OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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Table of Contents

1 Executive Summary 2
1.1 Recommendations 2
1.2 Phase IV Commitments 3
1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings 3
2 Question-Based Review 8
2.1 General Attributes of the drug 8
2.2 General Clinical Pharmacology 10
2.3 Intrinsic Factors 19
2.5 General Biopharmaceutics 28
2.6 Analytical Section 33
3 Detailed Labeling Recommendations 38
4 Appendices 40
4.1 Proposed Package Insert 40
4.2. Individual Study Review 68
4.3 Pharmacometric Reviews 102

4.4 Pharmacogenomics Review……122
4.5 OCP Filing Form 128

1 Executive Summary

This current submission is a response to the Protonix Pediatric Written Request (PWR) to fulfill PMC 1) Deferred pediatric study under PREA for the treatment of erosive esophagitis associated with gastroesophageal reflux disease in pediatric patients ages birth to seventeen years and 2) Deferred pediatric study under PREA for the maintenance of healing of erosive esophagitis in pediatric patients ages birth to seventeen years. (b) (4) The pediatric exclusivity was granted on February 17, 2009. Originally all the studies were submitted under NDA 22-020 SE5 on November 21, 2009. Because two different dosage forms were studied and the submission was later administratively unbound and NDA 20-987 SE5 was submitted on May 12, 2009 to support Pantoprazole Tablet for pediatric use.

1.1 Recommendations

The Division of Clinical Pharmacology 3 has reviewed the clinical pharmacology and biopharmaceutics information in NDA 22-020 and 20-987 and found it acceptable provided mutual agreement on labeling language can be reached between the Agency and the sponsor. The following recommendations should be resolved prior to the final action.

Recommendation for the weight-based dosing

Based on the population PK analysis across the age groups, the body weight was the most influencing covariate to clearance of pantorazole in pediatric patients older than 3 years of age while the age factor reduced clearance 20%-80% in pediatrics from birth to <1 year old. According to a population PK analysis, the sponsor's proposed (b) (4) would yield the mean AUC values in the pediatric population exceed the mean AUC in the adult range by approximately 26%. The highest exposure is seen in pediatric patients with the lowest body weight in each dose group.

Therefore, we recommend that doses be based on body weight as well as age to match the adult exposure more closely. By reducing dose by a half for children with body weight < 15 kg for 1-5 years old children and < 40 kg for 6-16 years old, AUC would be closer to that in adults after 40 mg tablet dosing. For pediatric patients birth to 11 months old, we do not have dosing recommendation as efficacy was not demonstrated in this age group in clinical trials.

Table 1. FDA proposed doses match adult exposures. Results are presented as mean (10^{th} percentile – 90^{th} percentile). Poor metabolizers are excluded from this analysis.

(b) (4)

*Geometric mean

Recommendation for pediatric CYP2C19 poor metabolizers

In pediatric poor metabolizers, the systemic exposure i.e. AUC of pantoprazole was greater than 6 folds higher than in extensive metabolizers which is similar to the observation in adults. As such, dose should be reduced for poor metabolizers of CYP2C19.

Although no dosage adjustment is recommended based on CYP2C19 in adults, for pediatric patients this should be done because 1) safety database for pediatric patients who are CYP2C19 poor metabolizers is limited (6 out of 226 genotyped patients); 2) safety of pantoprazole in pediatric patients can not be extrapolated from safety of pantoprazole in adults.

The prevalence of poor metabolizers is 3% in Caucasian and African American population and 17-23% in Asian population. If no genotyping or phenotyping would be conducted, a dose reduction for patients with Asian subjects to the lowest dose level should be considered based on a relatively higher prevalence of poor metabolizers in this population.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In response to PWR, total 8 studies were conducted including four PK alone or PK and PD studies in pediatric patients. The PD analysis was conducted only for preterm infants/neonates and infants 1-11 month old of age. There were 3 additional PK studies in pediatric subjects and 5 biopharmaceutics studies conducted in support of pediatric granules. Two delayed release formulations i.e. Protonix Delayed-Release Oral Suspension (pediatric granules hereafter) and Protonix Delayed Release Oral Tablet were used in pediatric patients.

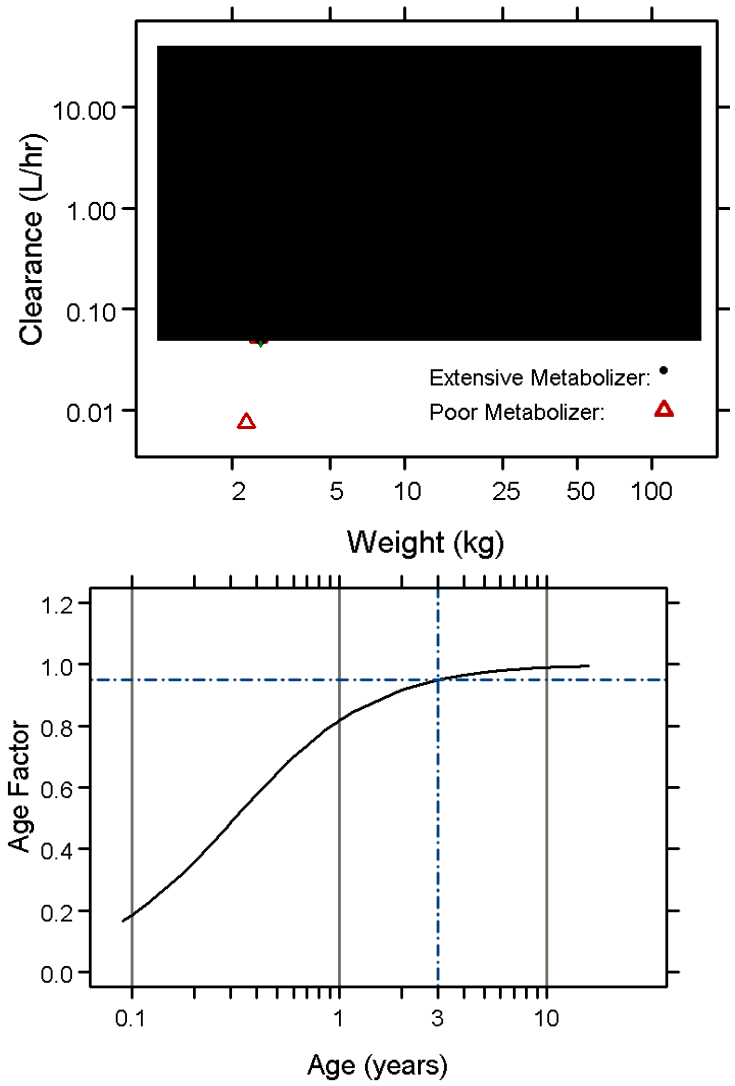
Pharmacokinetic/ Biopharmaceutics Properties

Pharmacokinetics in pediatric patients birth to 17 years old as requested in PWR was evaluated in four studies at two different dose levels for each age group.

Body weight is the key covariate for pantoprazole clearance in pediatric patients older than 3 years old

The sponsor's population pharmacokinetic model takes into account body weight, age, CYP2C19 metaboblizer status, and gender as covariates on clearance and/or volume of distribution. Population PK analyses suggested that the body weight is the key covariate for pantoprazole clearance in pediatrics >3 years of age. Age factor in the model had significant influence in pediatrics <1 year reducing clearance by 20% to 80% of the adult value. At 3 years of age the contribution of age factor was decreased to reduce clearance by 5%. The impact of gender and race on the PK was not found to be clinically meaningful.

Figure 1. Body weight is the key covariate for pantoprazole clearance in pediatric patients ≥3 years of age.



Systemic exposure of pantoprazole in pediatric patients in comparison to adults

Plasma concentrations of pantoprazole were highly variable in pediatric patients. The coefficient of variation for PK parameters was about 90 %. The variability was somewhat lower in children older than 12 years yet still it is in the range of 50-70%. Notably, several patients across the age groups did not have any measurable plasma concentrations of pantoprazole over 12-18 hours after a single dose and over 4 or 6 hours after multiple doses. In addition, in some patients, the absorption of pantoprazole was significantly delayed as indicated by a lag time of 4 to 6 hours as well as by a significantly delayed tmax of 4-12 hours. The comparison of PK parameters across age groups was confounded by a difference in formulation i.e. granules for children younger than 6 years old and tablets children older than 6 years old. Although the systemic exposure (i.e. AUC) of granules and tablets were bioequivalent when studied in healthy adult subjects, the possibility of under dosing can not be ruled out when granule formulation was administered to young children.

When approximately 0.6 mg/kg equivalent of the approved adult dose 40 mg was administered to infants through children 11 years old, the systemic exposure of pantoprazole was lower than that in healthy adults who received 40 mg pantoprazole tablet.

Systemic exposure of pantoprazole increased with an increase in dose in all age groups. However, the assessment of dose proportionality was limited by a high variability.

In a population pharmacokinetic analysis, compared to adults who received a single 40 mg dose, the systemic exposure (geometric mean AUC) was 103% higher in preterm infants and neonates with GERD receiving pantoprazole 2.5 mg, and 23% higher in infants 1 through 11 months of age with GERD receiving pantoprazole at approximately 1.2 mg/kg. In these patients, the apparent clearance (CL/F) increased with age (median clearance: 0.6 L/hr, range: 0.03 to 3.2 L/hr).

Following a 1.2 mg/kg equivalent dose, the estimated AUC for 1 to 5 year-old patients was 37% higher than for adults receiving a single 40 mg tablet. In these children the apparent clearance values had a median value of 2.4 L/h.

Table 2. Geometric Mean Pharmacokinetic Parameters after Single Dose Administration in Pediatric Patients less than 5 years of age (Population PK analysis)

Age Dose	Preterm infants/neonates 2.5 mg	1-11 months old 1.2 mg/kg	1-5 years 1.2 mg/kg
C_{max} (µg/mL)	0.86	0.91	0.74
t_{max} (h)	2.0	1.5	1.7
AUC (µg•h/mL)	8.4	5.1	5.4
CL/F (L/h)	0.3	1.4	3.1

The geometric mean AUC estimated from population PK analysis after a 40 mg PROTONIX tablet in pediatric patients was about 39% and 10% higher in 6 to 11 and 12 to 16 year-old children, respectively compared to that of adults.

Table 3. Geometric Mean Pharmacokinetic Parameters after Single Dose Administration in Pediatric Patients 6-16 years of Age (Population PK analysis)

Age Dose	6-11 years 40 mg	12-16 years 40 mg
Cmax (µg/mL)a	3.3	1.8
tmax (h)b	1.3	1.5
AUC (µg•h/mL)a	6.9	5.5
CL/F (L/h) (range)	6.6	6.8

The parameter values obtained from the population PK analysis were used for further analysis to come up with the dosing recommendation as listed in Table 1.

Relative BA and BE between pediatric granules and the marketed formulations

- **Mean AUC and Cmax of pantoprazole was 7-10% and 34-37% lower for pediatric granules compared to Tablet after a single dose of 40 mg pantoprazole.**

The relative bioavailability between pediatric granules and 40 mg tablet was compared in a randomized, open-label, 3-period crossover study. Under fasting conditions, AUC for pantoprazole 40 mg granules given sprinkled on a teaspoonful of applesauce or as a suspension in water with an inert powder blend was 7-10% lower and the peak concentration (Cmax) was 34-37% was lower than that of the pantoprazole 40 mg tablet.

Table 4. Mean Pharmacokinetic Parameters for Pantoprazole in Healthy Adults After Single-Dose Administration Of 40 mg Pantoprazole Under Fasted Condition (study 114)

Dosage regimen	Cmax (ng/mL) Mean (% CV) [geometric mean]	Geometic mean ratio to tablet 90% CI	AUC (ng*hr/ml) Mean (% CV) [geometric mean]	Geometic mean ratio 90% CI
Tablet	2958 (31) [2810]	--	6073 (100) [4982]	--
Granules sprinkled on applesauce	1865 (40) [1753]	62.4 (55.62-70.01)	5451 (107) [4498]	90.09 (84.67-95.85)
Granules suspended in water	1929 (26) [1855]	66.04 (58.86-74.08)	5629 (106) [4672]	93.8 (88.14-99.78)

- **The pediatric granules and the marketed Delayed-Release Oral Suspension were bioequivalent with respect to AUC but not with respect to Cmax**

The bioequivalence between the pediatric granules and the marketed Protonix Delayed-Release Oral Suspension was assessed by an open-label, single-dose, randomized, 2-period, 2-sequence crossover, in healthy men and women aged 18 to 50 years. Each product (40 mg) was sprinkled over a teaspoonful of applesauce and taken with 240 mL of room-temperature water after fasting for at least 10 hours

Table 5. Mean Pharmacokinetic Parameters For Marketed Granules And Pediatric Granules (N=24)

Dosage regimen	Cmax (ng/mL) Mean (% CV) [geometric mean]	Geometic mean ratio[1] 90% CI	AUC (ng*hr/ml) Mean (% CV) [geometric mean]	Geometic mean[1] 90% CI
Marketed Delayed-Release Oral Suspension	2361 ± 693 [2267]	118 (108-129)	8218 ± 7910 [6112]	106 (100-113)
Pediatric Granules	2036 ± 705 [1916]	--	7963 ± 8032 [5773]	--

[1]Ratio of Delayed-Release Oral Suspension to Pediatric Granules

The mean $C_{max,}$ of pantoprazole with the Protonix Delayed-Release Oral Suspension 40 mg was about 18% higher compared with the pediatric granules. For C_{max}, the 90% CI for the ratio of the geometric means between two formulations was from 108% to 129% and did not fall within the bioequivalence window of 80% to 125%.

The mean AUC of pantoprazole Protonix Delayed-Release Oral Suspension 40 mg was 6% higher compared with the pediatric granules. For AUC, the 90% CI for the ratio of the geometric means

between two products was from 100% to 113% meeting the bioequivalence criteria. As such, the pediatric granules and the marketed Protonix Delayed-Release Oral Suspension 40 mg were bioequivalent with respect to AUC but not with respect to Cmax.

High Fat Meal Reduced Oral Absorption Of Pediatric Granules

A concomitant high fat meal delayed the median Tmax of the absorption of pantoprazole administered sprinkled on a teaspoonful of apple sauce. The mean Cmax and AUC was decreased by 51% and 28%, respectively by a high fat meal compared to in fasting condition.

Effect of food was comparable when Pantoprazole was administered 60 min or 30 min prior to a high fat diet

To determine the optimal timing of meals relative to dose administration of the granules, pediatric granule was administered under 3 conditions: fasting (after an overnight fast of at least 10 hours); 30 minutes or 60 minutes before a standard high-fat breakfast after an overnight fast of at least 10 hours.

When pantoprazole was taken 30 or 60 minutes before a meal, only a mild food effect e.g. 16% to 18% decrease in mean AUC and 20% decrease in mean Cmax was observed. The administration of 60 minutes prior to a high fat meal did not significantly improve systemic exposure of pantoprazole compared to when pediatric granules were administered of 30 minutes prior to a high fat meal. Dose administration of the granules 30 minutes before meals for subsequent trials was decided based on these results.

Dose-Response Relationship

The effect of dose levels on PD parameters was evaluated at 0.6 mg/kg and 1.2 mg/kg in infants 1-11 months old by 24 hour pH-metry for intragastric and intraesophageal pH at baseline and at steady-state. There was no obvious dose-response between 0.6 mg/kg and 1.2 mg/kg. The higher dose of 1.2 mg/kg resulted in statistically significant increase in some PD parameters including the mean and median intragastric pH, the mean % of time for intragastric pH >3 and >4. On the other hand, the lower dose 0.6 mg/kg did not result in a statistically significant change in any PD parameters although numerical increase was observed in intragastric pH. However, there was no statistically significant difference between dose groups for changes in any PD parameters.

