable with the mean exposure level of 800 ng*h/mL in adults following the approved dose of 20 mg QD. Therefore, the proposed dose offers a reasonable safety margin from exposure perspective.

Figure 1. AUCs across different body weight with two dose regimen.
The solid line is the median of the simulated data using the final PK model, and the dashed line indicates the 95% prediction interval. The outer blue shaded ribbons are the 95% confidence intervals on the prediction intervals, and the inner red shaded ribbon is the 95% confidence interval on the median simulated data. The symbols are the AUCs derived from NCA assuming linear kinetics. Circles indicate Day 1 and crosses indicate Day 5 for RABGRD1002. A vertical reference line at 15 kg is presented.



Sources: Sponspor's Rabeprazole: Population PK Analysis page 90

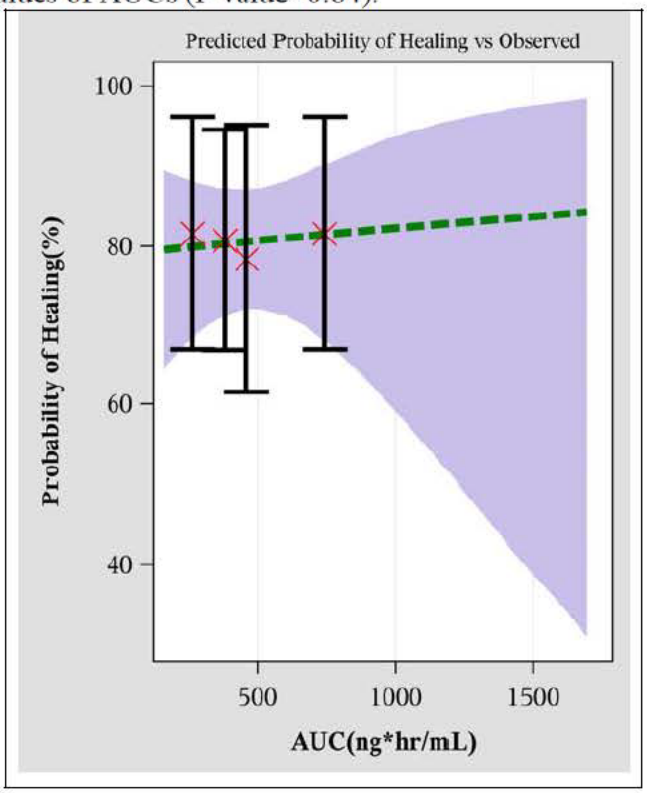
- Exposure-Response (E-R)

Furthermore, the E-R relationships for efficacy and safety support the proposed dose for pediatric patients aged 1 to 11 years. E-R analysis was conducted with exposure and response data from pediatric patients from the Phase 3 trial (RABGRD3003). As shown in **is** acceptable.

Figure 2, there is no evident E-R relationship for primary efficacy endpoint (i.e., healing) and relevant symptom scores (**Figure 8**). The overall lack of E-R for efficacy is likely due to the fact that the majority of subjects in pediatric Phase 3 Study (RABGRD3003) had AUCs near the target AUC that is associated with plateau of efficacy. In addition, there is also no evident E-R relationship for all adverse events of interest, including abdominal pain, headache and vomiting. Based on E-R analysis the proposed dose of 5 mg and 10 mg is acceptable.

Figure 2. No evident relationship between the probability of healing at week 12 and drug exposure (i.e., predicted AUCs at steady state)

Logistic regression model includes the probability of healing at week 12 as a function of steady state AUCs. The mean and 95% CI of the observed probability versus the median of each quartile of AUCs is represented by black bars while dashed green line and purple band represent the model predicted mean and 95% interval of the probability of healing across different values of AUCs (P value=0.84).



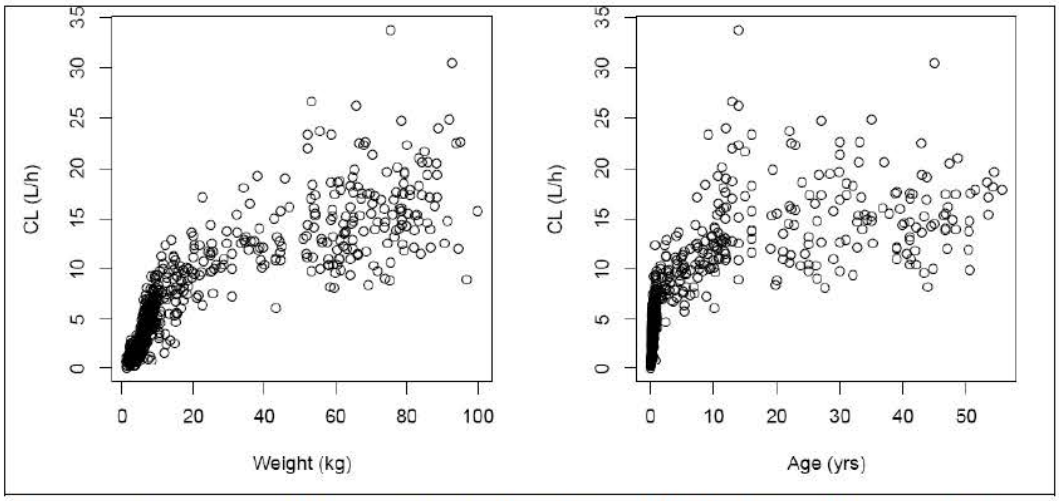
1.1.2 What are the PK characteristics of neonates and infants (1-11 month) and pediatric patient's age 1-11 years based on population PK model?

The PK parameters in pediatrics (0-11 years) are dependent on both age and body weight. The population PK model included the covariate effects of both weight and age on both CL and Vc in a nonlinear manner. Plot of the individual model estimates of CL is shown below in Figure 3. A summary of PK parameter estimates across different age groups is shown in Table 2.

In general, the clearance and volume of distribution increase with age and body weight. But the magnitude of effect of body weight on clearance is small with allometric exponent of 0.2. The age effect on CL in children age 1-11 years is negligible. Therefore, dosing regimen using 15 Kg as body weight cut-off for children 1-11 years may not optimal in terms of reducing the variability in exposure. Infact, as shown in Figure 1, 5 mg dose in pediatric patients < 15 kg will result in lower exposures than older pediatrics and adults. It is important to note however that 10 mg will be available as an option for these patients.

The age effect on CL in infants and neonates is much more pronounced than children 1-11 years mainly due to the enzyme and organ maturation in small children. Clearance in neonates (<1 month) is only around one forth of that of aged 1-11 month and one tenth of that of aged 1-11 years. In addition, the clearance in neonates is highly variable with CV% of 60% and has wide range from 0.054 to 3.44 L/h, which is reasonable given that neonates are in the fast stage of (relative) body size growth, enzyme and organ maturation. The effect of CYP2C19 phenotype on clearance could not be assessed due to the small number of poor metabolisers (2 PM subjects) and intermediate metabolisers (9 IM subjects) in population PK data set.

Figure 3. Individual Model-Predicted CL versus Weight (left) and Age (right)



Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 98

Table 2. Summary Statistics of PK Metrics Pooled by Age

Parameter/Metric	Neonates* (n=69)	1-11 MO (n=261)	1-11 yrs (n=119)	Adolescents (n=26)	Adults (n=122)
CL (L/h)	1.23 ± 0.745	4.51 ± 1.96	10.8 ± 3.27	17.7 ± 5.95	15.3 ± 4.05
	1.05	4.46	10.4	16.6	15.1
	(0.0543-3.44)	(0.822-12.4)	(4.27-23.4)	(8.94-33.8)	(8.14-30.5)
V_c (L)	1.36 ± 0.518	3.73 ± 1.09	9.53 ± 2.35	13.7 ± 1.47	15 ± 1.53
	1.27	3.73	9.32	13.6	14.9
	(0.212-2.77)	(1.39-6.92)	(4.55-15.6)	(11.1-17.9)	(11.4-22.8)
Half-Life (h)	0.926 ± 0.36	0.647 ± 0.295	0.635 ± 0.155	0.595 ± 0.217	0.715 ± 0.17
	0.828	0.581	0.617	0.563	0.693
	(0.503-2.71)	(0.318-3.75)	(0.378-1.43)	(0.292-1.39)	(0.427-1.21)

Results are presented (by row) as mean ± standard deviation, median and (range). MO=months old. *Includes neonates and pre-term infants with a corrected age of less than 44 weeks recruited in study RABGRD1005.

Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 100

1.2 Recommendations

Division of Pharmacometrics has reviewed the NDA and considers it to be approvable from a clinical pharmacology perspective. The proposed dose for the healing of GERD in pediatric patients aged from 1 to 11 years is acceptable provided mutual agreement is reached on labeling language. The clinical review division is not considering to grant the indication for the maintenance of healing in this age group; therefore the dose for maintenance indication is not relevant.

1.3 Label Statements

See Clinical Pharmacology Review for detailed labeling recommendations.

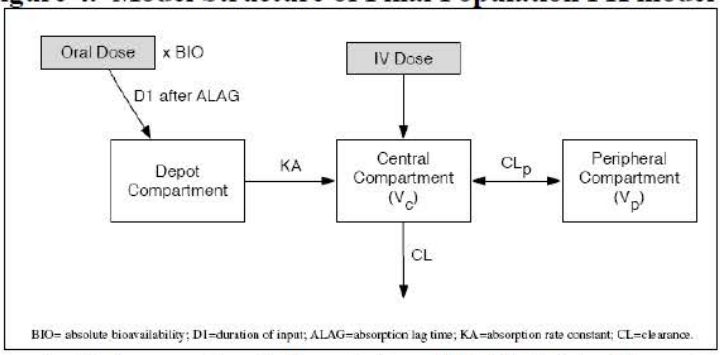
2 PERTINENT REGULATORY BACKGROUND

Rabeprazole is a gastric proton pump inhibitor (PPI) approved for adults and adolescents 12 years and above for the treatment of GERD and other diseases in the United States (US). The rabeprazole pediatric development program was initiated as a result of US FDA Phase 4 commitments issued in conjunction with the approvals of rabeprazole delayed-release tablets for the treatment of erosive and symptomatic GERD in adults. This NDA submission includes results of pediatric studies using the EC granule formulation on three age groups, including neonates and preterm infants (hereafter referred to as neonates), infants 1 to 11 months of age, and children 1 to 11 years of age.

3 RESULTS OF SPONSOR'S ANALYSIS

Sponsor developed two population PK models to identify and quantify covariate effects which explain the variability in the pediatric PK of rabeprazole. First model was developed for subjects above 1 years old, second model is developed by updating the first model with PK data from neonates and infants and by including age as covariate in CL to account for maturation process. The base structure model incorporated a sequential zero-order, first-order input following a lag time to describe absorption, together with a 2-compartment disposition model (**Figure 4**).