Assessment of a dose-response relationship for intragastric pH is confounded by a significantly high gastric pH at baseline for 0.6 mg/kg dose group. In patients in 0.6 mg/kg dose group, the mean gastric pH and % time intragastric pH>4 at baseline was comparable with those after 1.2 mg/kg pantoprazole treatment. The reason for this unbalanced baseline is unclear.

The reflux index % time intraesophageal pH <4 and mean intraesophageal pH was not significantly changed after at least 5 days of pantoprazole treatment regardless of doses. It was noted that the number of reflux episode numerically increased at steady-state from baseline and it is unknown if pantoprazole had any effect on it.

There was no obvious dose-dependent increase in efficacy based on the primary clinical endpoint, GERD Symptom Score in any age groups. Please, see Clinical Review by Dr. Il-Lun Chen for details.

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?

In the United States, the use of pantoprazole sodium was approved as follows:

- **February 2000**: Pantoprazole sodium delayed-release tablets for short-term treatment (up to 8 weeks) in the healing and symptomatic relief of EE (NDA 20-987).
- **March 2001**: The use of IV pantoprazole (NDA 20-988) for short-term treatment (7 to 10 days) of patients having GERD as an alternative to oral therapy in patients who are unable to continue taking oral pantoprazole
- **June 2001**: For maintenance of healing of EE and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with GERD (NDA 20-987/S-001)
- **October 2001:** For the treatment of pathological hypersecretory conditions associated with ZES (NDA 20-988/ S-003).
- **April 2002**: For pathological hypersecretory conditions including Zollinger-Ellison syndrome (ZES) (NDA 20-987/S-007)
- **November 2007:** The use of pantoprazole sodium for delayed-release oral suspension (hereafter referred to pantoprazole granules or granules) for the short-term treatment of EE associated with GERD, maintenance of healing of EE, and pathological hypersecretory conditions including ZES (NDA 22-020)
- **December 2004:** The use of IV pantoprazole for short-term treatment (7 to 10 days) of GERD and a history of EE (NDA No. 20-988/S-027)

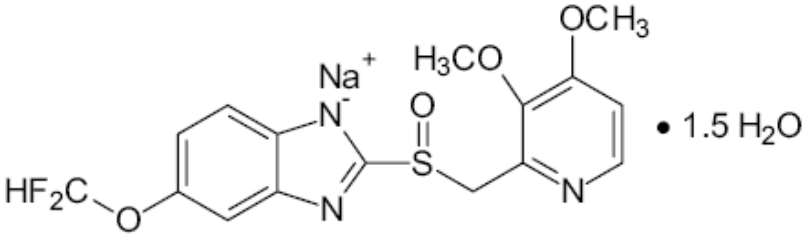
This current submission is a response to the Protonix Pediatric Written Request (PWR) and reflects studies evaluating the short-term use of pantoprazole sodium for the treatment of symptomatic GERD in pediatric patients from preterm infants and neonates through 16 years of age.

The PWR was originally issued on December 31, 2001 for pediatric studies for Protonix® (pantoprazole) Delayed-Release Tablets and I.V. for injection. The pantoprazole PWR was amended on July 3, 2002; Dec 18, 2002; May 7, 2004; Mar 15, 2006; and subsequently revised on May 17, 2007. The deadline for reporting the full study results from the requested studies is Dec 31, 2008.

During the period, FDA informed Wyeth that it did not consider pantoprazole I.V. to be an age-appropriate formulation for neonates/preterm infants because of potential safety concerns with administration of an intravenous formulation. It was agreed that the IV formulation would no longer be used for infants aged less than 1 year. The Agency agreed that Studies 1 and 2 of the WR for preterm infants and neonates and infants younger than 1 year would be conducted with the granule formulation for oral administration.

2.1.4. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Pantoprazole sodium is a chemical entity originally synthesized by Nycomed (formerly known as ALTANA Pharma, previously Byk Gulden) in Konstanz, Germany, and has been under further development for pediatric population in the United States by Wyeth Research. Pantoprazole sodium sesquihydrate, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1Hbenzimidazole, monosodium salt, sesquihydrate, which may also be referred to as pantoprazole or pantoprazole sodium, is a substituted benzimidazole derivative that binds covalently to the gastric acid pump H+, K+-ATPase.



M.W. 383.38 (free acid)
F.W. 432.40
pKa 3.92, 8.19
$C_{16}H_{14}F_2N_3NaO_4S \bullet 1.5\ H_2O$

Figure 2. Pantoprazole sodium

(b) (4)

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

Pantoprazole, a proton pump inhibitor (PPI), is a potent, acid-activated, irreversible inhibitor of the H+, K+-ATPase of parietal cells and produces prolonged suppression of gastric acid secretion. Like other benzimidazole derivatives such as omeprazole and lansoprazole, pantoprazole undergoes a molecular rearrangement in an acidic environment that is necessary for its activity. Although it is amphoteric, pantoprazole acts as a weak base (approximate pKa of 4.0) that is protonated in the low pH environment of the parietal cell secretory canaliculi. The protonated species forms a tetracyclic sulfenamide, which then becomes covalently bound to cysteine residues of the H+, K+-ATPase or gastric proton pump.

(b) (4)

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

(b) (4)

The sponsor is not seeking an indication for infants younger than 1 year old due to failure of demonstration of efficacy in this age group.

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?**

Wyeth Research has conducted 12 pediatric clinical studies to evaluate the pharmacokinetic, pharmacodynamic, efficacy, safety, tolerability, and clinical outcomes of pantoprazole sodium in granules, tablets, and intravenous injection in the pediatric population.

Eight (8) studies were conducted with oral pantorpazole per PWR. These studies were conducted in preterm infants and neonates with a (postmenstrual) corrected age less than 44 weeks, infants 1 through 11 months, children 1 through 11 years, and adolescents 12 through 16 years of age. Four additional studies were conducted in support of use of pantoprazole in pediatric population. Two of them were PK studies for the intravenous injection formulation.

Table 6. Clinical Studies With Oral Pantoprazole in Accordance to the Pediatric Witten Request

Age Group (Population)	Study No.	Formulation	Objectives and Study Design	No. of Patients in Safety Population	PWR
Neonates and preterm infants with a clinical diagnosis of GERD	3001B3-331-WW	Granules	Objectives: PK, PD, safety Design: Randomized, open-label, single and multiple-dose PK study, with 2 arms (1.25 mg and 2.5 mg). Treated for at least 5 days. PD at 2.5 mg only	59	1
1 through 11 months with presumed GERD	3001B3-333-WW	Granules	Objectives: PK, PD, safety Design: Randomized, open-label, single and multiple-dose PK, safety, and multiple-dose PD study, patients randomly assigned to 0.6 mg/kg or 1.2 mg/kg dose.	67	2
1 through 11 months with symptomatic GERD	3001B3-329-WW		Objectives: Efficacy and safety Design: A 4-week open-label treatment run-in phase, followed by a 4-week double-blind placebo-controlled, treatment-withdrawal phase (1.2 mg/kg or placebo).	129	3
1 through 11 years with endoscopically proven GERD	3001B3-334-US	Granules for ages < 6 years Tablets for ages ≥ 6 years	Objectives: PK and safety Design: Randomized, open-label, single and multiple-dose PK study. Treated for at least 5 days (0.6 mg/kg and 1.2 mg/kg)	41	4
1 through 5 years with endoscopically proven symptomatic GERD	3001B3-328-NA	Granules	Objectives: Exposure/response and safety Design: Randomized, double-blind, multiple-dose, parallel-treatment groups (0.3 mg/kg; 0.6 mg/kg; 1.2 mg/kg). Treated for 8 weeks.	60	4

5 through 11 years with endoscopically proven GERD	3001A1-322-US	Tablet	Objectives: Exposure/response, and safety Design: Randomized, double-blind, multiple-dose, parallel-treatment group (10, 20, or 40 mg). Treated for 8 weeks.	53	4
12 through 16 years with suspected GERD, symptomatic GERD, or endoscopically proven GERD	3001A3-337-US	Tablet	Objectives: PK and safety Design: Randomized, open-label, single-and multiple-dose PK study. Treatment group (20 or 40 mg). Treated for at least 5 days.	22	5
12 through 16 years with symptomatic GERD	3001A1-326-US	Tablets	Objectives: Safety and clinical outcomes Design: Randomized, double-blind, multiple-dose, parallel-treatment group study. Two (2) treatment groups (20 or 40 mg). Treated for 8 weeks.	136	5

Table 7. Additional Supportive clinical trials in pediatric patients

Age Group (Population)	Study No.	Formulation	Objectives and Study Design	No. of Patients in Safety Population
Infants 1- 12 months with presumed GERD.	3001B3-335-WW	Granules	Objectives: Safety Design: Open-label safety extension study, with patients assigned to 0.6 mg/kg or 1.2 mg/kg based on clinical response or pH-metry data in preceding studies (331-WW or 333-WW). Treated for 6 weeks.	58
5 through 16 yrs Children and adolescents who could benefit from acid suppression therapy	3001A1-109-US	Tablet	Objectives: Single dose PK, safety Design: Open-label, single-dose, randomized, age-stratified (5 through 10 yrs and 11 through 16 yrs), parallel-group study. Treated with 20 or 40 mg tablet.	24
2 through 16 yrs Hospitalized Children and adolescents who might benefit from acid suppression therapy	3001K1-110-US	IV	Objectives: Single-dose PK, PD, and safety Design: Open-label, single-dose (possibly 2-dose), randomized, parallel-group study. Stratified by 3 age groups (2 through 4 yrs, 5 through 10 yrs, and 11 through 16 yrs) and randomly assigned to receive 0.8 mg/kg or 1.6 mg/kg for 1 Day treatment.	19
1 through 2 yrs Hospitalized children who would benefit from acid suppression therapy	3001K1-117-US	IV	Objectives: Single dose PK, safety Design: Open-label, randomized, inpatient, single-dose study. Two (2) dose groups: 0.8 mg/kg or 1.6 mg/kg.	4

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or pharmacodynamics, (PD) and how are they measured in clinical pharmacology and clinical studies?

Pharmacodynamics

Per PWR, pharmacodynamic parameters were measured using 24 hour pH-metry in the preterm infants and neonates and infants younger than 1 year old. Comparisons were made from baseline (predose) to pantoprazole steady state. Pantoprazole plasma concentrations were considered to be at steady state after patients had received at least 5 consecutive daily doses of the drug.

The PD parameters are:

- Initial stomach pH
- Duration of pH measurement (h)
- The mean and median intragastric pH
- The percentage of time intragastric pH was >4
- The percentage of time intragastric pH was >3
- The mean and median intraesophageal pH
- The percentage of time with an intraesophageal pH <4 (the reflux index)
- AUC of esophageal pH < 4 (the reflux area)

- AUC and the normalized AUC of gastric H+ activity
- AUC and normalized AUC of esophageal H+activity

Data from 24 hour pH-metry were used to analyze the effect of pantoprazole on the inhibition of gastric acid as determined by measurement of the intragastric and intraesophageal pH with a dual electrode. The patient had an intragastric and intraesophageal pH assessment for up to 24 hours at each of those time points via a 2-channel intragastric and intraesophageal pH probe with an internal reference electrode placed transnasally into the stomach. The pH values from both the intragastric and intraesophageal electrodes were recorded continuously at the rate of 1 sampling every 4 seconds for up to 24 hours on a data storage unit.

On each of the pH-metry days, the patients were fed every 3 to 4 hours as appropriate, with each feeding lasting a maximum of 30 minutes. The pH probes were inserted after not feeding for approximately 2 hours. Because of the buffering effects of feeding, data collected during the 30-minute feeding and 30-minute postfeeding periods were excluded from data analysis. Only the pH recording lasted at least 16 hours was included for the PD assessment.

Primary Clinical Efficacy Endpoint

The efficacy of pantoprazole sodium in pediatric patients was assessed based on GERD Symptom Score (GSS) and composite symptom score (CSS) (Table 6). Please, see Clinical Review by Dr. Ii-Lun Chen for details.

Table 8. Primary Endpoint For Clinical Efficacy Assessment

	Infant	**Age 1-5 years**	**Age 5-11 years**	**Age 12-16 years**
Assessment Tool	CAGS-I	eDiary GSS (GSQ-YC + I-GERQ)	GASP-Q	GASP-Q
Primary Endpoint	Weekly GSS (five items)	Weekly GSS	CSS (eight items)	CSS*

* CSS: composite symptom score

The symptom score was calculated using GERD symptom assessment tools developed for use by parents of infants, young children, and adolescents as below.

- GERD Assessment of Symptoms in Pediatric Questionnaire [GASP-Q],
- GERD Symptoms Questionnaire for Infants [GSQ-I]
- GERD Assessment of symptoms questionnaire for young children [GSQ-YC]
- 2 age-specific GERD symptom daily eDiaries for use in studies 328 and 329.

Table 9. Symptom Assessment Tools Used in Efficacy Measurement Across Pediatric Studies

---------- 3001B3-329-WW ----------		---------- 3001B3-328-NA ----------		3001A1-322-US & -326-US
GSQ-I Screening/Baseline	Daily eDiary Treatment Period	GSQ-YC Screening Only	Daily eDiary Treatment Period	GASP-Q Weekly
Vomiting/Regurgitation Irritability/Fussiness Refusal to Feed Choking/Gagging Arching Back	Vomiting/Regurgitation Irritability/Fussiness Refusal to eat Choking/Gagging Arching Back **Respiratory symptoms:** cough (without a cold), aspiration (cough after choking/gagging), wheezing (noisy breathing out with wheezy whistling sound), and stridor (noisy breathing in with a barking, croupy sound)	Vomiting/Regurgitation Abdominal/Belly Pain Refuses to eat Choking when eating Difficulty Swallowing	Vomiting/Regurgitation Abdominal/Belly Pain Refusal to eat Choking when eating Difficulty Swallowing **Respiratory symptoms:** cough (without a cold), aspiration (cough after choking/gagging), wheezing (noisy breathing out with wheezy whistling sound), and stridor (noisy breathing in with a barking, croupy sound)	Vomiting/Regurgitation Abdominal/Belly Pain Pain after eating Choking when eating Difficulty Swallowing Burping/Belching Nausea Chest pain/Heartburn

Abbreviations: GERD = gastroesophogeal reflux disease; GSQ-I = GERD symptoms questionnaire for infants, GSQ-YC = GERD Assessment of symptoms questionnaire for young children, GASP-Q = GERD Assessment of Symptoms-Pediatric Questionnaire.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Please refer to the Analytical section for details.

2.2.4 Exposure-Response Evaluation

2.2.4.1 **What are the characteristics of the dose-response for efficacy?**

Pharmacodynamics

- **Intragastric pH**

Dose effect on the pharmacodynamic parameters was assessed in infants aged 1-11 months at two dose levels, 0.6 mg/kg and 1.2 mg/kg after at least 5 days of once daily dosing. A statistically significant increase in mean gastric pH and % of time intragastric pH>4 and >3 at steady-state from baseline was observed only at 1.2 mg/kg dose level not at 0.6 mg/kg dose level. There was no significant difference in a change from baseline to at steady-state between two dose groups. Based on these results, the dose of 1.2 mg/kg was chosen for the efficacy trial for patients 1-11 months old of age.

Reviewer's comments: *Dose-response relationship for intragastic pH is confounded by a high mean intragastric pH at baseline for 0.6 mg/kg dose cohort which was 4.2± 1.4 compared to that for 1.2 mg/kg dose cohort which was 3.0 ± 1.4. The baseline for pH parameters; %time for gastric pH >4, mean gastric pH for 0.6 mg/kg dose cohort was high and comparable to those after 1.2 mg/kg treatment. On the other hand, the initial stomach pH was comparable between two dose groups: 2.4 ± 1.5 for 0.6 mg/kg cohort and 2.8 ± 1.9 for 1.2 mg/kg cohort. The reason for apparent bias in baseline between two dose groups is unknown.*

For preterm infants and neonate, the PD parameters were measured at one dose level. Therefore, dose-response relationship could not be assessed.

The sponsor collected blood samples for patients for PD measurement; however, did not analyze exposure-response relationship.

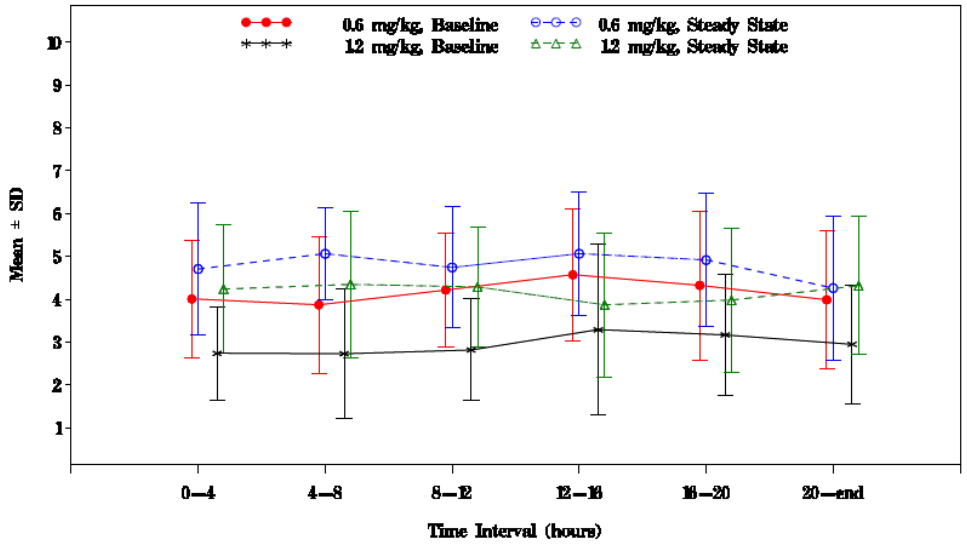
Table 10. Descriptive Summary Of Intragastric PD Parameters Studies In Infants Less Than 1 Year Of Age

Parameter	Preterm infants/neonates		Infants 1-11 months			
Dose	2.5 mg (n=16)		0.6 mg/kg (n=11)		1.2 mg/kg (n=10)	
Mean ± SD	Baseline	Steady State	Baseline	Steady State	Baseline	Steady State
Initial Stomach pH	2.61 ± 2.12[1]	4.13 ± 1.68[1]*	2.4 ± 1.5	2.6 ± 1.3	2.8 ± 1.9	2.8 ± 2.5
Mean Intragastric pH	4.3 ± 0.9	5.2 ± 1.0*	4.2 ± 1.4	4.8 ± 1.3	3.1 ± 1.4	4.2 ± 1.5*
% time intragastric pH>4	59.8 ± 20.7	79.3 ± 20.5*	55.5 ± 28.6	68.5 ± 28.3	32.2 ±24.1	56.6 ± 31.1*
% time intragastric pH >3	72.79 ± 19.35	86.24 ± 17.48*	68.4 ± 26.3	76.9 ± 24.5	43.5 ± 29.8	66.3 ± 30.5*

[1] n=15
* p<0.05

Reviewer's comments: *It was noted that 5 patients in preterm infants/neonates had the mean intragastric pH above 5 at baseline. The % time of gastric pH >4 for these patients was 72%-94% at baseline.*

Figure 3. Mean Intragastric pH Over Time (24 Hours): 1-11 month old



- **Intraesophageal pH**

The effects of pantoprazole on intraesophageal parameters in these infants were inconsistent and mostly insignificant. While the mean intragastric pH increased, from baseline at steady state, the mean intraesophageal pH actually decreased. The sponsor explained that the inconsistent results were attributed to 1) 50% increase in number of reflux episode at steady-state from baseline; 2) the majority of patients had a normal % time of intraesophageal pH <4 e.g. <10%. Because of the increased number

of reflux episode, even with an increase gastric pH the increased exposure time of esophagus to refluxant would have contributed to the decreased mean intraesophageal pH.

Reviewer's comments: *The number of reflux episode numerically increased at steady-state from baseline and it is unknown if pantoprazole had any effect on it. The percent patients whose % time for intraesohpageal pH <4 was >10% was not consistently decreased.*

Notably, the percentage time of intraesophageal pH <4 less than 10% is considered normal[1] *and 70-90% patients had intraesophageal pH < 4 for less than 10% time at baseline.*

Table 11. Intraesophageal pH In Preterm Infants/Neonates After At Least 5 Days Of Once Daily Dosing Of Pantoprazole

	Dose mg	Baseline Mean ± SD	Steady-state	Change from baseline Mean ± SD	P-value
Mean intraesophageal pH over 24 h	2.5	5.06 ± 0.28	4.91 ± 0.31	-0.16 ± 0.31	0.060
% time Intraesophageal pH <4 (reflux index)	2.5	8.65 ± 8.93	7.34 ± 8.63	-1.31 ± 12.34	0.676
Esophageal Reflux Area (pH•min) (time-pH area under pH <4)	2.5	73.86 ± 131.12	23.58 ± 34.36	-50.29 ± 139.54	0.170
AUC of esophgeal H+ activity (H*mmol/L)	2.5	5.84 ± 12.08	0.91 ± 0.70	-4.92 ± 12.17	0.126
Number of Reflux episode	2.5	124.00 ± 77.47	184.38 ± 189.85	60.38 ± 182.54	0.206

Table 12. Intraesophageal pH in infants aged 1-11 months

PD parameter	Dose mg/kg	Baseline Mean ± SD	Steady-state Mean ± SD	P-value
Mean intraesophageal pH over 24 h	0.6	5.7 ± 0.7	5.6 ± 0.8	0.347
	1.2	5.2 ± 0.4	4.9 ± 0.3	0.012
% time Intraesophageal pH <4 (reflux index)	0.6	4.6 ± 3.9	4.6 ± 5.6	0.982
	1.2	8.0 ± 5.6	9.4 ± 5.8	0.534
Esophageal Reflux Area (pH•min) (time-pH area under pH <4)	0.6	33.4 ± 25.2	24.5 ± 36.7	0.423
	1.2	57.5 ± 39.3	31.3 ± 13.3	0.066
AUC of esophgeal H+ activity (H*mmol/L)	0.6	2.1 ± 1.6	1.5 ± 2.4	0.387
	1.2	3.5 ± 2.3	1.5 ± 0.6	0.021
Number of Reflux episode	0.6	87.4 ± 59.9	109.1 ± 121.0	0.410
	1.2	143.2 ± 48.3	212.6 ± 112.6	0.144

[1] Vandenplas Y, Goyvaerts H, Helven R. Gastroesophageal reflux as measured by 24-hour pH monitoring in 509 healthy infants screened for risk of sudden infant death syndrome. *Pediatrics*. 1991;88:834-840.

Clinical endpoint

There was no obvious dose-dependent increase in efficacy based on the primary clinical endpoint, GERD Symptom Score in any age groups. For patients aged 1-11 months old, the efficacy was not demonstrated based on the primary efficacy endpoint, withdrawal rates. Please, see Clinical Review by Dr. Il-Lun Chen for details.

Table 13. Summary of the Weekly GERD Symptom Score From Baseline to the Final Evaluation - Children 1 Through 5 Years in mITT Population

		------ Pantoprazole Treatment Group ------		
Study Week	Weekly GERD Score[a] Statistics	Low (0.3 mg/kg) (n = 18)	Medium (0.6 mg/kg) (n = 19)	High (1.2 mg/kg) (n = 19)
Week -1 (Baseline)				
	Mean ± Standard deviation	3.21 ± 1.56	2.43 ± 1.58	3.36 ± 2.48
Final Week[b]	Mean ± Standard deviation	0.84 ± 0.72	1.79 ± 1.78	1.71 ± 1.69
Change from Baseline				
	Mean ± Standard deviation	-2.37 ± 1.74	-0.64 ± 1.40	-1.66 ± 1.64
	p-value[c]	< 0.001	0.063	< 0.001

Abbreviations: GERD = Gastroesophageal Reflux Disease; mITT = modified intent-to-treat.

a. Weekly GERD symptom score is defined as the sum of the 5 weekly mean frequency scores for e Diary items.
b. Final week is the last 7 days of symptom scores collected during the double-blind phase.
c. P-Value is obtained from the 2-sided paired t-test.

Table 14. Summary of Composite Symptom Scores of GERD Assessment From Baseline to the Final Evaluation - Children 5 Through 11 Years

		------ Pantoprazole Treatment Group ------		
Visit[a]	Weekly GERD Score[a] Statistics	10 mg (N = 19)	20 mg (N = 18)	40 mg (N = 16)
Baseline (Week -1)				
	Mean ± Standard deviation	129.2 ± 107.12	134.6 ± 108.19	132.4 ± 37.09
Last Visit				
	Mean ± standard deviation	35.7 ± 44.79	20.4 ± 29.73	29.3 ± 44.00
Change from Baseline				
	Mean[b] ± Standard error	-89.42 ± 9.58	-111.35 ± 10.02	-99.30 ± 10.46
	p-Value[c]	<0.001	<0.001	<0.001

Abbreviation: GERD = Gastroesophageal Reflux Disease.

a. Composite symptom score is defined as the sum of the 8 weekly mean frequency scores for the individual symptom scores.
b. Least square mean.
c. p-Value was calculated using analysis of covariance least squares means.

Data Source: For study 322: Table 9.4.1-1 and Table 9.4.2.3-1, CSR-54559.

Table 15. Summary of Composite Symptom Scores of GERD Assessment From Baseline to the Final Evaluation - Adolescents 12 Through 16 Years

Visit[a]	Weekly GERD Score[a] Statistics	------ Pantoprazole Treatment Group ------ 20 mg (N = 68)	40 mg (N = 68)
Baseline (Week -1)			
	Mean ± Standard deviation	177.7 ± 172.31	174.1 ± 332.20
Last Visit			
	Mean ± standard deviation	67.7 ± 128.79	59.9 ± 86.65
Change from Baseline			
	Mean[b] ± Standard error	-105.59 ± 11.87	-102.85 ± 11.87
	p-Value[c]	<0.001	<0.001

Abbreviation: GERD = Gastroesophageal Reflux Disease.

a. Composite symptom score is defined as the sum of the 8 weekly mean frequency scores for the individual symptom scores.

b. Least square mean.

c. p-Value was calculated using analysis of covariance least squares means.

2.2.4.2 What are the characteristics of the dose-response for safety?

Please, see Clinical Review by Dr. Ii-Lun Chen for details. There was no dose-dependent overall increase in the number of adverse events. Overall, 412 (67.1%) patients reported 1 or more TEAE. The most commonly reported TEAEs were headache, upper respiratory infection, rhinitis, infection, fever, diarrhea, accidental injury pharyngitis, abdominal pain, cough increased, vomiting, and otitis media (5.0%)

Overall, 12.2% of patients had TEAEs of any severity that were judged by the reporting investigator to be related to treatment with pantoprazole. The severity for drug-related TEAEs was mild for 5.7%, moderate for 5.2%, and severe for 1.3%.

Table 16. Patient (>2%) reporting TEAE by dose (from Dr. Ii-Lun Chen's review)

Body System AE	Low (n = 37)	Medium (n = 211)	High (n = 366)	Total (n = 614)
Any AE	35 (94.6)	135 (64.0)	242 (66.1)	412 (67.1)
Body as whole				
Headache	10 (27.0)	32 (15.2)	33 (9.0)	75 (12.2)
Infection	5 (13.5)	24 (11.4)	23 (6.3)	52 (8.5)
Fever	3 (8.1)	13 (6.2)	35 (9.6)	51 (8.3)
Accident. injury	7 (18.9)	20 (9.5)	16 (4.4)	43 (7.0)
Abdominal pain	3 (8.1)	16 (7.6)	19 (5.2)	38 (6.2)
Pain	3 (8.1)	5 (2.4)	6 (1.6)	14 (2.3)
Digestive system				
Diarrhea	6 (16.2)	8 (3.8)	33 (9.0)	47 (7.7)
Vomiting	3 (8.1)	9 (4.3)	22 (6.0)	34 (5.5)
Gastroenteritis	1 (2.7)	4 (1.9)	11 (3.0)	16 (2.6)
Constipation	1 (2.7)	1 (0.5)	13 (3.6)	15 (2.4)
Tooth disorder	1 (2.7)	3 (1.4)	11 (3.0)	15 (2.4)
Nausea	3 (8.1)	4 (1.9)	6 (1.6)	13 (2.1)
Respiratory system				
URI	8 (21.6)	16 (7.6)	47 (12.8)	71 (11.6)

Rhinitis	8 (21.6)	22 (10.4)	33 (9.0)	63 (10.3)
Pharyngitis	5 (13.5)	16 (7.6)	21 (5.7)	42 (6.8)
Cough inc	4 (10.8)	11 (5.2)	19 (5.2)	34 (5.5)
Sinusitis	2 (5.4)	6 (2.8)	8 (2.2)	16 (2.6)
Skin and appendages				
Contact dermatitis	0	5 (2.4)	14 (3.8)	19 (3.1)
Rash	1 (2.7)	5 (2.4)	11 (3.0)	17 (2.8)
Special senses				
Otitis media	1 (2.7)	6 (2.8)	24 (6.6)	31 (5.0)

According to Clinical Reviewer an overall withdrawal rate from the trials was higher for the high dose group for various reasons including higher AE, non-compliance and non-satisfactory results. Of 50 discontinued patients out of 366 patients in the high dose group, 3% (11 out of 366) was discontinued due to adverse events whereas 0.9% (2 out of 211) and 2.7% (1 out of 37) patients was discontinued from the medium dose and the low dose treatment group, respectively.

Table 17: Summary of Primary Reason for Discontinuation by Dose (from Dr. Ii-Lun Chen's review)

Conclusion Reason	Low (n = 37)	Medium (n = 211)	High (n = 366)	Total (n = 614)
Completed	35 (94.6)	200 (94.8)	316 (86.3)	551 (89.7)
Discontinued	2 (5.4)	11 (5.2)	50 (13.7)	63 (10.3)
Adverse event	1 (2.7)	2 (0.9)	11 (3.0)	14 (2.3)
Failed to return	0	1 (0.5)	2 (0.5)	3 (0.5)
Investigator request	0	0	2 (0.5)	2 (0.3)
Lost to f/u	0	0	1 (0.3)	1 (0.2)
Noncompliance	0	0	10 (2.7)	10 (1.6)
Other	1 (2.7)	2 (0.9)	2 (0.5)	5 (0.8)
Parent request	0	0	5 (1.4)	5 (0.8)
Patient request	0	4 (1.9)	2 (0.5)	6 (1.0)
Protocol violation	0	2 (0.9)	7 (1.9)	9 (1.5)
Unsatisfactory response	0	0	8 (2.2)	8 (1.3)

2.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

There was no clear evidence to show the superiority of the high dose for efficacy in pediatric patients based on the symptomatic score, although a definite conclusion of dose-response relationship could not be drawn due to a small number of subjects,

In adults, a dose-dependent healing of erosive esophagitis (EE) was observed. The EE healing rates after 8 week treatment was 66%, 83.5% and 92.6% for 10mg, 20mg and 40 mg treatment, respectively

while 39.7% for placebo group. A dose-response and superiority of 40 mg could only be demonstrated when healing of erosive esophagitis or maintenance of healing was assessed (Protonix label).

In pediatric program, eight patients with erosive esophagitis were enrolled in a dose-ranging study to assess dose response endoscopically. All 8 patients with erosive esophagitis healed their erosions within the 8 weeks of treatment in these studies while receiving either the medium or high doses. No patients in the low dose group had endoscopy.

(b) (4)

According to Dr, Earp's population PK analysis, (b) (4) Based on the population PK analysis, it is recommended that a dose should be based on both age and body-weight to maintain the systemic exposure within the range observed in adults. Please, see section 2.4.2. and 4.4.