Figure 4. Model Structure of Final Population PK model



Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 53

Continuous covariates such as weight and age were normalized to the population median values and modeled using the general equation:

$$TVP_i = P_{pop} \cdot \left(\frac{cov_i}{cov_{med}}\right)^{\theta}$$

where TVP_i represents the model predicted pharmacokinetic parameter (e.g. CL or Vc) for the typical individual with covariate value cov_i, Ppop represents the population central tendency for the pharmacokinetic parameter TVP, cov_{med} represents the population median value of the covariate. Categorical covariates, such as race and sex, were modeled in the following manner:

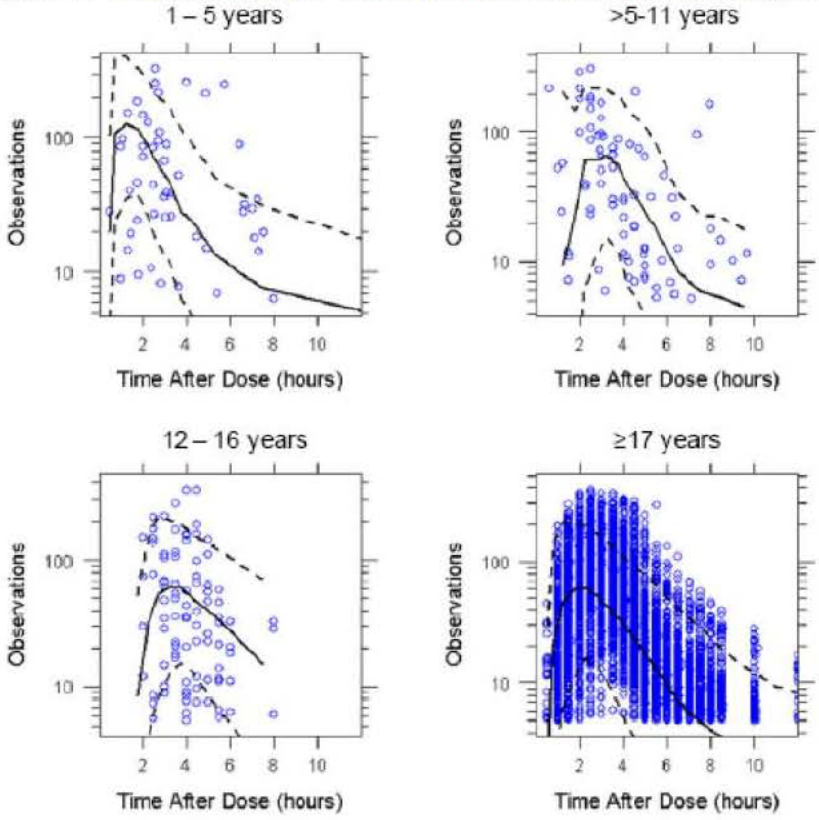
$$TVP_i = P_{pop} \cdot (1 + \theta)^{cov_i}$$

for example, for females ($cov_i = 1$) relative to males ($cov_i = 0$).

3.1 First Population PK model for pediatric patients (1-11 years), adolescent and adults

In general, **Figure 5** suggests that the first population PK model can describe the observed data well for subjects above 1 year old. The estimates of parameters are provided in Table 3.

Figure 5. Visual Predictive Check of Concentrations Following a 10 mg Dose



The open symbols are observed data, the solid and dashed lines are the median and 95% prediction intervals, respectively.

Sources: Sponsor's Rabeprazole: Population PK Analysis, Page 85

Table 3. Parameter Estimates for Population PK model for Subjects above 1 Years

Parameter		PK Parameter Population Mean (SE)	% CV Inter-individual Variability (SE)
CL (L/hr)	θ_1	10.7 (0.8)	30.17 (5.1)
Effect of weight	θ_{20}	0.218 FIX	
VC (L)	θ_2	11.5 (1.1)	39.62 (1.9)
Q (L/hr)	θ_3	4.22 (3.5)	NE
VP (L)	θ_4	98.7 (8.9)	NE
F1 (%)	θ_5	37.7 (2.4)	38.47 (6.7)
Effect of Study 1006	θ_{21}	-0.294 FIX	
Ktr (hr-1)			50.40 (0.9)
Formulation 1	θ_6	4.98 (4.7)	
Formulation 2	θ_7	5.1 (1.6)	
Formulation 3+6	θ_8	5.99 (2.9)	
Formulation 4	θ_9	5.69 (3.3)	
Formulation 5	θ_{10}	5.83 (2.3)	
Formulation 7	θ_{11}	5.62 (3.4)	
Formulation 8	θ_{12}	5.79 (2.6)	
Effect of food (ie, fed vs. fasting)	θ_{22}	-46.1% FIX	
Effect of weight	θ_{23}	-1.04 FIX	
Lag (hr)			NE
Formulation 1	θ_{13}	1.38 (3.2)	
Formulation 2	θ_{14}	0.127 (8.4)	
Formulation 3+6	θ_{15}	0.171 (19.3)	
Formulation 4	θ_{16}	0.143 (24.8)	
Formulation 5	θ_{17}	0.0879 (28.9)	
Formulation 7	θ_{18}	0.160 (27.9)	
Formulation 8	θ_{19}	0.199 (11.1)	
PROP residual error	θ_{24}	56.4 (0.5)	

SE – standard error; NE – not estimated; FIX indicates that the parameter value was fixed to an earlier estimated value. Formulation: 1 = tablet; 2 = Ph1 granule formulation Suspension (vehicle granules); 3 = Ph3 granule formulation Suspension (vehicle granules); 4 = Ph3 granule formulation - Sprinkle Yogurt; 5 = Ph3 granule formulation - Sprinkle Applesauce; 6 = Ph3 granule formulation - Suspension (vehicle tablet); 7 = Ph3 granule formulation - mixed with Milk; 8 = To-be-marketed granule formulation - Sprinkle Applesauce; 9 = IV.

Sources: Sponsor's Rabeprazole: Population PK Analysis, Page 83

***Reviewer Comments**: The model can adequately describe the observed PK data. This population PK model could be used for simulations to characterize the exposures for different age/body weight groups for different dosing scenarios. The main conclusions based on population PK model are discussed in Section 1.1.2.*

3.2 Second Population PK model for neonates, infants, pediatric patients (1-11 years), adolescent and adults

The data for population PK model are from both pediatrics and adults. The age of subjects ranged from 6 days (0.02 years) to 55.7 years, with total body weight (WT) ranging from 1.15 to 100 kg in a total of 324 male (54.3%) and 273 female (45.7%) subjects. The majority of subjects were of white race (79.1%), with 11.9% of black race.

The base model incorporated a sequential zero-order, first-order input following a lag time to describe absorption, together with a 2-compartment disposition model.

Parameter estimates for the base model are presented in Table 4 with the effects of weight and age on CL and Vc in equations:

$$CL = \theta_9 \cdot \left(\frac{Weight}{70}\right)^{\text{Effect of Weight}_{CL}} \cdot \left(\frac{Age^{\gamma CL}}{AGE_{50}^{\gamma CL} + Age^{\gamma CL}}\right)$$

$$V_c = \theta_6 \cdot \left(\frac{Weight}{70}\right)^{\text{Effect of Weight}_{Vc}} \cdot \left(\frac{Age^{\gamma Vc}}{AGE_{50}^{\gamma Vc} + Age^{\gamma Vc}}\right)$$

Table 4. Parameter Estimates for the Final Population PK Model

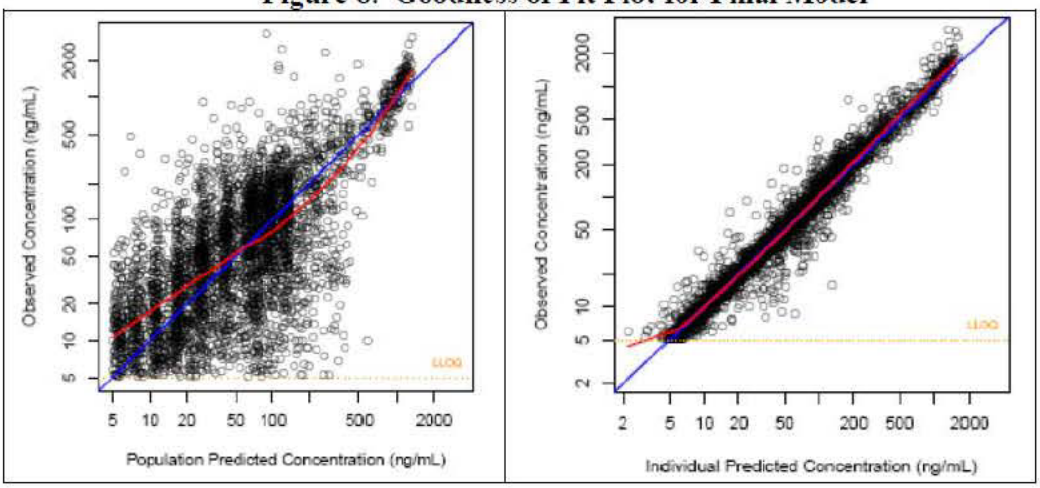
Parameter		Estimated Value (%SE)	BSV (%SE)	BOV (%SE)
Clearance (CL, L/h)	θ_{10}	15.5 (2.0)	41.2 (26.4)	
Effect of weight†	θ_{15}	0.353 (10.6)		
AGE_{50} (yrs)	θ_{12}	0.283 FIX		
γ_{AGE}†	θ_{11}	1.62 (20.1)		
Central volume of distribution (V_c, L)	θ_7	15.3 (2.8)	14.2 (35.4)	
Effect of weight†	θ_{16}	0.370 (14.5)		
AGE_{50} (yrs)	θ_{14}	0.310 (29.6)		
γ_{AGE}†	θ_{13}	1.01 (21.0)		
Intercompartmental clearance (CL_p, L/h)	θ_8	3.09 (5.1)	39.2 (30.1)	
Volume of distribution for the peripheral compartment (V_p, L)	θ_9	28.9 (16.5)	103 (26.5)	
Bioavailability for the Ph1 and Ph3 granules (BIO, %)	θ_1	42.2 (5.2)	45.9 (51.7)	109 (11.3)
Bioavailability for the tablet and to-be-marketed granules (BIO, %)	θ_{19}	56.0 (3.0)		
Absorption lag time for the tablet formulation (ALAG, h)	θ_2	2.00 (0.1)	48.8 (13.6)	37.9 (12.7)
Absorption lag time for the Ph1 and Ph3 granules ($ALAG_2$, h)	θ_3	0.467 (7.6)		
Absorption lag time for the to-be-marketed granules ($ALAG_3$, h)	θ_4	0.633 (2.4)		
Effect of nasogastric administration†	θ_{18}	1.31 (6.3)		
Duration of input into the depot compartment (D1, h^{-1})	θ_5	1.36 (4.4)	42.5 (17.7)	52.3 (11.9)
Effect of tablet formulation†	θ_{21}	0.576 (9.0)		
Absorption rate constant (KA, h^{-1})	θ_6	1.72 (6.9)	39.1 (21.3)	36.5 (15.4)
Effect of FED status (not fasted or unkrown status)†	θ_{17}	0.344 FIX		
Effect of tablet formulation†	θ_{20}	1.38 (9.6)		
Residual unexplained variability for oral formulations (%CV)	σ_1	32.4 (3.6)		
Residual unexplained variability the IV formulation (%CV)	σ_2	17.9 (8.7)		

SE=standard error; BSV=between subject variability; BOV=between occasion variability; AGE_{50}=age in years at which parameter has reached 50% of adult value; †No units.

Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 74

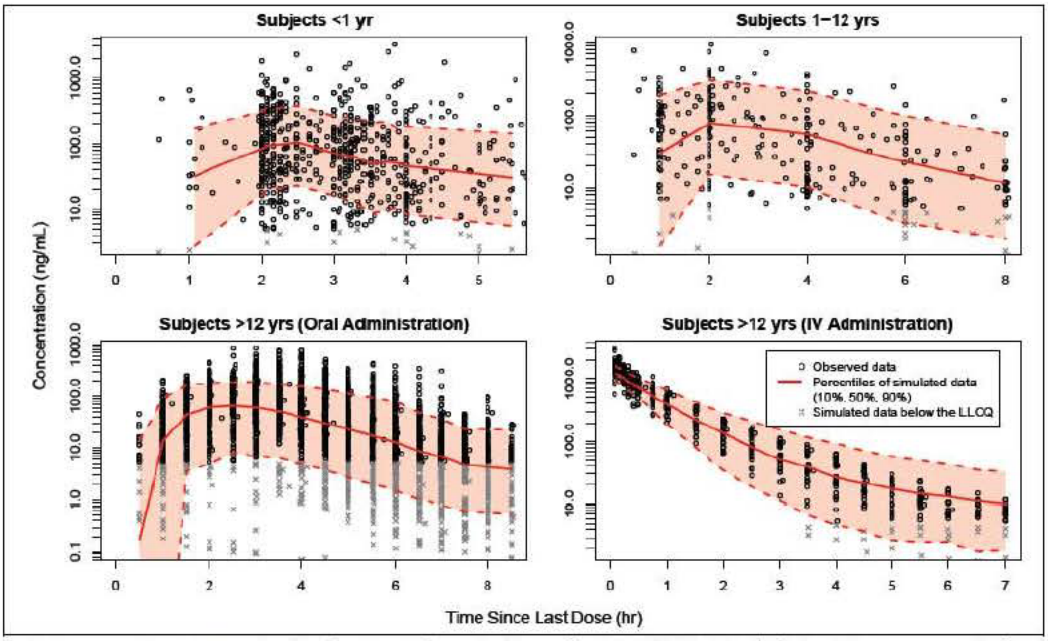
*Reviewer Comments: Table 4 shows that the unexplained between-subject variability (BSV) and between-occasion variability (BOV) for clearance and bioavailability of Phase 1 and Phase 3 is large. Standard diagnostics (graphically and numerically) and simulations suggest that the final population PK model could adequately describe the PK of rabeprazole for different age groups at a range of doses and in a range of formulations (***Figure 6*** *and* ***Figure 7****). The final model can be used for simulations to characterize the exposures for different age groups. The main conclusions based on population PK model were discussed in Section 1.1.2.*

Figure 6. Goodness of Fit Plot for Final Model



Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 77

Figure 7. Visual Predictive Check of the Final Model by Age



Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 86

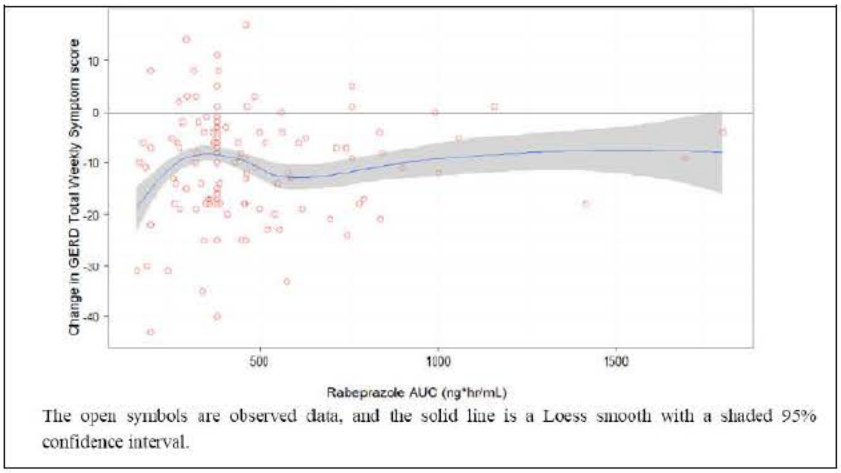
3.3 Results of Sponsor's E-R analysis for pediatric patients

3.3.1 E-R analysis for pediatric patients of 1-11 years

At the end of the healing stage, 108 subject's efficacy parameter observations were available.

Sponsor stated "Exploratory graphical evaluations of exposure–response relationship were conducted for data from the pediatric Phase 3 Study RABGRD3003 in children aged 1 to 11 years using individual estimated exposure (ie, AUC at steady-state). In general, there was no apparent relationship between measures of efficacy (change from baseline Hetzel Dent score, healing and change from baseline GERD weekly score) and rabeprazole exposure. The overall lack of relationship between rabeprazole exposure and responses is likely due to the fact that the majority of subjects in Study RABGRD3003 had rabeprazole AUC values near the target AUC (mean: 496 ng*h/mL, median: 424 ng*h/mL, range: 120 to 2122 ng.h/mL); an AUC value associated with response in adults. The apparent empirical relationships between individual safety parameters (ie, severity of abdominal pain, headache and vomiting) and individual exposure (AUC) of rabeprazole and rabeprazole thioether were also explored graphically. There were no visual relationships." (*Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 26)*

Figure 8. Change in GERD Total Weekly Symptom Score versus Rabeprazole Exposure



The open symbols are observed data, and the solid line is a Loess smooth with a shaded 95% confidence interval.

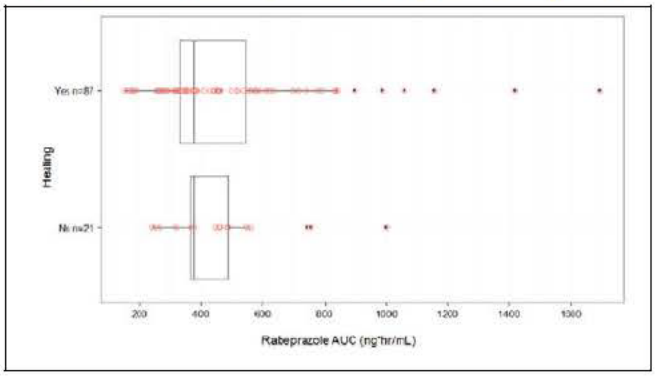
Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 121

Reviewer Comments:

1. *In general, reviewer agrees that no evident E-R relationship for efficacy and safety was identified based on data from the pediatric Phase 3 Study RABGRD3003 in children aged 1 to 11 years.*
2. *Boxplots by Sponsor for visualizing the E-R relationship for binary response variable (e.g. 'yes' or 'no' of healing, headache) may not be the best way to detect an underlying E-R relationship (***Figure 9***). Logistic regression with proper*

visualization of the observed data (e.g. quantiles plot) is recommended[1]. Please reviewer's independent analysis in Section 4.

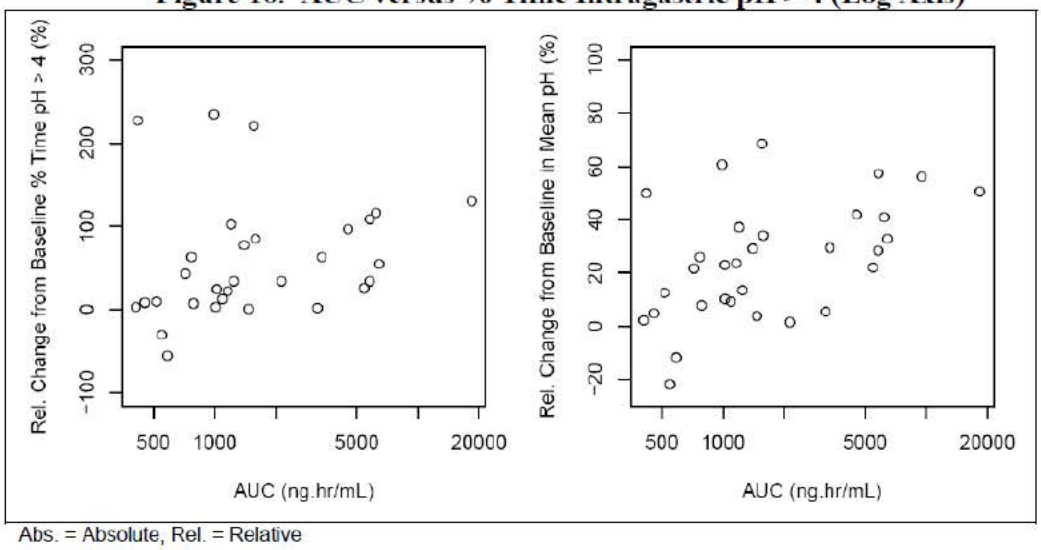
Figure 9. Healing versus Rabeprazole Exposure



3.3.2 E-R analysis for neonates and infants (1- 11 months)

Sponsor explored the PK/PD relationship by visualization of the relationship between rabeprazole exposure and PD. There were a total of 31 subjects included in the PK-PD graphical analysis that had matching viable PK and pH readings. 30 subjects were neonates from study RABGRD1005 and only 1 subject was infant from study RABGRD1003. **Figure 10** suggest there is a trend of exposure-response relationship between rabeprazole and intragastric acid suppression.

Figure 10. AUC versus % Time Intragastric pH > 4 (Log Axis)



Abs. = Absolute, Rel. = Relative

Sources: Sponspor's Rabeprazole: A Population PK Model in Neonates, Infants and Adults, Page 92

Reviewer Comments:

1. Comparison of PD and PK/PD relationship cannot be made among different age groups due to the lack of PD data in age groups of infants and children aged 1-11 years.