2.3 Intrinsic Factors

2.3.1 How the doses for pantoprazole were selected for pediatric patients?

The pediatric Written Request calls for 4 studies to evaluate PK in preterm infant/neonates (corrected gestational age < 44 weeks), infants (1-11 months old), children (1-11 years old) and adolescents (12-16 years old). The sponsor conducted 4 PK studies using pediatric granules and the marketed Protonix Delayed-Release Tablet.

Prior to the initiation of pediatric program, the sponsor conducted three pharmacokinetic studies in pediatric patients aged 1-16 years. Two PK studies (117 and 110) were conducted in hospitalized pediatric patients 1-16 years of age using intravenous pantoprazole and one PK study (109) was conducted in pediatric patients 5-16 years of age who by the judgment of the investigator would benefit from acid suppression therapy using Protonix tablets.

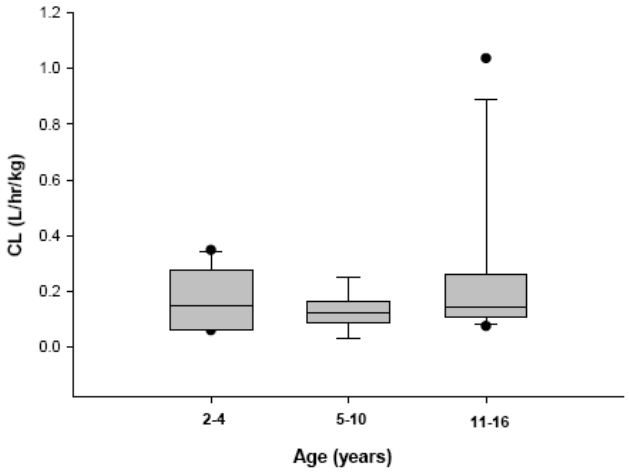
Table 18. List of Additional Pharmacokinetic Studies Conducted in Pediatric Patients

Wyeth Research Study Number	Study Description	Formulation	Number of Patients	Age of Patients (y)
3001K1-117-US CSR-61499	A Study of the Pharmacokinetics, Safety, and Tolerability of Intravenous Doses of Pantoprazole in Hospitalized Pediatric Patients	IV	4	1 – 2
3001K1-110-US CSR-48216	An Initial Study of the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Intravenous Doses of Pantoprazole in Hospitalized Pediatric Patients	IV	19	2 – 16
3001A1-109-US CSR-46354	A Study to Determine the Pharmacokinetics, Safety and Tolerability of a Single Oral Dose of Pantoprazole in Patients Aged 5 to 16 Years	Tablets	24	5 – 16

Abbreviations: CSR = clinical study report; IV = intravenous; US = United States.

In studies 117 and 110, the body-weight normalized clearance of pantoprazole in children 2-16 years old was similar to that in healthy adults after 40 mg Pantoprazole intravenous administration. On the other hand, the clearance (L/hr/kg) in children aged 1-2 years appeared higher than that of children older than 2 years. In children 1-2 years old, the systemic exposure of pantoprazole after administration of intravenous 1.6 mg/kg pantoprazole was similar to that after administration of 0.8 mg/kg intravenous pantoprazole in children 2-16 years old of age.

Figure 4. Body-Weight Normalized Total Clearance Following an Intravenous Pantoprazole Administration



In study 109, Protonix® tablets were studied at 20mg and 40 mg dose levels in children 5-16 years old. Similarly in adults, the median time to peak plasma concentration was 2-2.9 hr and the terminal half-life was 0.7-1.4 hours.

The sponsor chose the dose 0.6 mg/kg which is approximately equivalent to 40 mg for a 70 kg adult and a higher dose 1.2 mg/kg for children 1-5 years old. For preterm infants and neonates, two doses 1.25 mg and 2.5 mg were chosen for PK and PD study. This fixed dose of 1.25 mg and 2.5 mg is equivalent to 0.41 mg/kg and 0.82 mg/kg for a 3 kg infant, respectively. The dose of 20 mg and 40 mg were selected for subsequent studies in 6-16 years old pediatric patients with GERD.

Table 19. Doses for PK studies in pediatric Patients using oral formulation

Age	BW (kg)	Formulation	Low Dose		High Dose	
			mg	mg/kg	mg	mg/kg
Preterm infants/neonate	> 1.5 kg	Granule	1.25 mg		2.5	
1-11 mo	2.5-7	G	2.5 mg	0.3-1	5	0.6-2
	7-15	G	5 mg	0.3 -0.7	10	0.6-1.4
1-5 yr	>8.3 and <12.5	G	5 mg	0.4-0.6	15	1.2 -1.8
	12.5-25	G	10 mg	0.4-0.8	20	0.8-1.6
6-11	≥25	Tablet	20 mg	≤ 0.8	40	≤1.6
12-16 yr		T	20 mg		40	

2.3.2. What are Pharmacokinetic Characteristics of Pantoprazole in Pediatric Patients?

Mean AUC and Cmax in pediatric patients was lower than in healthy adults when the equivalent body-weight based dose was administered.

After administration of 0.6 mg/kg dose equivalent to 40 mg in a 60 kg adult to pediatric patients 1 month to 11 years old, the systemic exposure of pantoprazole was lower than in adults when PK parameters obtained by NCA analysis were compared.

Reviewer's comments:

Blood samples for PK analysis were collected over 18 hours from preterm infants and neonates in two sampling groups and over 12 hours for children 1-16 years old. The blood samples were collected at pre- and 0.5, 1, 2, 4, 6, and 12 hours post-dose in children 1 month through 11 years old and at pre- and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, and 12 hours post-dose in children 12 through 16 years old. For some subjects particularly in 1-5 years old group who exhibited a lag time and substantially delayed Tmax around 4-5 hours, blood samplings were not sufficient to obtain a full plasma concentration-time profile. As such mean AUC_T was used compared across age group between adults and pediatrics in this review.

PK parameters for pantoprazole in pediatric patients were highly variable. The % coefficient of variation for PK parameters was about 90 %. The variability was somewhat lower in children older than 12 years yet still in the range of 50-70%.

In most patients plasma concentrations of pantoprazole were close to or below LLOQ at last sampling time point. However, some patients particularly in 1-5 year old group exhibited a lag time of 4 to 6 hours and a tmax of 4-12 hours observed suggesting a significant delay in absorption. Because there were no PK samples collected between 6 to 12 hours, Cmax and AUC estimation is considered unreliable for these subjects. Because of insufficiency in the plasma sampling scheme, PK parameters estimated by population PK analysis would be more appropriate for younger age groups.

The sponsor originally analyzed PK parameters by Non-Compartmental Analysis except for preterm infants and neonates. Therefore, in this review the PK parameters mostly by Non-Compartmental Analysis were discussed. The population PK analysis is further discussed in detail in the Pharmacometics Review by Dr. Justin Earp in Appendix 4.3. Briefly, in a population PK analysis, the PK parameters were generally higher than what was estimated by Non-Compartmental Analysis across age groups. It may be in part due to variable and uncertain bioavailability especially with granule formulations. Nonetheless, those values were similar to what was later provided by the sponsor upon Agency's request.

- **Preterm infants and neonates:** In preterm infants and neonates, the 1.25 mg dose and 2.5 mg dose is equivalent to 0.3-0.8 mg/kg and 0.6-1.6 mg/kg, respectively for patients 1.5 kg to 4.5 kg of body weight. The mean AUC estimated in a population PK analysis for the low dose cohort in this age group was 44% lower to that in adults after 40 mg while AUC in the high dose cohort was about 13% higher than in adults receiving a single dose of 40 mg pantoprazole tablet.

- **Infants 1-11 months old of age:** The mean AUC_T in patients aged 1-11 months old after a single dose of 1.2 mg/kg was 35% lower than that in adults after 40 mg tablet dose.

- **Children 1-5 years old of age:** The mean AUC_T in patients aged 1-5 years old was about 60 % lower than that in adults after 40 mg tablet dose. Because of prolonged absorption indicated by delayed tmax to 6 hours and insufficient PK sampling, the AUC_T is very likely underestimated and Cmax is not reliable for several subjects in this group. Therefore, PK parameters based on Non-compartmental analysis is not considered reliable. As such parameter estimates by population PK analysis was used for further evaluation.

- **Children 6-11 years old of age and 12-16 years old of age:** The mean PK parameters between age groups of 6-11 years old and 12-16 years old were in general comparable. When compared to adults receiving 40 mg tablet, geometric mean AUC_T of pantoprazole given as 40 mg tablet was about 30% lower and mean Cmax was about 14-20% lower.

Table 20. Single-Dose Pharmacokinetic Parameters for Different Age Groups from Pediatric Written Request Studies in preterm infants/neonates and infants 1-11 months old of age (Non-Compartmental Analysis)

Age	<44 weeks[a]		1-11 months old		Adults [c,d]	
Dose	1.25 mg [b] (n=14)	2.5 mg [b] (n=17)	0.6 mg/kg (n=21)	1.2 mg/kg (n=20)	40 mg* Granules (n=24)	40 mg Tablet (n=24)
Cmax (ng/ml)	ND	ND	503 (100) [295]	1384 (94) [796]	1855	2810
Tmax (hr) (min-max)	ND	ND	1.03 (0.98-11.8)	1.02 (0.5-4)	2 (1-4)	2.5 (1.5-4.0)
AUCt (ng*hr/ml)	ND	ND	842 (108) [604]	3187(102) [1725]	4574	4870
Number of subjects[e]			n=13	n=18		
AUC_∞ [c] (ng*hr/ml)	3540 (79) [2785]	7270 (72) [5631]	1137 (99) [778]	3709 (90) [2229]	4672	4982
t1/2 (h) (± SD)	3.1 ± 1.5	2.7 ± 1.1	1.3± 0.7	1.6 ± 1.4		
CL/F (L/h/kg)	0.21 (57)	0.23 (91)	1.02 (75)	0.9 (155)		

[a] Corrected gestational age
[b] population PK analysis
[c] Study 114
[d] geometric mean
[d] number of subjects for AUC_∞, CL/F and $t_{1/2}$
ND: Not determined
* pediatric granules suspended in water

Table 21. Single-Dose Pharmacokinetic Parameters for Different Age Groups from Pediatric Written Request Studies in children and adolescents 1-16 years old of age (Non-Compartmental Analysis)

Age	1-5 years old		6-11 years old		12-16 years old		Adults [1]	
Dose	0.6 mg/kg (n=7)	1.2 mg/kg (n=10)	20 mg (n=10)	40 mg (n=11)	20 mg (n=9)	40 mg (n=10)	Granules[2] 40 mg (n=24)	40 mg Tablet (n=24)
Cmax (ng/ml)	228 (85) [166]	653 (99) [406]	1643 (75) [1351]	2429 (44) [2223]	987 (39) [924]	2690 (49) [2423]	1753	2810
Tmax (hr) (min-max)	5.8 (1-6)	3 (1-6)	2 (1-4)	2 (1-2.3)	1.5 (1-3)	1.5 (1-8)	2.5 (1.5-5.0)	2.5 (1.5-4.0)
AUCt (ng*hr/ml)	563 (76) [377]	1920 (89) [1205]	2448 (82) [1946]	3748 (48) [3377]	1264 (49) [1146]	3800 (73) [3472]	4366	4870
Number of subjects[3]	n=2	n=6				n=8		
AUC_{∞} [c] (ng*hr/ml)	294 (70) [266]	1840 (87) [1194]	2497 (84) [1972]	3782 (48) [3403]	1305 (47) [1194]	4262 (72) [3510]	4488	4982
t1/2 (h) (± SD)	1.1 ±0.1	1.5 ±0.5	0.8 ±0.2	0.7 ±0.1	0.9 ±0.5	0.8 ±0.4		
CL/F (L/h/kg)	2.4 (67)	1.46 (79)	0.41 (155)	0.40 (75)	0.28 (60)	0.18 (44)		

[1] Study 114
[2] Pediatric granules sprinkled on apple sauce
[2] after excluding subjects without reliable estimation
[ ]: geometric mean

Reviewer's comments: *Notably, several patients across the age group did not have any measurable plasma concentrations of pantoprazole after a single dose or after multiple doses at two sampling time points. This lack of measurable plasma concentrations was observed predominantly for neonates and infants at the low dose level. This may be due to incomplete dosing especially in younger children given granule formulation and/or delayed absorption which could not be captured under the studied PK sampling scheme.*

Table 22. Number of Subjects Who Did Not Have Any Measurable Plasma Concentrations Of Pantoprazole

Age	Preterm infants/neonates		1-11 mo		1-5 yr		6-11 yr		12-16 yr	
Formulation	Granule		Granule		Granule		Tablet		Tablet	
Dose Group	Low	High	Low	High	Low	High	Low	High	Low	High
Single	5	2	0	1	0	1	0	1	1	0
Multiple	4	2	4	1	0	0	3	2	1	2

The accumulation of pantoprazole following multiple doses was assessed by comparing plasma concentration change between two time points between and PK profile after a single-dose administration. Plasma concentrations after multiple doses were highly variable with %CV ranging 60-125% and samples were generally collected after Tmax. This is not considered adequate to assess the accumulation after multiple doses. Nonetheless, significant accumulation is not expected with once

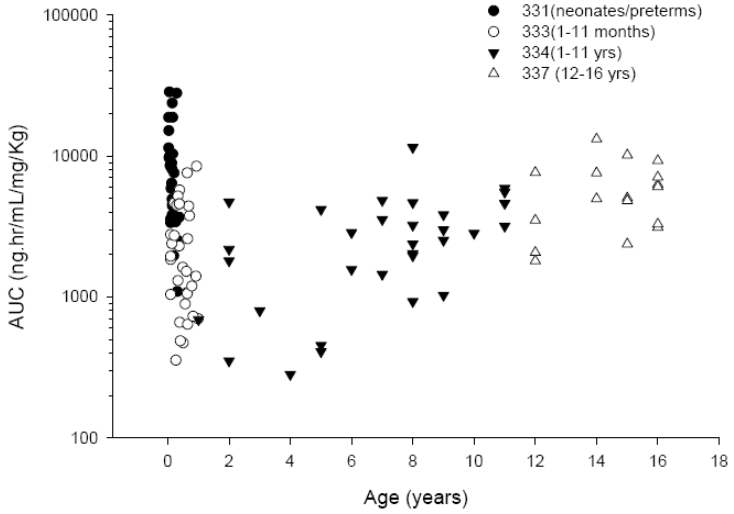
daily dosing because plasma concentrations of pantoprazole were close to LLOQ at 12 hours in most subjects after a single dose. In case of other proton pump inhibitor, e.g. esomeprazole, a significant increase in AUC was observed after multiple doses which may be attributed to auto-inhibition of metabolism as esomeprazole is a strong inhibitor of CYP2C19 enzyme. Nonetheless, the accumulation was not observed for pantoprazole even in adults.

2.3.3. What are the Intrinsic Factors Influencing Pharmacokinetics of Pantoprazole in Pediatric Patients?

The effect of age on PK properties was examined based on PK results pooled across individual studies. A higher AUC was observed in preterm infants and neonates. This may be attributed to the not well developed clearance pathways in this population. Infants around 1 year age tended to have lower AUC values compared with other children. This is possibly due to increased clearance per kilogram of body weight and variation in the amount of granules ingested in patients aged 1 month to 4 years.

The comparison of PK parameters among groups of children older than 6 years and younger than 5 years is confounded by formulation difference i.e. tablets for children older than 6 years vs. granules for children younger than 5 years. The systemic exposure i.e. AUC between granules and Tablets in healthy adults were similar and in adults; nonetheless, granules sprinkled on a teaspoonful of applesauce was administered with 240 mg water for adults and may have contributed to relatively consistent results in terms of plasma concentrations at early time points. .

Figure 5. Dose (mg/kg) Normalized AUC of Pantoprazole vs Age

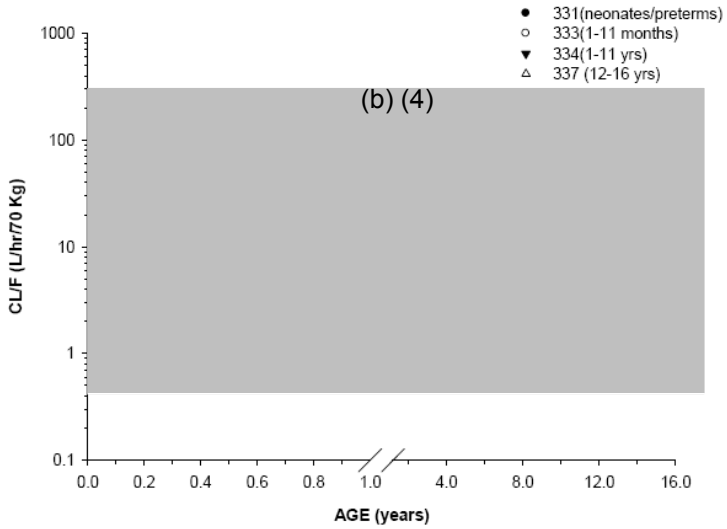


The apparent oral clearance varied across age groups. The CL/F was lowest in preterm infants and neonates and infants of age 1-11 months old. The CL/F was highest in 1-5 year old children and decreased in children older than 6 years. Similar trend of clearance variation over age was reported for lansoprazole[2].

[2] Tran et al. (2000) Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children, Clin Pharmacol Ther 2002;71:359-67

Reviewer's comments: *The PK parameters for 1-5 year old children are not considered reliable due to high variability in plasma concentrations. It is unclear to what degree incomplete dosing is contributing to low systemic exposure of pantoprazole in this age group.*

Figure 6. Pantoprazole Allometrically-Scaled Clearance vs Age



The CL/F increases up to about 1 year of age and reaches a plateau. The increase in CL/F up to 1 year can be attributed to the increasing CYP enzyme activity and maturation of clearance mechanisms after birth.

Population PK analysis

Population PK analysis suggests that the body weight is the key covariate for pantoprazole clearance in pediatrics >3 years of age. Age factor had significant influence in pediatrics <1 year reducing clearance 20% to 80% of the adult value and at 3 years of age the age factor reduces clearance 5%. Please, see Pharmacometics Review by Dr. Justin Earp in Appendix 4.3.

Figure 7 Body weight is the key covariate affecting pantoprazole clearance in pediatrics >3 years of age.

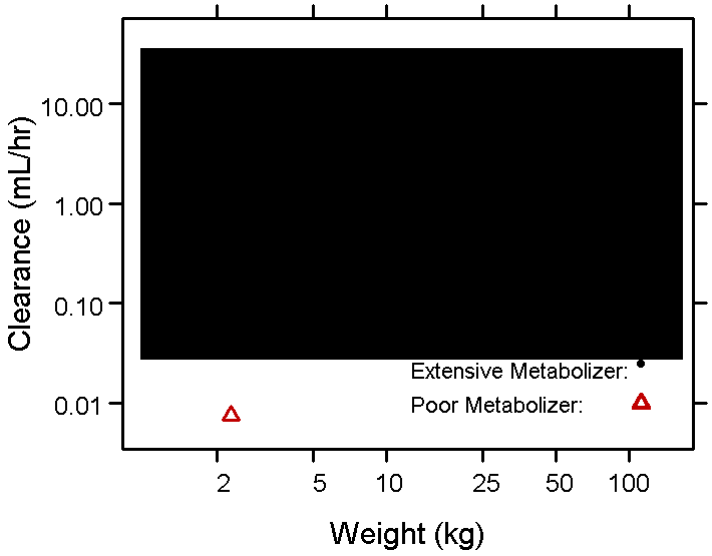
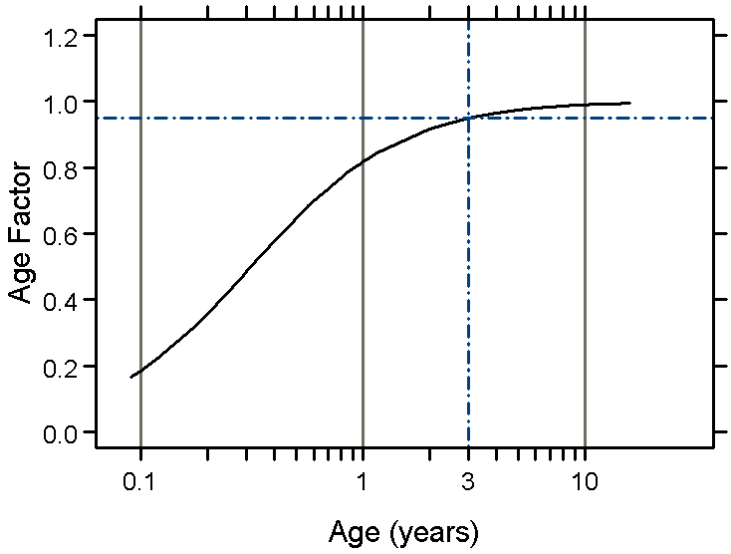


Figure 8. Age factor (Age/(Age+A_{50}) vs. age. Age does not significantly influence clearance for pediatric patients older than 1-3 years of age.



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

Pantoprazole is mainly metabolized by CYP2C19 followed by sulfation and to a less extent by CYP3A4. CYP2C19 displays a known genetic polymorphism. In adults the elimination half-life was increased to 3.5 to 10 hours in poor metabolizers for CYP2C19 compared to approximate 1 hour in extensive metabolizers for CYP2C19 and AUC of pantoprazole was 5-6 folds higher in poor metabolizers than in extensive metabolizers.

For pediatric patients, genotyping for CYP2C19 was conducted in 6 studies. Out of 226 patients, six patients were poor metabolizer genotype carriers i.e. CYP2C19 *2*2 and among them 4 patients had systemic exposure.

In pediatric patients, the dose-normalized AUC significantly varied depending on CYP2C19 genotypes. For patients who were CYP2C19 *2*2 carriers, the dose-normalized AUC was greater than 6 folds higher than extensive metabolizers e.g. CYP2C19*1*1 carriers and intermediate metabolizers e.g. CYP2C19 *1*2 carriers. One intermediate metabolizer was genotyped as CYP2C19 *1*4 carrier. The AUCt was used for poor metabolizers for a comparison since accurate AUCinf could not be derived because of sustained plasma concentrations beyond blood sampling period. Thus the AUC difference between extensive metabolizers and poor metabolizers is expected be greater than 6 folds.

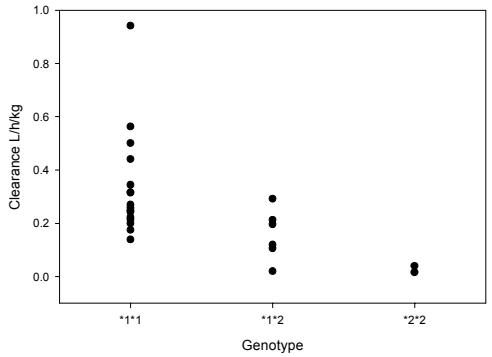
According to Dr. Il-Lun Chen, there was no obvious difference in safety profile for these poor metabolizers compared to the rest. However, it should be noted that the safety database for this subgroup of patients is limited in this submission and the safety of pantoprazole for adult poor metabolizers can not adequately represent the safety profile for pediatric patients. As such, the increased systemic exposure in pediatric poor metabolizers is concerning especially for infants and children and a dose-reduction should be considered for poor metabolizers for CYP2C19.

Table 22. Dose-normalized AUC for patients with CYP2C19 genetic variants (Study 109)(Table was generated by the reviewer)

Genotype	AUC/Dose (h/L)	CL/F (L/h/kg)
*1*1(n=16)	0.1 ± 0.05	0.34 ± 0.20
*1*X (n=6) [1]	0.29 ± 0.40 (0.13 ± 0.04) [2]	0.16 ± 0.10 (0.18± 0.08) [2]
*2*2 (n=2)	0.92 (0.63[3])	0.03

[1] n=5:CYP2C19 *1*2; .n=1: CYP2C19*1*4
[2] Without one subject (*1*2) with poor metabolizer phenotype

Figure 8. Effect Of Genotype On The Oral Apparent Clearance Of Pantoprazole In Children 5-16 Years Old



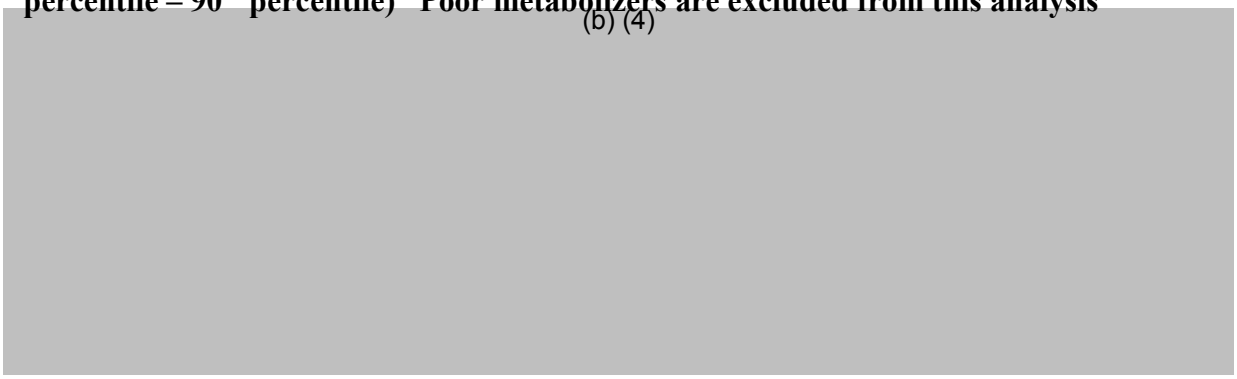
2.4.3 What issues related to dose are unresolved?

The sponsor proposes (b) (4) (b) (4) Under this dose, the mean AUC values in the pediatric population exceed the mean AUC in the adult range by approximately 26% when dosing 20 mg to pediatric patients 1-5 years of age and 40 mg to pediatric patients 6-17 years. The highest exposure is seen in pediatric patients with the lowest body weight in each dose group. The observations that 1) AUC increases with decreasing body weight and 2) AUC does not change significantly with age suggest that dosing by body weight will better match adult exposure consistently across pediatric patients. (For details, please see Pharmacometrics Review by Dr. Justin Earp in Appendix).

Therefore, the dose should be also based on the body-weight to match closely to the mean systemic exposure observed in adults following 40 mg administration and to reduce variability in systemic exposure.

Table 23. FDA proposed doses match adult exposures. Results are presented as mean (10th percentile – 90th percentile) Poor metabolizers are excluded from this analysis

(b) (4)



2.5 General Biopharmaceutics

2.5.2 What is the relative bioavailability of the delayed-release granules used in pediatric patients and the marketed formulations i.e. Protonix Delayed-Release Tablet and Protonix Delayed Release Suspension?

The new formulation of pantoprazole sodium in the form of delayed-release granules used in pediatric patients was a prototype formulation during the development of approved delayed-release oral suspension for adults who have difficulty in swallowing tablets. The approved Delayed-Release Oral Suspension 40 mg was further modified from the prototype formulation used in this application to qualitatively match the marketed tablets and to allow inclusion of color. Of note, the marketed Delayed-Release Oral Suspension was not used in pediatric studies.

Pediatric Granules vs. Delayed-Release Tablet 40 mg

For pediatric studies, Tablet

In clinical trials, the granules were orally administered by 2 methods depending on the age of patients:

- Sprinkled on a teaspoonful of applesauce or in apple juice for children older than 1 year old
- Suspended in water with an inactive powder blend for infants younger than 1 year old.

The relative bioavailability between pediatric granules and 40 mg Tablet was compared in healthy adult volunteers under fasting condition in a randomized, open-label, 3-period crossover study (n=24; Study 114). The AUC for pantoprazole 40 mg granules sprinkled on a teaspoonful of applesauce or as a suspension in water with an inactive powder blend was 7-10% lower and the peak concentration was 34-37% was lower than that of the pantoprazole 40 mg tablet. As such, bioequivalence criterion was met by AUC but not by Cmax between pediatric granules and Tablet 40 mg.

Reviewer's comments*: In relative bioavailability study, granules were taken with 240 ml water. It is unclear if water or other liquid was provided to young children to rinse down the granules.*

Table 24. Comparison of Compositions of PROTONIX®(Pantoprazole Sodium) Delayed-Release Tablets and Pantoprazole Sodium Delayed-Release Granules

Ingredient	Function	Approved PROTONIX® Tablets, 40 mg mg/204 mg	Approved 40 mg Delayed-Release Granules (Manufactured by Nycomed) mg/207 mg	Pediatric Delayed-Release Granules Clinical Formulation (Wyeth)[a] mg/206 mg
(b) (4)				

Table 25. Single-dose PK parameters for pantoprazole in healthy adult volunteers after administration of 40 mg pantoprazole under fasted condition (study 114)

Formulation	Statistic	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (h)	AUC (ng.h/mL)
Tablet	Mean ± SD[a]	2958 ± 927	1.5	2.5	5810± 5287	6073 ± 6146
	Range	1204 – 4826	0.3 – 3.0	1.5 – 4.0	1559 – 29544	1592 – 33978
	Geometric Mean	2810			4870	4982
Spheroids sprinkled on applesauce	Mean ± SD	1865 ± 708	0.2	2.5	5168 ± 4891	5451 ± 5845
	Range	1022 – 3376	0.0 – 2.0	1.5 – 5.0	2305 – 27450	2353 – 32335
	Geometric Mean	1753			4366	4488
Spheroid suspension	Mean ± SD	1929 ± 550	0.3	2.0	5408 ± 4947	5629 ±5653
	Range	1173 – 2001	0.0 – 1.0	1.0 – 4.0	2306 – 27695	2343 – 31335
	Geometric Mean	1855			4574	4672
Geometric Mean Ratio[b]		62.40	---	---	89.63	90.09
Geometric Mean Ratio[c]		66.04			93.91	93.78
90% Log-Transformed CI[b]		55.62 – 70.01	---	---	84.21 – 95.40	84.67 – 95.85
90% Log-Transformed CI[c]		58.86 – 74.08	---	---	88.23 – 99.96	88.14 – 99.78

Abbreviations: C_{max} = peak concentration, t_{lag} = lag time; t_{max} = time peak concentration occurs; AUC_T = area under the concentration-time curve to the last observable concentration (C_T) at time T; AUC = total area under the concentration-time curve ($AUC_T + C_T/\lambda_z$ for single dose; AUC_{0-T} for multiple dose); SD = standard deviation; and CI = confidence interval.

a. Median values reported for t_{lag} and t_{max}.

b. Ratio of tablet to spheroids sprinkled on applesauce.

c. Ratio of tablet to spheroid suspension.

Data source: WR clinical pharmacology department

Pediatric Granules vs. Protonix Delayed-Release Oral Suspension

The bioequivalence between the pediatric granules and the marketed Delayed-Release Oral Suspension was assessed by an open-label, single-dose, randomized, 2-period, 2-sequence crossover, in-patient study in healthy men and women aged 18 to 50 years (n=24; Study 119). Each subject received the test article according to the randomization chart of the study protocol, with 240 mL of room-temperature water after fasting for at least 10 hours. Pantoprazole granules (40 mg) in capsule (Wyeth and Altana formulations) were sprinkled over a teaspoonful of applesauce for administration.