*2. Given the limited number of subjects and high variability of the PD data in neonates, E-R relationship was assessed only by visual inspection. It appears that PD response increase with exposure in neonates (**Figure 10**). But the results needs to be interpreted with caution due to the small sample size (n=31).*

4 REVIEWER'S ANALYSIS

4.1 Introduction

As mentioned in reviewer's comments in section 3.2.1, sponsor used boxplots to reveal the E-R relationship for binary response variable of efficacy and safety (e.g. 'yes' or 'no' of healing, headache) for pediatric patients aged 1-11 years, which may not be the best way to detect the underlying E-R relationship[1]. So reviewer conducted independent E-R analysis for efficacy (i.e., healing) by logistic regression model with quantiles plot.

4.2 Objectives

Analysis objectives are:

- Exposure-response analysis for primary efficacy endpoint, the healing probability at the end of healing stage.

4.3 Methods

The E-R analysis were conducted using the estimated exposure (ie, AUC at steady-state) of rabeprazole for children aged 1 to 11 years enrolled in the Phase 3 study RABGRD3003. At the end of the study period of Part 1 (ie, Week 12), 108 subject's efficacy parameter observations were available.

4.3.1 Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR
RABGRD3003	heal-auc.xpt	\\cdsesub1\EVSPROD\NDA204736\\0000\m5\datasets\pop-pk\analysis\legacy\datasets\heal-auc.xpt

4.3.2 Software

SAS 9.2 was used for analyses and graphical exploration.

4.3.3 Models

A univariate logistic regression was conducted to assess the E-R relationship for efficacy and safety endpoints.

APPEARS THIS WAY ON ORIGINAL

4.4 Results

As shown in Figure 2, no evident E-R relationship for probability of healing was identified based on data from the pediatric Phase 3 Study RABGRD3003 in children aged 1 to 11 years.

4.5 References

1. Shailly Mehrotra, Jeffry Florian Jr, Jogarao Gobburu, Don't Get Boxed In: Commentary on the Visual Inspection Practices to Assess Exposure-Response Relationships From Binary Clinical Variables, *J Clin Pharmacol* December 2012 vol. 52 no. 12 1912-1917

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Healing_AUC_logistic.sas	E-R for efficacy endpoints (binary variable only)	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Rabeprazole_NDA204736_JYU\ER_Analyses

4.2 Pharmacogenomics Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	204736
Submission Date	09/27/2012
Applicant Name	Eisai, Inc.
Generic Name	Rabeprazole
Proposed Indication	Healing and improvement of GERD symptoms and maintenance of healing of GERD
Primary Reviewer	Jeffrey Kraft, PhD
Secondary Reviewer	Mike Pacanowski, PharmD, MPH

1 Background

Aciphex (rabeprazole sodium) is a proton pump inhibitor that is approved for the healing of erosive or ulcerative gastroesophageal reflux disease (GERD) and for the maintenance of healing of erosive or ulcerative GERD (originally approved on August 19, 1999). The current submission is a pediatric supplement (NDA#204736). Many proton pump inhibitors, including rabeprazole, are metabolized by CYP2C19. As such, the sponsor included CYP2C19 genotyping assessments in the trials supporting the current submission. The purpose of this review is to evaluate the genotype information submitted by the sponsor regarding CYP2C19 genotype effects on the disposition of rabeprazole.

2 Submission Contents Related to Genomics

The sponsor collected optional genomic samples from 3 clinical trials: E3810-A001-119 (adolescents), RABGRD1006 (adults), and RABGRD3003 (1-11 years old). Subjects (n=100) were genotyped for the *2 and *3 alleles of CYP2C19 and metabolizer status was determined as follows: Poor Metabolizers (PMs) = *2/*2, *2/*3, and *3/*3; Intermediate Metabolizers (IMs) = *1/*2 and *1/*3; and Extensive Metabolizers (EMs) = *1/*1. A total of 3 PMs, 14 IMs, and 83 EMs were identified.

Table 2 – Studies Utilized for PopPK Analysis of CYP2C19

Protocol ID	***Population***	***Study Design***	***Doses***	***Genotyped Subjects n/N (%)***
E3810-A001-119	12-16 Years	Open Label, Single and Multiple Dose	10 and 20 mg	14/24 (58.3%)
RABGRD1006	Adults	Open-label, Randomized, Crossover	10 mg	27/36 (75.0%)

RABGRD3003	1-11 Years	Double-Blind, Parallel Group	5 and 10 mg	51/127 (40.2%)

*Comment: Reviewer did not replicate the sponsors analysis except to verify that predicted metabolizer status was correctly assigned based on CYP2C19 genotype. The *17 allele was not genotyped and as such, is it assumed that some IMs and EMs carry this high expression allele.*

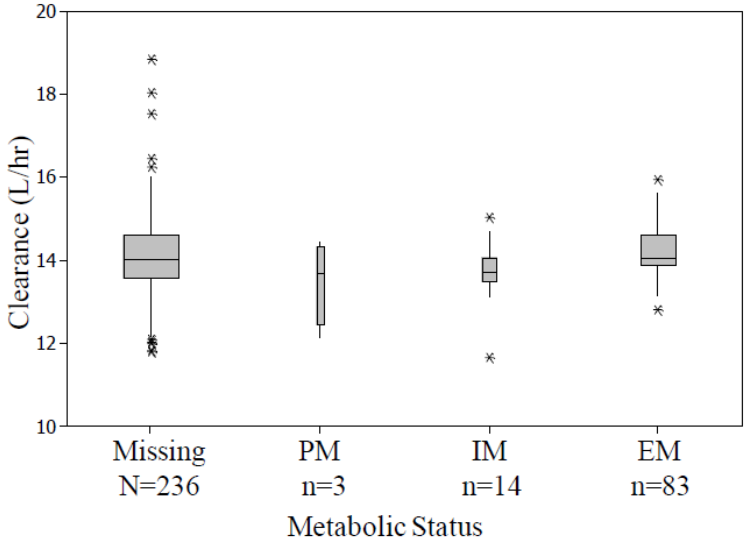
3 Key Questions and Summary of Findings

3.1 Does CYP2C19 phenotype have a significant effect on the PK of rabeprazole?

No. Clearance of rabeprazole was similar across CYP2C19 metabolic subgroups based on retrospective analysis of a subset of the adult and pediatric trials.

The sponsor provided analysis investigating the relationship of rabeprazole clearance by predicted metabolizer status as shown in the figure below. IMs tended to have slightly lower clearance as compared to EMs, although no major differences were observed between the phenotype groups. Too few PMs were available to draw firm conclusions although the clearance values in PMs were within the range of those reported for IMs and EMs.

Figure 1: Effect of Predicted CYP2C19 Phenotype on Clearance of Rabeprazole, for the Combined Database, Including Children, Adolescents and Adults



The solid line in the box is the median value, the lower and upper edges of the box are the 25th and 75th percentiles, respectively, and the lower and upper whiskers are the 2.5th and 97.5th percentiles. Outliers are designated as asterisk symbol.

4 Summary and Conclusions

CYP2C19 metabolizer status did not seem to have a significant effect on clearance values of rabeprazole as determined by the sponsor's analysis. Limited conclusions can be drawn from the

current analysis because of the small sample size. However, this finding is consistent with the relationship between CYP2C19 status and rabeprazole currently described in the labeling.

5 Recommendations

The current labeling for rabeprazole adequately describes the relationship between CYP2C19 status and the PK of rabeprazole. No additional action is necessary.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

4.3 Individual Study Summary

Study RABGRD1007 - Pivotal study to assess the bioequivalence of the to-be-marketed sprinkle capsule formulation and the phase 3 sprinkle capsule formulation of rabeprazole sodium in fasted condition and to assess the effect of food on the to-be-marketed formulation in healthy adult subjects.

Study Design: A randomized, open-label, single-dose, 3-way crossover in 78 healthy adult subjects. The study was conducted in SGS Life Science Services, Antwerp, Belgium.

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· **Treatment**

Three treatments were separated with a washout period of at least 7 days.

- Treatment A: 10 mg (10-mg capsule) rabeprazole to-be-marketed sprinkle capsule granule formulation in a fasted state. The granules were sprinkled on applesauce.
- Treatment B: 10 mg (2x5-mg capsules) rabeprazole Phase 3 sprinkle capsule granule formulation administered in a fasted state. The granules were sprinkled on applesauce.
- Treatment C: 10 mg (10-mg capsule) rabeprazole to-be-marketed sprinkle capsule granule formulation administered 30 minutes after consumption of a standardized high-fat high-caloric breakfast. The granules were sprinkled on applesauce.

· PK sampling:
Blood samples: predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 10, 12, 14 and 16 hours after dosing.

· Safety evaluation
Adverse events, clinical laboratory tests, ECG, vital sign and physical examination

· Bioanalysis
The plasma concentrations of rabeprazole and its thioether metabolite were analyzed using a validated LC-MS/MS method. Bioanalysis was conducted in (b) (4).

Demographics

All 76 of 78 subjects assigned to a treatment sequence completed the study. Forty eight (61.5%) of subjects were female and all except one were White. The subjects' mean age was 38.0 (18-55) years and mean BMI was 24.3 (18.4-29.9) kg/m^2.

Results:

The bioequivalence between the to-be-marketed formulation and the phase 3 formulation

The rabeprazole to-be-marketed sprinkle capsule granule formulation (10-mg capsule) is bioequivalent to the rabeprazole Phase 3 sprinkle capsule granule formulation (2x5-mg capsules) in fasted conditions, as shown by the ratio of their geometric mean values of C_{max} and AUCs, and corresponding 90% CIs being contained within the bioequivalence limits of 80% to 125%.

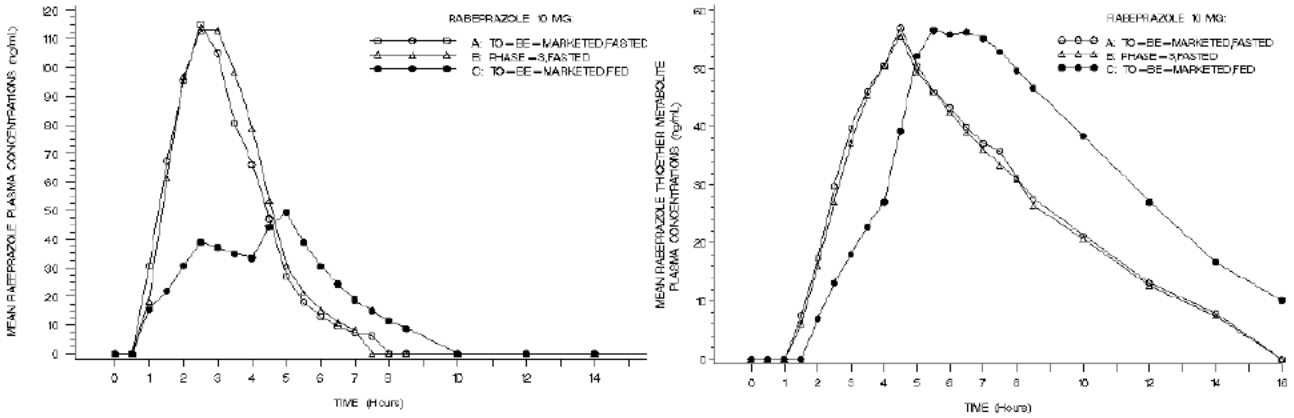

Figure 1. Mean plasma concentration-time profile of rabeprazole (left) rabeprazole thiolether metabolite (right), captured from sponsor's study report.