Table 26. Summary of Mean Pharmacokinetic Parameters for Both Treatments (n=24)

Mean ± SD (CV%) [Geometric Mean]	Treatment ALTANA		Treatment WYETH	
C_{max} (ng/mL)	2361 ± 693 [2267]	(29)	2036 ± 705 [1916]	(35)
t_{max} (h)	2.00 (1.50, 4.00)		2.00 (1.50, 5.00)	
$t_{1/2}$ (h)	2.23 ± 1.99 [1.77]	(90)	2.24 ± 1.93 [1.78]	(86)
AUC_T (ng*h/mL)	7821 ± 6983 [5984]	(89)	7597 ± 7135 [5656]	(94)
AUC (ng*h/mL)	8218 ± 7910 [6112]	(96)	7963 ± 8032 [5773]	(101)
t_{lag} (h)	0.50 (0.00, 1.50)		0.50 (0.00, 1.50)	

Table 27. Summary of Bioequivalence Analysis

	C_{max}	AUC_T	AUC
Ratio of Least Square Geometric Means (%)	118	106	106
90% Confidence Interval around Ratio	108-129	100-112	100-113
Probability <80%	<0.001	<0.001	<0.001
Probability >125%	0.153	<0.001	<0.001
Statistical Power	99.1	100.0	100.0

Abbreviations: AUC_T = area under the concentration-time curve to the last observable concentration (C_T) at time T; AUC = area under the concentration-time curve; C_{max} = peak concentration.

Ratio of Delayed-Release Oral Suspension to Pediatric Granules

The mean C_{max}, of pantoprazole with the Protonix Delayed-Release Oral Suspension (=Altana formulation) was about 18% higher compared with the pediatric granules (=Wyeth formulation). For C_{max}, the 90% CI for the ratio of the geometric means between the Altana and the Wyeth granules was from 108% to 129% and did not fall within the bioequivalence window of 80% to 125%.

The mean AUC of pantoprazole with the Altana formulation was 6% higher compared with the Wyeth formulation. For AUC, the 90% CI for the ratio of the geometric means between the Altana and the Wyeth granules was from 100% to 113% and was within the bioequivalence window of 80% to 125%. As such, the Altana and Wyeth treatment formulations were bioequivalent with respect to AUC but not with respect to Cmax.

Reviewer's comments: *The relative BA was not evaluated between 20 mg Protonix tablet and 20 mg pediatric granules. Nonetheless, because two 20 mg tablets are bioequivalent to one 40 mg table and pediatric granule 20 mg is identical in component and compositionally proportional to pediatric granule 40 mg, a relative BA between 20 mg tablet and 20 mg pediatric granules is expected to be the same as to that between 40 mg tablet vs.40 mg pediatric granule.*

The relative BA of granules sprinkled in apple juice was not compared. The chemical stability of pantoprazole in apple juice was comparable to that in apple sauce. Please, see CMC review for detail by Dr. Sharon Kelly. During the clinical trials, pantoprazole was administered sprinkled on either apple juice or apple sauce.

In a dose-ranging study (study 322), 10 mg tablet was used but this tablet was not a commercially available product and no in vivo BA or BE study was conducted for this 10 mg tablet. (b) (4)

The sponsor provided study 322 which was submitted previously for pharmacodynamic comparability between Delayed-Release Oral Suspension and Tablet. This study was previously reviewed by Dr. Abimbola Adebowale. Please, see Clinical Pharmacology Review for supplements to NDA 22-020 dated May 12, 2006 and August 2, 2007.

Nonetheless, this information is not considered adequately supporting the comparability of the marketed tablet and the pediatric granules because 1) it is not a direct comparison between the pediatric granules and the tablet and 2) the pediatric granules is not bioequivalent to the tablet for Cmax and 3) there is no PK comparison between the approved Delayed-Release Oral Suspension and the tablets, that may have been useful to interpret the difference in Cmax between the pediatric granules and tablet.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

High fat meal decreases absorption of pantoprazole from pediatric granules
Note that granules were called spheroids in some studies.

Effect of a high fat meal on the absorption of pantoprazole granule was evaluated in a randomized, open-label, 2-period, 2-sequence crossover, inpatient study in 2 groups of healthy adult subjects (Study 115). Each group was assigned to a specific dose regimen. Doses were administered 30 min after a standard high-fat breakfast following an overnight fast of at least 10 hours by either sprinkled on a teaspoonful of applesauce or by suspended in water with an inactive powder blend.

Regardless of administration methods the high fat meal delayed the absorption of pantoprazole delaying median tmax by 2 hours and decreases mean Cmax by 51-53% and AUC by 28-32% compared to under fasting condition.

Table 28. Pharmacokinetic Parameters for Pantoprazole pediatric granules in Applesauce

Treatment	Statistics	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (h)	AUC (ng.h/mL)
Fasted	Mean ± SD[a]	2471 ± 1226	0.0	2.0	7961± 10393	8429 ± 12131
Condition	Range	795 – 5994	0.0 – 0.5	1.5 – 4.0	2124 – 47430	2152 – 54764
(n=17)	Geometric Mean	2218			5788	5881
Fed	Mean ± SD	1198 ± 595	0.5	4.0	5698 ± 7455	6087 ± 8805
Condition	Range	506 – 2773	0.0 – 2.0	3.0 – 6.0	1983 – 34098	2048 – 39807
(n=17)	Geometric Mean	1078			4190	4295
Geometric Mean Ratio		48.33	---	---	72.25	72.87
90% Log-transformed CI		37.07 – 63.00	---	---	60.51 – 86.28	61.23 – 86.73

a: median values reported for t_{lag} and t_{max}

The effect of a high fat meal was comparable when pantoprazole was taken 30 or 60 minutes before a high fat meal

To determine the optimal timing of meals relative to dose administration of the granules, a randomized, open-label, 3-period, 6-sequence crossover, inpatient study in healthy subjects (study 118) was conducted. Test article was administered under 3 conditions: fasting (after an overnight fast of at least 10 hours); 30 minutes before a standard high-fat breakfast after an overnight fast of at least 10 hours; and 60 minutes before a standard high-fat breakfast after an overnight fast of at least 10 hours.

When pantoprazole was taken 30 or 60 minutes before a high fat meal, only a mild food effect e.g. 16% to 18% decrease in mean AUC and 20% decrease in mean Cmax was observed. The administration of 60 minutes prior to a high fat meal did not significantly improve systemic exposure of pantoprazole compared to administration of 30 minutes prior to a high fat meal. Dose administration of the granules 30 minutes before meals for subsequent trials was suggested based on the results of study 118.

Table 29. Summary of Pharmacokinetic Parameters for Pantoprazole Sodium Delayed-Release Granules in Suspension

Regimen	Statistics	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (ng.h/mL)	AUC (ng.h/mL)
Fasting	Mean ± SD[a]	1876 ± 675	0.25	2.0	4322± 2611	4364± 2625
	Range	967 – 3318	0.0 – 1.0	1.0 – 4.0	1739 – 12483	1877 – 12600
	Geometric Mean	1771			3777	3822
Fed30	Mean ± SD	1584 ± 690	0.25	1.5	3571± 1993	3650± 1976
	Range	481– 2889	0.0 – 1.0	0.5 – 4.0	1596 – 8530	1619– 8630
	Geometric Mean	1418			3149	3245
Fed60	Mean ± SD	1676 ± 786	0.25	1.5	3620± 2124	3679 ±2117
	Range	194 – 2962	0.0 – 1.0	0.5 – 4.0	1230 – 9264	1367 – 9332
	Geometric Mean	1407			3134	3217
Geometric Mean Ratio[b]		80.06	---	---	83.37	84.89
Geometric Mean Ratio[c]		79.45			82.99	84.16
90% Log-transformed CI[b]		63.98 – 100.19	---	---	77.67 – 89.59	79.74 – 90.37
90% Log-transformed CI[c]		63.49 – 99.41	---	---	77.32 – 89.08	79.06 – 89.60

a. Median values reported for t_{lag} and t_{max}.

2.6 Analytical Section

2.6.1 How is pantoprazole is measured in the plasma?

Plasma samples were analyzed for pantoprazole concentrations by a validated LC/MS/MS method except in studies 109, 110 and 114 for which HPLC with UV detector was used for analysis. The assay validation report RPT-54260 titled "Bioanalytical Method Validation Report for the Determination of Pantoprazole in Human Plasma, with Heparin as Anticoagulant, by LC/MS/MS" was submitted.

Briefly, pantoprazole and the added internal standard, (b) (4) are extracted from sodium heparin human plasma using liquid-liquid extraction. This extract is then subjected to reverse phase high performance liquid chromatography using a Aquasil C18 column. Pantoprazole and (b) (4) in the effluent are detected using a PE/Sciex API 365 and API III Plus LC/MS/MS systems in MRM mode. Quantitation is achieved by monitoring the product and precursor ions (384→200 m/z for pantoprazole and 346→198 m/z for (b) (4). The limit of quantitation was established at 10 ng/mL, and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma. In-run quality control was done at 25, 2000 and 4000 ng/ml and the precision and accuracy of the method was acceptable.

For studies 109, 110 and 114, pantoprazole in plasma was analyzed by HPLC method with UV detector: The assay method validation report titled "The method validation of HPLC analysis of pantoprazole in the presence of (b) (4) in human plasma (GTR-30693)" was submitted. The method is linear between 25 and 5000 ng/ml and the precision and accuracy of the method was acceptable.

2.6.3 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

HPLC-UV

Table 30. Precision And Accuracy Of HPLC Method Using A UV Detector For Analysis Of Pantoprazole In Plasma

	Precision (%)	Accuracy (%)
Intra-batch	0.8-7.2	97.8-103.1
Inter-batch	1.9-4.3	98.7-103
LLOQ	12.1	94

HPLC-MS/MS
The limit of quantitation was established at 10 ng/mL, and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma. In-run quality control was done at 25, 2000 and 4000 ng/ml.

The selectivity of the method was also demonstrated by the analysis of blank samples (6 or more lots) and human plasma matrix effect Quality Control (QC) pools and found acceptable. The inter-batch precision and accuracy was 11.81% and 0.32%, respectively at LLOQ meeting acceptance criteria.
2.3.4. How was genotyping conducted?
The accuracy, precision, specificity, and robustness of the methods to detect CYP polymorphisms was reviewed and found by Genomics Reviewer Dr. Li Zhang (please see Appendix 4.4 for more details)

Table 31. Sponsor's Genotyping Method In Each Study

Sample No.	Genotyping Method
Study 109: 24	PCR-RFLP (CYP2C19 *2, *3, *2B, *4, *5, *6, *7, *8)
Study 334: 59	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 333: 67	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 331: 59	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 337: 22	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 117: 4	PCR-RFLP (CYP2C19 *2, *3, *4, *5)

1) PCR-RFLP (PCR- restriction fragment length polymorphism)
A restriction fragment length polymorphism is a variation in the DNA sequence of a genome that can be detected by breaking the DNA into pieces with restriction enzymes and analyzing the size of the resulting fragments by gel electrophoresis. PCR-RFLP is a technique fragmenting a sample of DNA by a restriction enzyme, which can recognize and cut DNA wherever a specific short sequence occurs, in a process known as a restriction digest. The resulting DNA fragments are then separated by length through a process known as gel electrophoresis, and transferred to a membrane via the Southern blot procedure. Hybridization of the membrane to a labeled DNA probe then determines the length of the fragments which are complementary to the probe. A RFLP occurs when the length of a detected fragment varies between individuals. Each fragment length is considered an allele, and can be used in gene
Analysis of RFLP variation is an important tool in genome mapping and genetic disease analysis.

2) ASA-PCR (Allele-Specific Amplification PCR)
This diagnostic or cloning technique is used to identify or utilize single-nucleotide polymorphisms (SNPs). It requires prior knowledge of a DNA sequence, including differences between alleles, and uses primers whose 3' ends encompass the SNP. PCR amplification under stringent conditions is much less efficient in the presence of a mismatch between template and primer, so successful amplification with an SNP-specific primer signals presence of the specific SNP in a sequence [3].

3) Assay Validation: PCR-RFLP assay (CYP3A4*2, *3) and ASA-PCR assay **(**CYP3A4*1B)
i) Intra-Assay Precision
The testing was completed by the three scientists. Upon re-amplification and sample testing in duplicate, all repeat samples passed interpretation and matched with expected results.

ii) Inter-Assay Precision
The final genotypes from each sample run in triplicate, in tests performed by three scientists were identical. All samples amplified successfully during repeat testing.

iii) Accuracy
The genotypes determined by sequencing were identical to the genotypes detected by the PCR-RFLP.

iv) Specificity
The generated sequences aligned with the sequence found in Genbank.

v) Conclusion
The performances of assays resulted in definitive and unambiguous result interpretation on the test samples and controls. The performance of the assays successfully met all pre-determined acceptance criteria. Post validation monitoring procedures are also applied.

Table 32. Summary Of Bioanalytical Assay Validation

	Acceptance Criteria	**Method Performance**
Methodology		
Instrumentation		LC/MS/MS
Extraction		Type 3: Liquid/Liquid, organic transfer, complete dryness
Plasma Volume		100 µL
Specificity		
Matrix		Human Plasma
Anticoagulant		Sodium Heparin
Anticoagulant	See Table 5 for evaluation	Lithium Heparin (Addendum Number 4, Table 5)
Pantoprazole:		
Model		y = a + bx
Weighing		$1/x^2$
Linearity		
Correlation Coefficient (r^2)	(b) (4)	≥ 0.994
% Recovery LLOQ		0.17%
% Recovery above LLOQ		-5.42 to 5.10%
Analytical Range		10.00-5000.00 ng/mL
Sensitivity (LLOQ)		10.00 ng/mL
Accuracy (Among Batch)		0.32% (LLOQ); -0.76 to 4.96% (Above LLOQ)
Accuracy (Within Batch)		-13.65 to 12.13% (LLOQ); -3.15 to 10.93% (Above LLOQ)
Precision (Among Batch)		11.81% (LLOQ); 3.45 to 7.13% (Above LLOQ)
Precision (Within Batch)		4.86 to 9.48% (LLOQ); 2.16 to 7.55% (Above LLOQ)
Stability		
Freeze/Thaw (human plasma; -20 °C/37 °C)		4 cycles – complies
Freeze/Thaw (human plasma; -20 °C/RT)		3 cycles – complies
Freeze/Thaw (human plasma; -70 °C/37 °C)		3 cycles - complies
Room Temperature (plasma; 25 °C)		30 hours (December 2006 Addendum)
Autosampler (extract; 25 °C)		102.77 hours for pantoprazole
Refrigerator (extract; 4 °C)		103.98 hours for pantoprazole
Long-Term (plasma; -20 °C)		59 months (V1265 P1 Sep 2003 Addendum)
Long-Term (plasma; -70 °C)		29 months (V1265P1 Dec 1999 Addendum)
Whole Batch Reinjection Integrity		291.65 hours
Individual Sample Reinjection Stability		10.32 hours
Dilution (2x, 4x, and 10x)		Complies (4x and 10x Addendum Number 4, Table 7)
Matrix Effect		Complies
Extraction Recovery (Pantoprazole)		~ 87%
Extraction Recovery (b) (4) IS)		~ 90%

	Acceptance Criteria	**Method Performance**
Solution Stability		
Pantoprazole		
100 µg/mL primary (4 °C)	(b) (4)	6 months (V1879P1)
100 µg/mL primary (6 hour, 25 °C)		Complies (V1879P1)
(b) (4) Internal Standard; IS)		
100 µg/mL primary (4 °C)		9 months (V1292P1)
100 µg/mL primary (6 hour, 25 °C)		Complies (V1879P1)
Working Internal Standard (4 °C)		4 months (V2191P1)
Working Internal Standard (6 hour, 25 °C)		Complies, (V2191P1)
Incurred Sample Analysis	See Table 6 for evaluation	Completed (Addendum Number 4, Table 6)

3 Detailed Labeling Recommendations

(b) (4)

FOLLOWING THIS PAGE, 30 PAGES WITHHELD IN FULL - DRAFT LABELING - B4

4.2. Individual Study Review

Study 117

A study of the pharmacokinetics, safety, and tolerability of intravenous doses of pantoprazole in hospitalized pediatric patients

Study design

This was an open-label, randomized, inpatient study of a single IV dose of pantoprazole administered to pediatric patients at least 1 year but less than 2 years of age. Patients were randomly assigned to receive either pantoprazole intravenous 0.8 mg/kg infused over 15 minutes or pantoprazole IV 1.6 mg/kg infused over 15 minutes.