- **Food effect**

Food intake (standardized high-fat high-caloric FDA breakfast) prior to administration of the to-be-marketed formulation decreased C_{max} and AUCs of rabeprazole by 55% and 27% (AUC_{∞}) to 32% (AUC_{last}), respectively, and increased C_{max} and AUCs of its thioether metabolite by 14% and 25%, respectively, compared with the fasted state. A shift in median t_{max} was observed with food (shift with 2 hours for rabeprazole and 1 hour for its thioether metabolite).

Table 1. Summary of PK parameters and statistical analysis of rabeprazole.

PK Parameter	Treatment A N=78	Treatment B N=78	Treatment C N=76	Point estimate (90% CI) of LS geometric means ratio	
				Treatment A vs B	Treatment C vs A
t_{lag} (h)*	0.50 (0.00-1.52)	0.50 (0.00-2.00)	0.50 (0.00-4.50)		
C_{max} (ng/mL)	157±64.0 (40.7-331)	168±76.6 (43.3-447)	73.3±34.8 (9.44-201)	94.72 (86.014~104.27)[e]	45.03 (40.91~49.58)[e]
t_{max} (h)	2.50 (1.00-6.50)	2.50 (1.50-5.00)	4.50 (0.50-6.50)		
AUC_{last} (ng.h/mL)	353±169 (99.3-845)	373±192 (101-1137)	246±124 (15.4-576)	95.80 (89.37~102.70)[e]	67.60 (63.05~72.46)[e]
AUC∞ (ng.h/mL)	378±173 (103-862)[a]	388±198 (107-1159)[b]	266±123 (68.3-621)[c]	96.41 (90.44~102.77)[f]	72.73 (68.22~77.53)[f]
$t_{1/2}$ (h)	1.33±0.645 (0.48-3.85)[a]	1.22±0.54 (0.47-2.65)[b]	1.69±0.80 (0.59-3.77)[d]		

Arithmetic mean ± S.D(range), *median
a: N=34, b: N=31

Table 2. Summary of PK parameters and statistical analysis of rabeprazole thioether metabolite.

PK Parameter	Treatment A N=78	Treatment B N=78	Treatment C N=76	Point estimate (90% CI) of LS geometric means ratio	
				Treatment A vs B	Treatment C vs A
t_{lag} (h)	1.00 (0.50-4.00)	1.00 (0.50-2.50)	1.50 (0.50-4.00)		
C_{max} (ng/mL)	60.7±26.5 (22.2-153)	58.5±23.0 (19.6-139)	69.9±31.9 (16.6-170)	102.70 (96.72~109.06)[d]	113.79 (107.16~120.83)[d]
t_{max} (h)	4.50 (3.00-7.50)	4.50 (2.50-8.00)	5.50 (3.00-10.00)		
AUC_{last} (ng.h/mL)	374±213 (86.8-1137)	361±200 (91.0-1096)	463±244 (70.6-1179)	103.12 (97.32~109.26)[d]	125.34 (118.29~132.81)[d]
AUC∞ (ng.h/mL)	415±239 (102-1321)[a]	414±225 (124-1308)[b]	511±269 (106-1332)[c]	102.97 (97.28~108.99)[e]	124.62 (117.74~131.90)[e]
$t_{1/2}$ (h)	3.01±0.64 (1.63-4.49)[a]	3.11±0.64 (2.12-4.94)	2.98±0.86 (1.72-6.05)		

a: N=77, b: N=74, c: N=73, d: N=76. e: N=68

Safety

Rabeprazole was generally well tolerated when administered in healthy adult subjects as the to-be-marketed sprinkle capsule granule formulation in fasted and in fed conditions and as the rabeprazole Phase 3 sprinkle capsule granule formulation in fasted conditions.

Incidence of TEAEs tended to be higher in dosing at fasted state (A: 20.5% and B: 20.5%) than that at fed state (C: 14.3%). The most frequently observed TEAEs were headache and nausea. One subject discontinued treatment due to SAE (pyrexia at the period of to-be-marketed at fasted). There were no clinical relevant changes or abnormalities in clinical laboratory values, vital signs, and ECG.

Reviewer's comments:

- The study design was acceptable to evaluate bioequivalence of two rabeprazole formulations and the effect of food on the bioavailability of rabeprazole.
- The independent analysis by (b) (4) software conducted by this reviewer resulted in the consistent conclusion. The 90% CI for ratio of Cmax and AUC between the to-be-marketed formulation and the phase 3 formulation was 85.98-104.35 and 89.52-102.95, respectively.
- The sponsor analyzed data with and without correction for the measured drug content according to the certificates of analysis of the test and reference formulations of rabeprazole. All statistic results of corrected parameters were comparable with them of uncorrected values.
- The consistent effect of high fat meal on PK of rabeprazole was observed with the phase 3 formulation in Study RABGRD1006.
- Notably, the significant effect of a high fat meal on the bioavailability of rabeprazole was different from the insignificant food effects on marketed ACIPHEX tablets. A high fat meal did not significantly altered the C_{max} and AUC of rabeprazole.

Study RABGRD1004 - Relative bioavailability study of rabeprazole sodium sprinkle capsule formulation using different dosing vehicles following single-dose administration in healthy adult subjects.

Study Design: A randomized, open-label, single-center, single-dose, 5-way crossover in 35 healthy adult subjects. The study was conducted in SGS Life Science Services, Antwerp, Belgium.

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· **Treatment**

A washout period among treatments was at least 1 week. Subjects were assigned to 5 treatment sequences (ABCDE, EABCD, BCDEA, DEABC and CDEAB).

- A (reference): 10 mg (2 x 5 mg) rabeprazole sprinkle capsules. After the capsules were opened, the granules were added to a vehicle suspension from strawberry-flavored vehicle granules.
- B (test): 10 mg (2 x 5 mg) rabeprazole sprinkle capsules. After the capsules were opened, the granules were sprinkled on plain yoghurt (1 tablespoon).
- C (test): 10 mg (2 x 5 mg) rabeprazole sprinkle capsules. After the capsules were opened, the granules were sprinkled on applesauce (1 tablespoon).
- D (test): 10 mg (2 x 5 mg) rabeprazole sprinkle capsules. After the capsules were opened, the granules were mixed with infant milk (5 mL).
- E (test): 10 mg (2 x 5 mg) rabeprazole sprinkle capsules. After the capsules were opened, the granules were added to a vehicle suspension from a vehicle tablet.

·

· PK sampling

Blood samples: predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 10, 12, 14 and 16 hours after dosing.

·

· Capillary blood and dry blood spot sampling:

Capillary blood and dry blood spot sampling were taken in order to compare PK of rabeprazole using capillary or blood dried spots versus venous blood sampling as an additional exploratory objective.

·

· Bioanalysis

The plasma concentrations of rabeprazole and metabolite were analyzed using a validated LC-MS/MS method. Bioanalysis was conducted at (b) (4).

Results:

Effects of dosing vehicle

- The test treatments, sprinkled on a small amount of foods including infant milk, yoghurt and applesauce, showed similar PK profile of rabeprazole and its thioether metabolite with the reference treatment using a vehicle suspension from strawberry-flavored vehicle granules in the administration method which used in the phase 3 clinical trials.
- The bioavailability and pharmacokinetics of rabeprazole and its thioether metabolite following administration of the pediatric rabeprazole sprinkle capsule granule Phase 3 formulation in different dosing vehicles i.e. apple sauce, yogurt, and infant formula as used in pediatric clinical studies, were similar. .

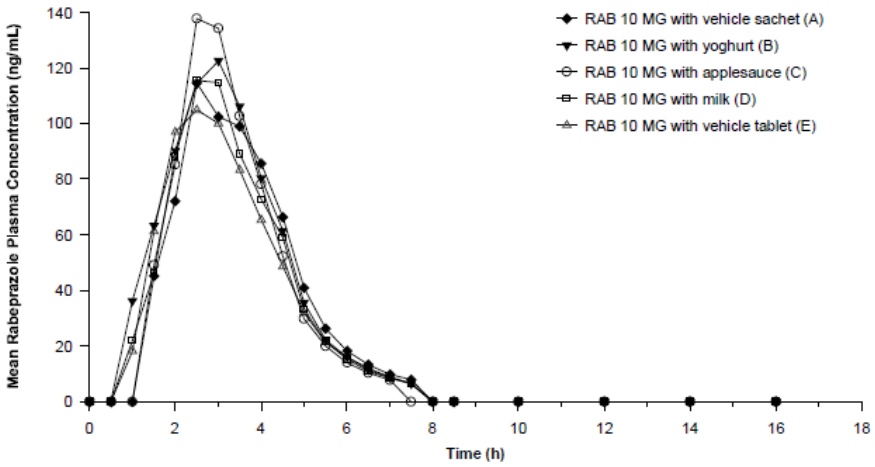

Figure 2. Mean plasma concentration time profile of rabeprazole (captured from sponsor's report).

Table 1. Summary of pharmacokinetic parameters and statistical analysis of rabeprazole (quoted from sponsor's study report).