PK sampling

Blood samples for PK analysis were collected at 2 hours before test article administration and at 0.25, 0.50, 0.75, 1, 1.5, 2, 4, 8, and 12 hours after the start of the infusion

Bioanalytical assay and Genotyping assay

Plasma samples were analyzed for pantoprazole concentrations by a validated LC-MS-MS method. The limit of quantitation was 10 ng/mL and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma.

	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte, ng/mL	Conc.	CV %	Bias %	Conc.	CV %	Bias %	Conc.	CV %	Bias %
Pantoprazole	25	7.13	1.49	2500	2.10	2.19	3750	3.24	3.92

Abbreviations: conc. = concentration; CV = coefficient of variation; QC = quality control sample.

Genotype assessments of whole blood were performed using polymerase chain reaction (PCR) and restriction-fragment analysis

Reviewer's comment: *According to the protocol, buccal cells were supposed to be collected for pharmacogenomics analysis.*

Patient disposition

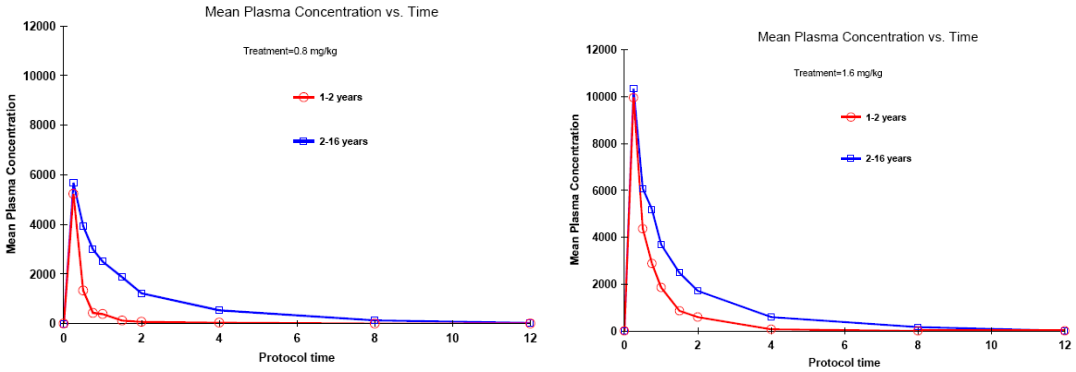
Two (2) patients were diagnosed with gastrointestinal reflux, 1 patient had diarrhea and vomiting, and 1 patient had normal gastrointestinal function at study entry. Two patients aged 12 and 13 months old were given 0.8mg/kg and two patients aged 17 months old were given 1.6 mg/kg.

PK results

Individual Pantoprazole Pharmacokinetic Parameters by Dose Group (1-2 yr)

Patient	Dose mg/kg	Age (month)	BW (kg)	Cmax (ng/ml)	Tmax (h)	$T_{1/2}$ (h)	AUCinf (ng h/ml)	CL (L/h/kg)	Vss (L/kg)
1	0.8	13	7.6	5613	0.25	1.12	2223	0.36	0.22
21		12	13.2	4846	0.25	2.54	1761	0.47	0.4
2	1.6	17	11.3	11355	0.25	0.38	4362	0.37	0.15
4		17	8.5	8555	0.25	0.75	7553	0.21	0.20

Mean plot of plasma concentration-time profiles following administration of 0.8 mg/kg intravenous pantoprazole in pediatric patients aged 1-2 years old



Pharmacogenomics

The genotype of all 4 patients in this study was consistent with an extensive metabolizer phenotype for CYP2C19.

Sponsor's conclusion

The Cmax and AUC of pantoprazole increased with dose from 0.8 mg/kg to 1.6 mg/kg pantoprazole. Pantoprazole sodium given as a 15-minute infusion was well tolerated by hospitalized pediatric patients aged 1 to 2 years.

Study 110

An initial study of the harmacokinetics, pharmacodynamics, safety, and tolerability of intravenous doses of pantoprazole in hospitalized pediatric patients:

Study Design

This was an open-label, single-dose, randomized, age-stratified, parallel-group study in hospitalized pediatric patients aged 2 to 16 years, inclusive, who could benefit from acid suppression therapy. A second dose of IV pantoprazole was permitted if the treating investigator determined that further acid suppression therapy was needed and if the first dose had been well tolerated.

Patient disposition

A total of 19 patients (11 males, 8 females) were enrolled in this study and stratified by age into groups ranging in age from 2 to 4 years (6 patients), 5 to 10 years (6 patients including 1 patient aged 5 years and 1 patient aged 7 years), and 11 to 16 years (7 patients including 2 patients aged 11 years, 1 patient aged 12 years, and 1 patient aged 13 years). Sixteen (16) of the 19 patients completed the study, 8 in each dose group. The overall study population was predominately white (52.6%, 10 of 19 patients) and included 11 male patients (57.9%) than 8 female patients (42.1%).

PK sampling and pH monitoring flow chart

Study procedure	Predose[a]			Postdose[a]														
	-0.5	-0.33	-0.16	0	0.25	0.5	0.75	1	1.25	1.5	1.75	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Gastric pH	X	X	X	X	X	X	X	X	X	X	X	X	--	--	--	X	--	--
Blood sample collection for pantoprazole levels (1 mL)	--	X	--	--	X	X	X	X	--	X	--	X	--	--	--	X	--	--

	Postdose[a]																		
Study procedure	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	10.5	11.0	11.5	12.0	14.0	16.0	18.0	20.0	22.0	24.0
Gastric pH	--	X	--	--	--	X	--	--	--	X	--	--	--	X[a]	X	X	X			
Blood sample collection for pantoprazole levels (1 mL)	--	--	--	--	--	X	--	--	--	--	--	--	--	X	--	--				

a In hours relative to the start of IV pantoprazole administration.

At each pH monitoring time point, gastric pH was assessed 3 times, and an average of the 3 values was documented in the CRF.

Bioanalytical assay method and genotyping

Plasma samples were analyzed for pantoprazole concentration by a high-performance liquid-chromatography (HPLC) method with ultraviolet detection following a solid phase extraction. The limit of quantitation was 25 ng/mL and the assay was linear up to 5000 ng/mL using 0.5 mL of human plasma.

Bioanalytical summary of pantoprazole

	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte, ng/mL	Conc.	CV %	Bias %	Conc.	CV %	Bias %	Conc.	CV %	Bias %
Pantoprazole	60	10.0	2.3	2000	5.0	6.0	4000	6.0	6.5

Abbreviations: conc = concentration; CV = coefficient of variation; QC = quality control sample

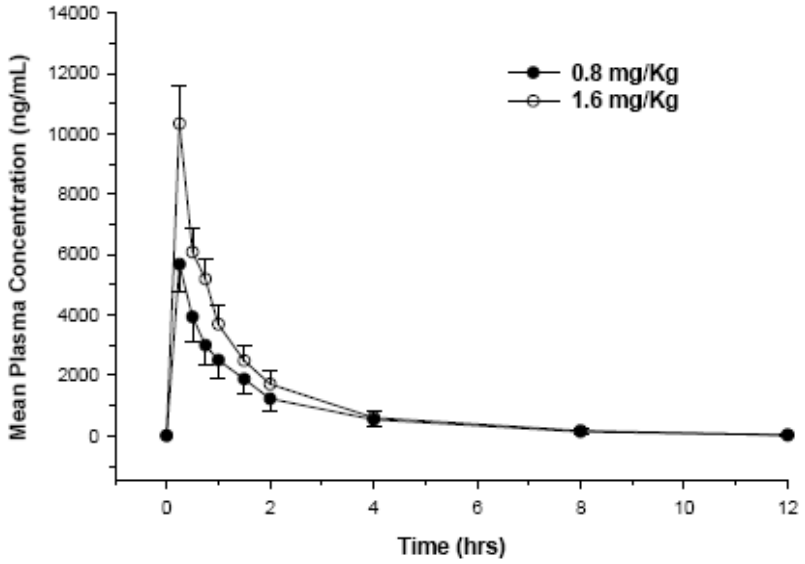
Genotype assessments of whole blood were made by means of polymerase chain reaction (PCR) and restriction-fragment analysis

RESULTS

Genotype

The genotype of the patients in this study was consistent with an extensive metabolizer phenotype for CYP2C19.

MEAN (SE) PLASMA CONCENTRATION-TIME PROFILE OF IV PANTOPRAZOLE AT 0.8 AND 1.6 mg/kg IN PEDIATRIC PATIENTS AGED 2 TO 16 YEARS.

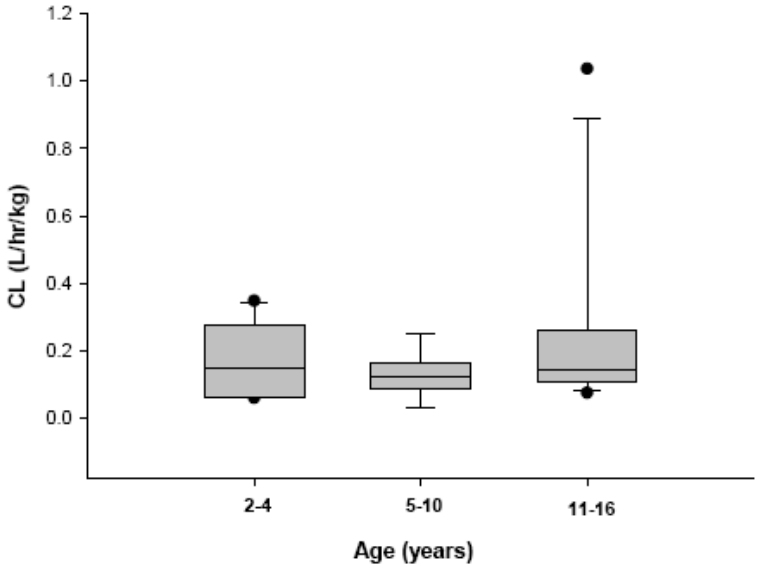


Summary of PK parameters of IV pantoprazole by dose in pediatric patients aged 2 to 16 years

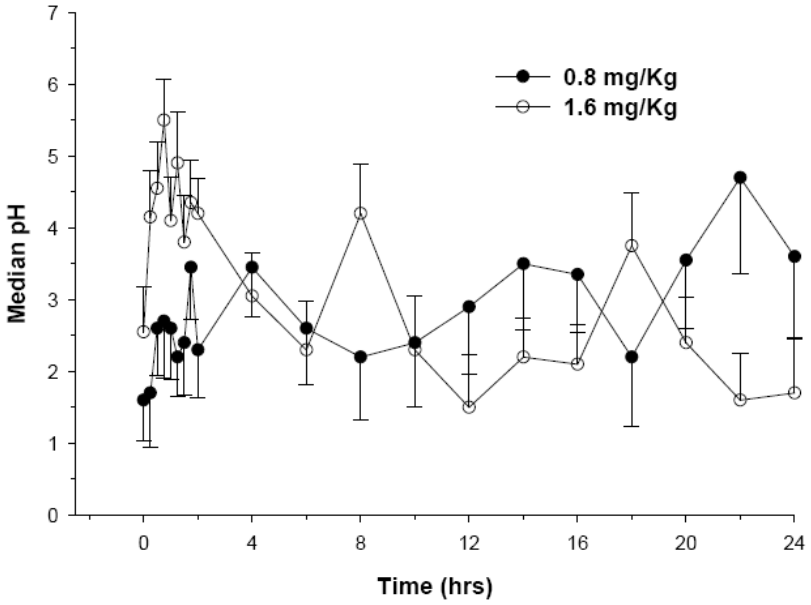
Dose	Statistic	C_{max} (ng/mL)	AUC_T (ng•h/mL)	AUC_∞ (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h/kg)	V_{ss} (L/kg)	MRT (h)
0.8 mg/kg	N	9	9	9	9	9	9	9
	Mean	5746.17	8268.92	8449.87	1.23	0.16	0.20	1.61
	SD	2686.90	7029.52	7223.29	0.67	0.11	0.09	0.96
	SE	895.63	2343.17	2407.76	0.22	0.04	0.03	0.32
	Minimum	2506.44	2082.03	2288.35	0.49	0.03	0.08	0.76
	Median	6606.91	6449.57	6540.92	0.97	0.12	0.19	1.37
	Maximum	8910.54	24345.65	25145.84	2.45	0.35	0.33	3.64
	CV,%	46.76	85.01	85.48	54.87	71.42	48.26	59.30
	Geometric mean	5124.78	6175.72	6338.29	1.08	0.12	0.18	1.42
1.6 mg/kg	N	9	9	9	9	9	9	9
	Mean	10332.50	11372.26	11728.93	1.21	0.24	0.25	1.48
	SD	3739.07	6452.68	6725.56	0.69	0.30	0.18	0.85
	SE	1246.36	2150.89	2241.85	0.23	0.10	0.06	0.28
	Minimum	2011.22	1457.24	1537.85	0.44	0.06	0.14	0.55
	Median	11928.49	11081.67	11124.13	1.12	0.14	0.17	1.33
	Maximum	14093.41	24062.17	25395.16	2.61	1.04	0.69	3.16
	CV,%	36.19	56.74	57.34	56.46	124.12	70.43	57.78
	Geometric mean	9237.86	9220.93	9533.31	1.05	0.17	0.22	1.28

Abbreviations: SD=standard deviation; SE=standard error of the mean; CV=coefficient of variation; h=hour; C_{max}=peak plasma concentration; AUC_T=area under the plasma concentration-time curve to the last observable concentration at time T; AUC_∞=area under the plasma concentration-time curves from time 0 to infinity; $t_{1/2}$=terminal-phase elimination half-life; CL=clearance; V_{ss}=steady-state volume of distribution; MRT=mean residence time.

Reviewer's comment: ***The geometric mean AUCi was 5.4 µg·h/mL and Cmax was 5.5 µg·h/mL following in adult*** *extensive metabolizers receiving a 40 mg dose (approximately 0.6 mg/kg for 70 kg body weight) of PROTONIX I.V. (Protonix label).*



Median (SE) pH-time profile of IV pantoprazole in pediatric patients aged 2 to 16 years



Sponsor's Conclusion

Intravenous pantoprazole at both doses evaluated was well tolerated by hospitalized pediatric patients aged 2 to 16 years. The pharmacokinetics of pantoprazole were similar in the age groups 2 to 4 years, 5 to 10 years, and 11 to 16 years. The mean Cmax and AUC values increased with dose from 0.8 mg/kg to 1.6 mg/kg. No trends toward a change with age were observed in the dose-independent PK parameters (CL and Vss) normalized by body weight in pediatric patients aged 2 to 16 years. The values of CL and $t_{1/2}$ of IV pantoprazole in these pediatric patients were similar to those previously observed with IV pantoprazole (40 mg) in healthy adult subjects. The safety and PK profiles of pantoprazole from this study should provide a basis for dose selection for future studies in pediatric patients with similar ages.

Study 109

Pharmacokinetics, safety, and tolerability of a single oral dose of pantoprazole in children:

Study design

This was an open-label, single-dose, randomized, age-stratified, parallel-group study of 2 dose levels in children aged 5 to 16 years who could benefit from acid suppression therapy. Two (2) age groups (5 to 10 years and 11 to 16 years) of 12 subjects each were studied. Within each age group, subjects were randomly assigned on a 1:1 basis to receive a single dose of either pantoprazole 20 mg or pantoprazole 40 mg (2 x 20 mg)

Rationale for dose selection

The pharmacokinetics of pantoprazole in adults is dose-proportional and the resulting pharmacodynamic (PD) effect is related to serum concentration. PK/PD modeling suggests that the area under the concentration-time curve (AUC) is the best predictor for the lowering of acid output in patients. Because the mechanism of proton pump inhibition and the concentrations-effect relationship is the same for all age groups, if similar therapeutic exposure is achieved for the pediatric and adult populations, the safety and efficacy in the pediatric population should match those observed in adults. Based on the

pharmacokinetic profile of pantoprazole, the doses selected for this study, 20 mg and 40 mg once daily, should produce a therapeutic exposure in pediatric subjects similar to that seen in adults.