PK Parameter	Treatment					Geometric mean ratio (90% CI)			
	A N = 35	B N = 35	C N = 34	D N = 35	E N = 34	B/A N= 33	C/A N= 33	D/A N= 33	E/A N= 33
C_{max} (ng/mL)	185±80.0	183±81.1	182±103	171±75.9	154±73.7	96.99 (89.41~ 105.21)	91.68 (84.52~ 99.45)	92.12 (84.93~ 99.93)	82.60 (76.14~ 89.60)
t_{max} (h)*	3.00 (1.50-5.00)	2.50 (1.50-5.00)	2.50 (1.48-4.50)	2.50 (1.50-4.50)	2.50 (1.00-5.00)				
$t_{1/2}$ (h)	1.33±0.780 [a]	1.39±0.767	1.27±0.616	1.27/0.587[a]	1.43±0.699				
AUC_{last} (ng.h/mL)	370±185	396±201	375±205	360±174	348±171	107.09 (101.45~ 113.04)	99.50 (94.26~ 105.03)	98.27 (93.10~ 103.73)	95.16 (90.15~ 100.45)
AUC∞ (ng.h/mL)	378±192[a]	409±207	387±209	365±177[a]	360±176	105.53[b] (100.13~ 111.23)	99.03[b] (93.96~ 104.38)	97.83[b] (92.82~ 103.11)	94.40[b] (89.56~ 99.49)

Arithmetic mean ± S.D, *median(range), [a] N=34, [b] N=31

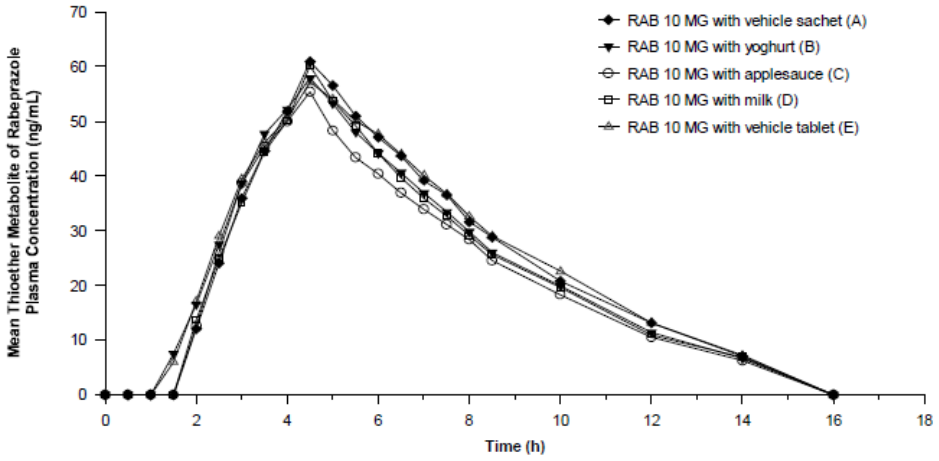

Figure 3 Mean plasma concentration time profile of rabeprazole thioether metabolite (captured from sponsor's report).

Table 2. Summary of pharmacokinetic parameters and statistical analysis of rabeprazole thioether metabolite (quoted from sponsor's study report).

PK Parameter	Treatment					Geometric mean ratio (90% CI)			
	A N = 35	B N = 35	C N = 34	D N = 35	E N = 34	B/A N= 33	C/A N= 33	D/A N= 33	E/A N= 33
C_{max} (ng/mL)	65.9±21.2	62.8±22.9	57.2±18.8	63.3±26.3	63.4±19.1	92.78 (85.11~ 101.15)	87.63 (80.38~ 95.53)	93.83 (86.07~ 102.29)	99.29 (91.07~ 108.25)
t_{max} (h)*	4.50 (3.00-6.00)	4.50 (2.50-5.00)	4.50 (2.98-8.00)	4.00 (2.50-5.50)	4.50 (2.50-6.50)				
$t_{1/2}$ (h)	2.77±0.631[a]	2.85±0.566	2.95±0.564[c]	2.81±0.57[a]	2.95±0.687				
AUC_{last} (ng.h/mL)	370±185	364±166	336±156	354±173	385±171	95.19 (87.12~ 104.00)	89.67 (82.08~ 97.97)	92.19 (84.38~ 100.72)	106.61 (97.58~ 116.48)
AUC∞ (ng.h/mL)	401±177[a]	396±178	383±164[b]	403±187[b]	424±194	96.31 (88.28~ 105.07)[d]	90.34 (82.82~ 98.55)[d]	94.56 (86.68~ 103.16)[d]	106.68 (97.79~ 116.38)[d]

Arithmetic mean ± S.D, *median(range)
a: N=34, b: N=32, c: N=33, d: N=28

Safety

Treatment-emergent adverse events (TEAEs) were observed in 21 subjects (60.0%) during the study. Four (11.4%), 8 (22.9%), 6 (17.6%), 5 (14.3%) and 8 (22.9%) subjects had at least one TEAE during treatments A, B, C, D and E, respectively. Three (8.6%) subjects reported a TEAE (diarrhea, nausea and headache, in 1 subject each) that was considered possibly related to the study drug by the investigator. There was no meaningful or abnormal finding of vital signs, physical examination and ECG evaluations.

Reviewer's comments:

· All study methods including design, sample size and analyzing method were acceptable.

Study RABGRD1006 - A phase 1, open-label, randomized, crossover study to assess the relative bioavailability of rabeprazole from the phase 3 pediatric bead formulation versus the phase 1 pediatric bead formulation (granules) in fasted state, and effect of food on the pharmacokinetics of rabeprazole from the phase 3 pediatric bead formulation in healthy subjects.

Study Design: A randomized (12 possible treatment sequences, 3 subjects per sequence), open-label, single-center, single-dose, 3-way crossover in 36 healthy adult subjects and conducted in at (b) (4) .

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· **Treatment**

A washout period among treatments was at least 1 week. All subjects received treatment A and B. Half of the subjects received treatment C and the other half received treatment D.

- A: 10mg Phase 3 pediatric bead formulation administered under fasting conditions (as a strawberry-flavored suspension).
- B: 10mg Phase 1 pediatric bead formulation administered under fasting conditions (as a strawberry-flavored suspension).
- C: 10mg Phase 3 pediatric bead formulation administered under fed (standardized high-fat breakfast) conditions (as a strawberry-flavored suspension).
- D: 10mg Phase 3 pediatric bead formulation administered under fed (sprinkled onto 1 ounce of plain yogurt) conditions.

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· PK samplings

Blood samples: predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 10, 12, 14 and 16 hours after dosing.

· Pharmacogenomics: The genotype of CYP2C19.

· Bioanalysis

The plasma concentrations of rabeprazole and metabolite were analyzed using a validated LC-MS/MS method. Bioanalysis was conducted at (b) (4).

Demographics

Twenty-six subjects were white, 9 subjects were black, and 1 subject was Native Hawaiian or Other Pacific Islander. The subjects' mean age was 31.8 (19-53) years and mean BMI was 25.3 (20.7-30.0) kg/m^2.

Results

1) Formulation comparison

Mean C_{max} and AUC of rabeprazole tended to be higher in the Phase 3 formulation than the Phase 1 formulation. On the other hand, mean plasma concentrations of rabeprazole thioether metabolite appeared to be lower in the Phase 3 formulation than the Phase 1 formulation. The C_{max} and AUC were lower after the Phase 3 formulation than the Phase 1 formulation. The t_{max} and $t_{1/2}$ for rabeprazole and its thioether metabolite were similar between two formulations.

For the thioether metabolite, the Phase 3 pediatric bead formulation exhibited lower exposure in comparison with the Phase 1 beads; C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}last}$ Cmax, AUC0-inf, and AUC0-last values were lower by approximately 32%, 26%, and 28%, respectively.

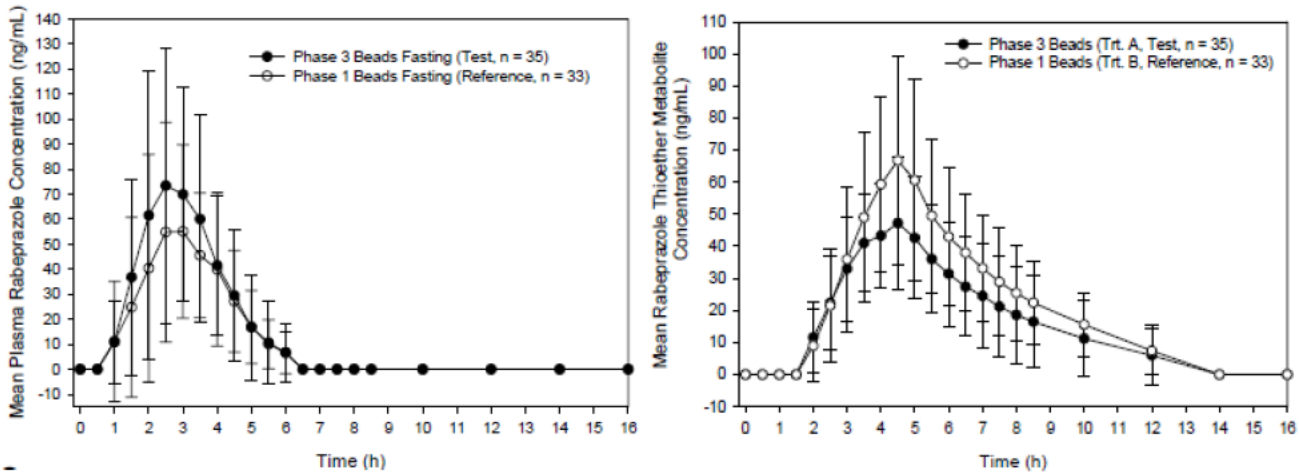

Figure 1. Mean plasma concentration-time profile of rabeprazole and thioether metabolite after oral administration of Phase 3 or Phase 1 rabeprazole formulations (captured from sponsor's report).

Table 1. Summary of PK parameters and statistical analysis of rabeprazole and thioether metabolite after oral administration of Phase 3 or Phase 1 rabeprazole formulations (quoted from sponsor's study report).

PK parameter	Summary of PK parameters				Point estimate (90% CI) of LS geometric means ratio (Phase 1/ Phase 3)	
	Rabeprazole		Rabeprazole thioether metabolite		Rabeprazole	Rabeprazole thioether metabolite
	Phase 3 N=35	Phase 1 N=33	Phase 3 N=35	Phase 1 N=33		
t_{max} (hour)*	2.5(1.5 to 5.0)	3.0(1.0 to 5.0)	4(3.0 to 7.5)	4.0(2.5 to 5.0)		
C_{max} (ng/mL)	122(±46.9)	87.5(±36.6)	52.4(±20)	75.3(±31)	141.00 (118.46, 167.83)	68.47 (62.02, 75.58)
$t_{1/2}$ (hour)	0.93(±0.53)	0.995 (±0.46)[a]	2.62(±0.70)	2.57(±0.60)		
$AUC_{0\text{-last}}$ (ng·h/mL)	214(±87.7)	170(±83.8)	251(±133)	329(±144)	128.75 (114.40, 144.89)	72.35 (65.55, 79.85)
$AUC_{0\text{-inf}}$ (ng·h/mL)	222(±90.9)	183 (±84.1)[a]	279(±146)	357(±150)	123.01 (111.98, 135.12)	74.37 (67.50, 81.96)

Arithmetic mean ± S.D, *median(range), [a] N=32

2) Food effect evaluation

When compared with fasted state, median t_{max} was delayed from 2.5 to 4.5 under fed condition. Mean rabeprazole C_{max}, $AUC_{0\text{-inf}}$, and $AUC_{0\text{-last}}$ values for the Phase 3 pediatric bead formulation were decreased by approximately 70%, 31%, and 40%, respectively, by consumption of a high-fat breakfast compared to the fasted state.

Treatment at the fed state with yogurt showed similar mean plasma concentrations-time profile of rabeprazole and thioether metabolite when compared with the reference administration phase.

Table 2. Summary of PK parameters and statistical analysis of rabeprazole and thioether metabolite after administration of Phase 3 rabeprazole formualtion at fasting state, fed state of high-fat food and fed state of yogurt (quoted from sponsor's study report).

PK parameter	Summary of PK parameters						Point estimate (90% CI) of LS geometric means ratio (Fed/ Fasting)			
	Rabeprazole			Rabeprazole thioether metabolite			Rabeprazole		Rabeprazole thioether metabolite	
	Fasting N=35	High fat N=18	Yogurt N=17	Fasting N=35	High fat N=18	Yogurt N=17	High fat / Fasting	Yogurt / Fasting	High fat / Fasting	Yogurt / Fasting
t_{max} (hour)*	2.5(1.5 to 5.0)	4.5 (1.5 to 6.0)	3.0 (1.5 to 4.5)	4.0(3.0 to 7.5)	6.5(4.5 to 12)	4.5(3.5 to 5.0)				
C_{max} (ng/mL)	122 (±46.9)	44.5 (±31.9)	112 (±49.8)	52.4 (±20)	56.2 (±22.7)	50.5 (±20.4)	30.34 (24.32, 37.87)	94.05 (74.92, 118.05)	103.73 (91.51, 117.57)	97.47 (85.71, 110.85)
$t_{1/2}$ (hour)	0.930 (±0.53)	1.20 (±0.47)[a]	0.870 (±0.33)	2.62 (±0.70)	2.7 (±0.87)[b]	2.53 (±0.86)				
$AUC_{0\text{-last}}$ (ng·h/mL)	214 (±87.7)	156 (±139)	202 (±94.4)	251 (±133)	351 (±188)	238 (±94.5)	59.94 (51.60, 69.61)	97.91 (83.97, 114.17)	132.21 (116.68, 149.80)	99.27 (87.32, 112.84)
$AUC_{0\text{-inf}}$ (ng·h/mL)	222 (±90.9)	180 (±147)[a]	210 (±97.2)	279 (±146)	383 (±209)[b]	263 (±105)	69.11 (61.06, 78.22)	98.76 (87.52, 111.43)	134.82 (118.85, 152.95)	98.04 (86.42, 111.22)

Arithmetic mean ± S.D, *median(range), [a] N=16, [b] N=17

The effect of CYP2C19 genotype on the disposition of rabeprazole in this study was not characterized as one subject who was determined as a poor metabolizer(*2/*2) showed relatively higher exposure of rabeprazole.

Safety

Twelve of 36 subjects (33.3%) reported TEAEs during the study. There was no difference in the overall incidence of TEAEs between two formulations or fasting conditions. There was no clinical relevant or abnormal finding of clinical laboratory, vital signs, physical examination and ECG evaluations.

Reviewer's comments:

- Administration of rabeprazole bead formulation (granule formulation) as a suspension is not proposed for pediatric patients 1-11 years old and not relevant to this NDA submission.

(b) (4)

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/s/

INSOOK KIM
03/06/2013

JINGYU YU
03/06/2013

JEFFREY B KRAFT
03/06/2013

MICHAEL A PACANOWSKI
03/06/2013

NITIN MEHROTRA
03/06/2013

SUE CHIH H LEE
03/06/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	204-736	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Dates:	September 27, 2012 January 10, 2013 February 15, 2013		
Division:	DGIEP	**Team Leader:** Angelica Dorantes, Ph.D. **Acting Supervisor:** Richard Lostritto, Ph.D.	
Applicant:	EISAI INC		
Trade Name:	AcipHex®	**Date Assigned:**	October 2, 2012
Generic Name:	Rabeprazole Sodium	**GRMP Date:** **Clinical Date:** **PDUFA Date:**	March 1, 2013 March 13, 2013 March 27, 2013
		Date of Review:	February 28, 2013
Indication:	Healing and maintenance of healing of gastroesophageal reflux disease (GERD) and the improvement of GERD symptoms in children 1 to 11 years of age	**Type of Submission:** Original NDA Review	
Formulation/strengths	Delayed-Release Sprinkle Capsule/ 2.5 mg, 5 mg, and 10 mg		
Route of Administration	Oral		

Biopharmaceutics Review Topics:

- Dissolution test method and acceptance criteria,
- Dissolution Stability
- In-vitro food compatibility studies with dosing vehicles
- Biowaiver Request

SUBMISSION:

NDA 20-973 for 20 mg AcipHex® (rabeprazole sodium) delayed release tablet was approved on August 19, 1999. NDA 204-736 seeks approval for 2.5 mg, 5 mg, and 10 mg AcipHex® (rabeprazole sodium) delayed-release sprinkle capsule in the treatment of children 1 to 11 years of age with gastroesophageal reflux disease (GERD). The intent of this submission is to fulfill the erosive and symptomatic GERD Phase 4 commitments as well as satisfy the Pediatric Written Request Amendment 7 requirements for neonates, children aged 1 to 11 months, and children aged 1 to 11 years. The clinical program included four studies to evaluate this formulation in the pediatric population.

Additionally, the applicant performed four bioavailability/bioequivalence studies:

- **Study (E3810-A001-015)** assessed the relative bioavailability of the Phase 1 granule formulation (2x5 mg) versus the tablet (1x10 mg);
- **Study (RABGRD1006)** assessed 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;
- **Study (RABGRD1007)** assessed 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; and

- **Study (RABGRD1004)** assessed the relative bioavailability of the Phase 3 granule formulation (2x5 mg) with different dosing vehicles.

The proposed drug product is a hypromellose hard capsule. The capsule contains enteric coated granules prepared by layering drug substance on core mannitol spheres that are subsequently coated with an under-coating film and an outer enteric coating film. The different strengths are achieved by varying the amount of the same granules filled into the capsule. Two administration methods are proposed for pediatric populations: by sprinkling on food (for children); and by a nasogastric (NG) tube (for neonates). The rabeprazole granule sprinkle capsules are not intended to be swallowed intact.

BIOPHARMACEUTIC INFORMATION:

This review is focused on the evaluation and acceptability of 1) the in vitro dissolution method and acceptance criteria, 2) the product stability with dosing vehicles, and 3) the waiver request for the lower dosage strengths (2.5 mg and 5 mg).

CONCLUSIONS:

1. **Dissolution Method**

   The following proposed dissolution method conditions for the Acid Stage (Table 1) and Buffer Stage (Table 2), and acceptance criteria (Table 3) for each stage are acceptable.

Table 1: Dissolution Conditions for *Acid Stage*

Item	Condition
Apparatus	Paddle apparatus (Apparatus 2) in accordance with USP <711>
Dissolution medium	0.1 mol/L hydrochloric acid
Volume of dissolution medium	750 mL
Number of capsules per vessel	Enteric coated granules in 1 capsule [a]
Temperature of dissolution medium	37 ± 0.5 °C
Paddle rotation speed	75 rpm
Sampling Time	2 hours

[a] Only enteric coated granules in one capsule are sprinkled into each vessel and tested.

Table 2: Dissolution Conditions for *Buffer Stage*

Item	Condition
Apparatus	Paddle apparatus (Apparatus 2) in accordance with USP <711>
Dissolution medium	0.05 mol/L phosphate buffer, pH 6.8
Volume of dissolution medium	1000 mL
Number of tablets per vessel	Enteric coated granules in one capsule (successively taken granules used *Acid Stage*)
Temperature of dissolution medium	37 ± 0.5 °C
Paddle rotation speed	60 rpm

Table 3: Final (Regulatory) Dissolution Acceptance Criteria of Rabeprazole Sodium Sprinkle Capsules, 2.5, 5, 10 mg

Test Item	Acceptance Criteria	Analytical Procedure
Dissolution	(b) (4)	Apparatus 2, USP<711> 3.2.P.5.2.4

[a] Cumulative time is the sum of acid stage (2.0 hours) and the duration of the buffer stage.
[b] Conforms to Acceptance Table 3 in Delayed-Release Dosage Forms, USP <711>.
[c] Conforms to Acceptance Table 4 in Delayed-Release Dosage Forms, USP <711>.

2. **Dissolution Stability**
   The dissolution data support the proposed 24 months and is acceptable from the dissolution test perspective.
3. **In-vitro food compatibility studies with dosing vehicle**
   At mixing time of 15 minutes, the acid resistance was not impacted after the enteric coated granules filled in the capsule are sprinkled on a small amount of soft food or mixed with a small amount of infant formula.
4. **Biowaiver request**
   A waiver of bioequivalence studies to qualify the lower strengths (5mg and 2.5 mg) is granted, provided bioequivalence Study (RABGRD1007) is found acceptable by OCP.
5. **Alcohol Dose Dumping Effect**
   The Applicant did not evaluate the alcohol dose dumping potential of their proposed modified release dosage form. On February 15, 2013, the Applicant made the post-approval commitment to assess the effect of alcohol on the drug release of AcipHex Delayed Release Sprinkle Capsules and submit the study results no later than August 8, 2013.

RECOMMENDATION
From the perspective of Biopharmaceutics, NDA 204-736 for AcipHex® (rabeprazole sodium) delayed-release sprinkle capsules (2.5 mg, 5 mg, and 10 mg) is recommended for APPROVAL.

APPROVAL SIGNATURES: {see electronic signature page}

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: *NDA 204-736 DARRTS, RLostritto*

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/s/

HOUDA MAHAYNI
03/04/2013

ANGELICA DORANTES
03/04/2013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	204,736	**Brand Name**	AcipHex
OCP Division (I, II, III, IV, V)	III	**Generic Name**	Rabeprazole
Medical Division	DGIEP	**Drug Class**	Proton Pump Inhibitor
OCP Reviewer	Insook Kim, Ph.D.	**Indication(s)**	Healing, Maintenance of Healing and Improvement of Symptoms in Pediatric Patients Aged 1 to 11 Years with GERD
OCP Team Leader	Sue-Chih Lee, Ph.D.	**Dosage Form**	Delayed-release sprinkle capsules
Pharmacometrics Reviewer	Jingyu Yu, Ph.D.	**Dosing Regimen**	For children weighing less than 15 kg, 5 mg once daily (b) (4) (with an option to increase to 10 mg after clinical reassessment). For children ≥ 15 kg, 10 mg once daily (b) (4)
Date of Submission	9/27/2012	**Route of Administration**	Oral
Estimated Due Date of OCP Review	2/20/2013	**Sponsor**	Eisai
Medical Division Due Date	3/1/2013	**Priority Classification**	P
PDUFA Due Date	3/27/2013		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**1**		**45-0302: LC/MS/MS assay validation in human plasma**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	**x**	**1**		**L110011:**
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**x**			
multiple dose:	**x**			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	**x**			
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:	**x**			
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**4**		**RABGRD1002:** PK/PD in children 1-11 years old **RABGRD1003:** PK/PD in infants 1-11 months old **RABGRD1005:** population PK/PD in neonates or pre-term infants **E3810-A001-119:** population PK/PD in children 12 to 16 years old with GERD
Phase 3 clinical trial:	**x**	**3**		**RABGRD3003:** Dose-response without placebo: clinical efficacy and PD (pH below 4) in children 1-11 years old, Sparse PK sampling **RABGRD3004:** Dose-response, Clinical efficacy, in infants 1-11 months old, Sparse PK sampling for pooled pop PK **E3810-A001-202:** Safety of 10- and 20 mg tablets in children 12-16 years old
Population Analyses -	**x**	**2**		Pop PK 1-11 year old Pop PK 1-11 month old
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -	**x**			
solution as reference:				
alternate formulation as reference:		**3**		**E3810-A001-015:** Relative BA study between enteric-coated microgranules and 10 mg tablet **RABGRD1006:** Relative BA between Phase 3 pediatric granule formulation and Phase 1 pediatric granules
Bioequivalence studies -	**x**			
traditional design; single / multi dose:		**1**		**RABGRD1007:** BE between to-be-marketed sprinkle capsule granule vs. Phase 3 sprinkle capsule granule Food effects
replicate design; single / multi dose:				
Food-drug interaction studies	**x**			**RABGRD1004:** Administration vehicle e.g. milk, yogurt
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Genotype/phenotype studies		**1**		**Study 3003: CYP2C19 genotyping was performed. PK samples are available from some subjects.**
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**15 (2 population PK analysis reports)**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x		Only the genotype results were reported
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-	x			

	response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	x			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			Pending further review
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Fileable____

The OSI inspection of the clinical and the bioanalytical sties for the Study RABGRD1007 was requested on 11/7/12.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

It is unclear if a bioanalytical assay report was submitted for Study RABGRD1005. Please provide the bioanalytical assay report for Study RABGFD1005. Please guide the reviewer to the location of the information.

We note that the genotype information was collected in Study 3003 but it is unclear if the method of genotyping was submitted. If so, please guide the review to the location of the information.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

The sponsor conducted studies in response to the WR as below.

Written Request Study Number	Written Request Study Description	Protocol / Clinical Study Report
1	Pharmacokinetic (PK), Pharmacodynamic (PD) and Safety Study in Neonates and Pre-Term Infants with a Corrected Age Less Than 44 Weeks	RABGRD1005
2	Efficacy and Safety Evaluation of Pediatric Patients 1 to 11 Months of Age	RABGRD3004
3	Pharmacokinetic, Exposure/Response, and Safety Study in Pediatric Patients 1 To 11 Years of Age	RABGRD1002 RABGRD3003 Part 1 RABGRD3003 Part 2

Written Request Study 4 (adolescents) which included studies E3810-A001-119 and E3810-A001-202 was submitted as NDA 020973 S-022 on 27 December 2007 and approved on 30 June 2008.

Three dose strengths (2.5, 5, and 10 mg) of sprinkle capsules were developed. These three strengths of sprinkle capsules contain (b) (4) rabeprazole granules; doses are adjusted by (b) (4)

There were two different formulations used in clinical trials. Phase 1 granule formulation was used in PK/PD studies and Phase 3 granule formulation was used in phase 3 efficacy and safety studies. In a relative bioavailability study, the mean plasma exposure of rabeprazole was higher with the Phase 3 granule formulation compared with the Phase 1 granule formulation (approximately 23% and 42% higher for AUCinf and Cmax, respectively) but this difference was not considered to be clinically relevant and the Phase 3 granule formulation was used in the pediatric Phase 3 study RABGRD3003. The content of the sprinkle capsule (i.e., the granules) was to be sprinkled on small amounts of soft food before administration.

Reviewer's comments: A difference in the systemic exposure to rabeprazole between phase 1 and phase 3 granules should be taken into consideration for the pooled population PK analysis.

The changes made to the Phase 3 granule formulation were the material grade of magnesium oxide, capsule size, capsule logo, and bottle size. In addition, the manufacturing site was changed; the to-be-marketed granule formulation was manufactured in (b) (4), while the Phase 3 granule formulation was manufactured in (b) (4). Bioequivalence of the to-be-marketed granule formulation and the Phase 3 granule formulation was demonstrated between 1x10 mg of the to-be-marketed formulation and 2x 5 mg of the phase 3 formulation in study RABGRD1007. In phase 3 trials, 2.5 mg and 5 mg capsules were used. The proposed dose is 5 mg and 10 mg in patients weighing < 15 kg and > 15 kg, respectively.

Reviewer's comments: The inspection of the clinical and bioanalytical sites is needed for the pivotal BE study (Study RABGRD1007).

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

The proposed granule formulation may be favored over the tablet by patients older than 12 years who have a difficulty in swallowing tablets. There is no direct comparison of bioavailability between the tablet and the to-be-marketed or the formulation used in the phase 3 trials.

Insook Kim, Ph.D.	11/8/2012
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	11/8/2012
Team Leader/Supervisor	Date

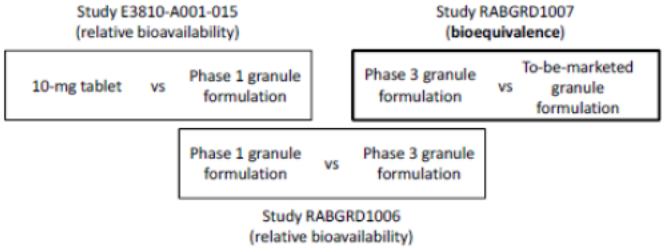

Figure 2 Schematic Overview of Oral Bioavailability and Bioequivalence Studies – Bridging Strategy

Study Number	Type of Study	Dose Strength (mg)	Formulation (Lot No.)	Drug Product Manufacturing Site
Studies in Healthy Adult Subjects				
E3810-A001-015	Phase 1, relative bioavailability	10 5	Tablet formulation (P4Y005ZZA) Phase 1 granule formulation (P51026ZZA)	(b) (4)
RABGRD 1006	Phase 1, relative bioavailability	5 2.5	Phase 1 granule formulation (P5Z005AAD) Phase 3 granule formulation (P82007AZA [a])	
RABGRD 1007	Phase 1, bioequivalence	5 10	Phase 3 granule formulation (P8X004CAA) To-be-marketed granule formulation (P02017CZA)	
RABGRD 1004	Phase 1, relative bioavailability	5	Phase 3 granule formulation (P8X004CAA [b])	
Studies in Pediatric Neonatal Subjets				
RABGRD 1005	Phase 1, PK, PD and safety	1	Phase 1 granule formulation (P85003AA, P92013AA)	
Studies in Pediatric Subjets from 1 to 11 Months Old With GERD				
RABGRD 1003	Phase 1, PK, PD and safety	1 5	Phase 1 granule formulation (P5Z005AAC, P85003AAA, P90213AAB) Phase 1 granule formulation (P5Z005AAD, P85003AAB, P92013AAA)	
RABGRD 3004	Phase 3, efficacy, and safety	2.5	Phase 3 granule formulation (P8X004BAA, P92014BAA)	
Studies in Pediatric Subjects from 1 to 11 Years of Age With GERD [c]				
RABGRD 1002	Phase 1, PK, PD and safety	1 5	Phase 1 granule formulation (P5Z005AAC, P85003AAA) Phase 1 granule formulation (P5Z005AAD, P85003AAB)	
RABGRD 3003	Phase 3, efficacy, and safety	2.5 5	Phase 3 granule formulation (P8X004BAA, P92014BAA) Phase 3 granule formulation (P8X004CAA, P92014CAA)	

GERD = gastroesophageal reflux disease; a: Lot No. P82007AZA corresponds to lot No. 8GTK004 that was used in the study report; b: Lot No. P8X004CAA corresponds to lot No. 8JTK02E that was used in the study report; c: These studies are summarized in Module 2.7.2.

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/s/

INSOOK KIM
11/08/2012

SUE CHIH H LEE
11/12/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-736
Submission Date	September 27, 2012
Product name, generic name of the active	AcipHex (rabeprazole sodium)
Dosage form and strength	Delayed-Release Sprinkle Capsule, 2.5 mg, 5 mg, and 10 mg
Indication	Healing and maintenance of healing of gastroesophageal reflux disease (GERD) and the improvement of GERD symptoms in children 1 to 11 years of age
Applicant	Eiasi Inc.
Clinical Division	GIEP
Type of Submission	Original New Drug Application, New Dosage Form intended to meet Phase 4 commitments and satisfy Written Request Amendment 7 requirements for neonates, children aged 1 to 11 months, and children aged 1 to 11 years.
Biopharmaceutics Reviewer	Houda Mahayni, Ph.D.
Biopharmaceutics Team Leader (Acting)	Tapash Ghosh, Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS
A. INITIAL OVERVIEW OF THE NDA APPLICATION FOR FILING

	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		The following dissolution method is proposed for routine testing: (b) (4) [redacted]
2.	Is the dissolution test part of the DP specifications?	x		Proposed dissolution acceptance criteria: (b) (4) [redacted]
3.	Does the application contain the dissolution method development report?		x	The Applicant used compendial dissolution method (USP<711>) for delayed-release dosage forms (Apparatus 2, Method A)

4.	Is there a validation package for the analytical method and dissolution methodology?	x		The analytical method UV spectroscopy was used for analysis of samples collected during dissolution testing.
5.	Does the application include a biowaiver request?		x	All three strengths were tested clinically (the Applicant performed BE study comparing the Phase 3 (5 mg) formulation to the TBM (10 mg) formulation. Also, the 2.5 mg Phase 3 formulation was assessed in a BA study).
6.	Does the application include an IVIVC model?		x	
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?		x	The dosage form is indicated for children up to 11 years of age
8.	Is information such as BCS classification mentioned, and supportive data provided?		x	
9.	Is information on mixing the product with foods or liquids included?	x		The Applicant provided food compatibility results.
10.	Is there any in *vivo* BA or BE information in the submission?	x		Several BA studies are included. These studies will be reviewed by OCP.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		• The NDA is fileable from Biopharmaceutics Perspective. • The acceptability of the proposed dissolution method and acceptance criteria will be a review issue. • The adequacy of the data provided to support the bridging between the Phase 3 and the TBM formulations will be a review issue.
12.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not Applicable.
13.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not Applicable.
14.	Are there any **potential review** issues identified?	x		• It is noted that there is not enough data to substantiate the discriminating capability of the dissolution method.

15.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	• A dissolution method development report was not included in your submission. Although you stated that (b) (4) [redacted]

{See appended electronic signature page}
Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer Date
Office of New Drug Quality Assessment

{See appended electronic signature page}
Tapash Ghosh, Ph.D.
Acting Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

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/s/

HOUDA MAHAYNI
10/30/2012

TAPASH K GHOSH
10/30/2012