Patient disposition

A total of 24 patients (16 males, 8 females) were enrolled in this study and stratified by age into groups ranging in age from 5 to 10 years (12 patients), and 11 to 16 years (12 patients). There was one 11-year old in the 11- to 16-year group. All patients were then randomly assigned to receive treatment with oral pantoprazole at a dose of 20 mg (12 patients) or 40 mg (12 patients). All patients completed the study.

Bioanalytical analysis method and genotype analysis

Plasma samples were analyzed for pantoprazole concentration by a high-performance liquid-chromatography method with ultraviolet detection following a solid phase extraction. The limit of quantitation is 25 ng/L and the assay is linear up to 5000 mg/L using 0.5 mL of human plasma.

Summary of bioanalytical assay

	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte, ng/mL	Conc.	CV %	Bias %	Conc.	CV %	Bias %	Conc.	CV %	Bias %
Pantoprazole	60	8.5	1.8	2000	7.1	4.3	4000	5.3	0.0

Abbreviations: conc. = concentration; CV = coefficient of variation; QC = quality control sample.

Genotype analysis was performed on whole blood using polymerase chain reaction (PCR) and restriction-fragment analysis. The PCR reactions used polynucleotide primers for the 7 known allelic variants of CYP2C19, none of which have enzymatic activity.

PK sampling

Blood samples for PK analysis were collected at pre- and 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 7, 8, 10 and 12 hours post-dose.

RESTULTS

Pharmacokinetic Parameters For Pantoprazole

Group	Statistic	C_{max} (mg/L)	t_{max} (h)	$t_{1/2}$ (h)	AUC (mg • h/L)	CL/F (L/h/kg)	Vz/F (L/kg)
20 mg	Mean ± SD	2.38 ± 2.07	2.0 ± 0.6	0.55 ± 0.10	2.22 ± 1.44	0.37 ± 0.29	0.27 ± 0.14
Age 5 to 10	% CV	87.1	31.6	18.9	64.9	76.5	51.1
	Geometric mean	1.74	1.9	0.54	1.84	0.31	0.25
	Range	0.61-6.11	1.5-3.0	0.38-0.71	0.60-4.73	0.18-0.94	0.14-0.52
40 mg	Mean ± SD	5.03 ± 1.98	2.7 ± 0.9	1.40 ± 1.96	11.9 ± 15.3	0.27 ± 0.17	0.27 ± 0.10
Age 5 to 10	% CV	39.3	32.8	140	129	64.2	35.6
	Geometric mean	4.66	2.5	0.86	7.62	0.21	0.26
	Range	2.16-7.72	1.5-4.0	0.55-5.41	3.09-43.0	0.04-0.56	0.19-0.45
20 mg	Mean ± SD	1.95 ± 1.31	2.6 ± 0.7	2.41 ± 2.78	7.34 ± 9.05	0.18 ± 0.16	0.19 ± 0.05
Age 11 to 16	% CV	67.2	28.5	115	123	90.1	25.1
	Geometric mean	1.68	2.5	1.27	3.55	0.10	0.18
	Range	0.88-4.49	1.5-3.5	0.39-6.52	1.09-21.9	0.02-0.44	0.14-0.26
40 mg	Mean ± SD	2.53 ± 0.69	2.9 ± 0.4	0.72 ± 0.3	3.34 ± 1.01	0.25 ± 0.15	0.22 ± 0.08
Age 11 to 16	% CV	27.1	12.9	41.5	30.1	59.2	34.2
	Geometric mean	2.45	2.9	0.67	3.20	0.22	0.21
	Range	1.50-3.47	2.5-3.5	0.42-1.20	1.81-4.89	0.11-0.50	0.17-0.37

Abbreviations: Cmax= peak concentration; tmax= time peak concentration occurs; t1/2= terminal-phase elimination half-life (0.693/λz); AUC= total area under the concentration-time curve; CL/F= apparent oral dose clearance (dose/AUC); Vz/F= apparent volume of distribution; SD=standard deviation; CV = coefficient of variation.

a. n=6 for each group.

As indicated by a $t_{1/2}$ greater than 3.5 hours, 3 subjects have the slow metabolizer phenotype for CYP2C19. Of these three, two subjects were confirmed as CYP2C19 *2*2 carriers and one subject was genotyped as a CYP2C19 *1*2 carrier. The presence of these slow metabolizers caused a large intersubject variability in the AUC and $t_{1/2}$ values for these 2 groups

***Reviewer's comment**: The dose-normalized AUC significantly varied depending on CYP2C19 genotypes. Especially for CYP2C19 *2*2 carriers, the dose-normalized AUC was greater than 6 folds higher than extensive metabolizers e.g. CYP2C19*1*1 carriers and intermediate metabolizers e.g. CYP2C19 *1*2 carriers. One intermediate metabolizer was genotyped as *1*4 carrier. The AUCt was used for poor metabolizers for a comparison since accurate AUCinf could not be derived because of sustained plasma concentrations beyond blood sampling period.*

Dose-normalized AUC for patients with CYP2C19 genetic variants (Table was generated by the reviewer)

Genotype	AUC/Dose (h/L)	CL/F (L/h/kg)
*1*1(n=16)	0.1 ± 0.05	0.34 ± 0.20
*1*X (n=6) [1]	0.29 ± 0.40 (0.13 ± 0.04) [2]	0.16 ± 0.10 (0.18± 0.08) [2]
*2*2 (n=2)	0.92 (0.63[3])	0.03

[1] n=5:CYP2C19 *1*2; .n=1: CYP2C19*1*4
[2] Without one subject (*1*2) with poor metabolizer phenotype
[3]AUCt/Dose

Sponsor's Conclusion

The pharmacokinetics of pantoprazole in children between 5 and 16 years of age are similar to those in healthy adults. In general, pantoprazole was well tolerated. The findings in this study support the use of 20-mg and 40-mg doses of pantoprazole in pediatric patients aged 5 to 16 in future clinical trials.

Study 118

An open-label, randomized, 3-period crossover study to determine the effect of a high-fat meal on the relative bioavailability of a single 40 mg dose of pantoprazole sodium enteric-coated spheroids administered orally to healthy subjects

Reviewer's comments:

Note that the terms spheriods and granules were used interchangeably in the study report. The granules were administered as suspended in water with an inactive powder blend.

Study design

This was a randomized, open-label, 3-period, 6-sequence crossover, inpatient study in healthy subjects. Test article was administered under 3 conditions: fasting (after an overnight fast of at least 10 hours); 30 minutes before a standard high-fat breakfast after an overnight fast of at least 10 hours; and 60 minutes before a standard high-fat breakfast after an overnight fast of at least 10 hours.

Treatment

The high-fat meal was the standard US Food and Drug Administration (FDA) breakfast and consisted of 2 eggs fried in butter, 2 pieces of bacon, 2 pieces of toast with butter, 4 ounces of hashed brown potatoes cooked in butter, and 8 ounces of whole milk. All subjects were to fast during the first 4 hours after test

article administration. Water was not permitted in the 2 hours before and 4 hours after dose administration. Beginning 4 hours after test article administration, standardized medium-fat meals and snacks was served throughout each inpatient period. Identical meals (other than the high-fat breakfast) were consumed on study day 1 of each study period. Pantoprazole sodium enteric-coated granules were administered orally as suspended in water with inactive powder blend on study day 1 of each study period at approximately 0800 hours with 240 mL of room-temperature water.

PK sampling

Blood samples for PK analysis were collected at -2 0 0.25 0.5 1 1.5 2 2.5 3 4 5 6 8 10 12 and 16.

Bioanalytical assay method

The plasma samples were analyzed for pantoprazole by a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay. The lower limit of quantitation (LLOQ) is 10 ng/mL in serum and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma.

Summary of bioanalytical assay

	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte, ng/mL	**Conc.**	**CV %**	**Bias %**	**Conc.**	**CV %**	**Bias %**	**Conc.**	**CV %**	**Bias %**
Pantoprazole	25	5.26	-2.95	2500	4.16	-2.09	3750	3.96	-4.60

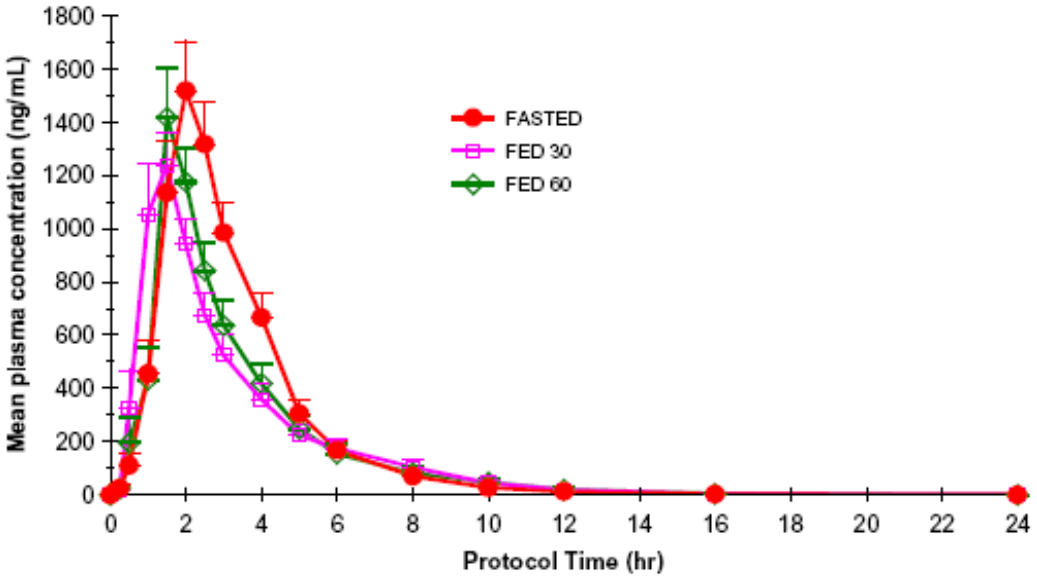
Abbreviations: conc. = concentration; CV = coefficient of variation; QC = quality control sample.

Subject disposition

Twenty four subjects were enrolled and completed the study. Subjects in this study were predominantly black (14; 58.3%) and men (100%).

PK results

Mean (SE) Plasma Concentration Time Profiles Following Administration of 40 mg Pantoprazole Sodium Granules in Suspension to Healthy Adult Subjects (N=24)



Summary of Pharmacokinetic Parameters for Pantoprazole Sodium Granules in Suspension

Regimen	Statistics	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (ng.h/mL)	AUC (ng.h/mL)
Fasting	Mean ± SD[a]	1876 ± 675	0.25	2.0	4322± 2611	4364± 2625
	Range	967 – 3318	0.0 – 1.0	1.0 – 4.0	1739 – 12483	1877 – 12600
	Geometric Mean	1771			3777	3822
Fed30	Mean ± SD	1584 ± 690	0.25	1.5	3571± 1993	3650± 1976
	Range	481– 2889	0.0 – 1.0	0.5 – 4.0	1596 – 8530	1619– 8630
	Geometric Mean	1418			3149	3245
Fed60	Mean ± SD	1676 ± 786	0.25	1.5	3620± 2124	3679 ±2117
	Range	194 – 2962	0.0 – 1.0	0.5 – 4.0	1230 – 9264	1367 – 9332
	Geometric Mean	1407			3134	3217
Geometric Mean Ratio[b]		80.06	---	---	83.37	84.89
Geometric Mean Ratio[c]		79.45			82.99	84.16
90% Log-transformed CI[b]		63.98 – 100.19	---	---	77.67 – 89.59	79.74 – 90.37
90% Log-transformed CI[c]		63.49 – 99.41	---	---	77.32 – 89.08	79.06 – 89.60

a. Median values reported for t_{lag} and t_{max}.

[a] Median values reported for t_{lag} and t_{max}
[b] ratio of Fed30 to fasting
[c] ratio of Fed60 to fasting

When granules were administered 30 min or 60 min before a high fat meal, the median tmax was similar between under fasting condition and fed condition regardless of timing of administration. The mean C_{max} and AUC for the granules in suspension were lower under fed condition than under fasting condition.

. The mean AUC values was about 16% lower and mean Cmax was about 20% lower under the fed condition than under fasting condition. On the other hand, the systemic exposure of pantoprazole was similar when it was administered 60 minutes before a high fat meal to when 30 minutes before a high fat meal. Therefore administering the granules 30 minutes before the meal will avoid majority of the food effect and administering the granules 60 minutes before a meal does not have any additional advantage.

Study 114

A randomized, 3-period, crossover; relative bioavailability study comparing a new pantoprazole enteric-coated spheroid formulation, administered in 2 different dose regimens, and the currently marketed tablet formulation of pantoprazole in healthy adult subjects

Study design

This was a randomized, open-label, 3-period, crossover study. Single oral doses of test article were administered to healthy subjects after an overnight fast of at least 10 hours on study day 1 in each of 3 periods. The test article was prepared according to instructions in the protocol and was dispensed as either 40 mg of pantoprazole sprinkled on a tablespoonful of applesauce (A), suspended by using an inactive powder blend and water (B), or as the marketed 40 mg pantoprazole tablet (C).

Each subject was administered a single oral dose of test article (40-mg dose of pantoprazole) on study day 1 in each of 3 periods at approximately 8:00 AM with 240 mL of room-temperature water and after an overnight fast of at least 10 hours. Each dose was separated by 72 hours.
Blood samples were to be collected for determination of pantoprazole concentrations at pre- and at 0.33, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after test article administration.

Bioanalytical assay method
Plasma samples were analyzed for pantoprazole concentrations by a high-performance liquid chromatography (HPLC) method with ultraviolet detection after a solid phase extraction. The limit of quantitation was 25 ng/mL and the assay was linear up to 5000 ng/mL using 0.5 mL of human plasma.

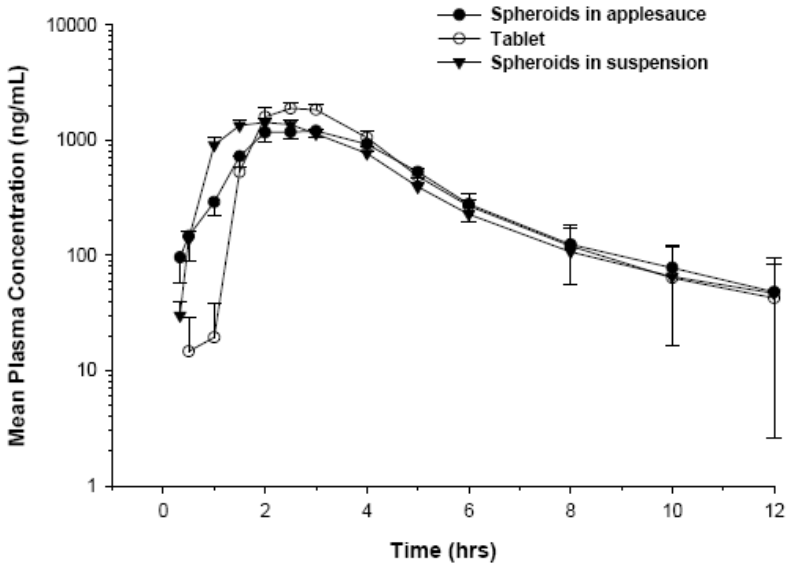
Analytical Summary of Pantoprazole

	QC 1			QC 2			QC 3		
Analyte, ng/mL	Conc.	CV %	Bias %	Conc.	CV %	Bias %	Conc.	CV %	Bias %
Pantoprazole	75	5.65	2.46	2000	3.13	4.33	4000	3.87	2.11

Abbreviations: conc. = concentration; CV = coefficient of variation; QC = quality control sample.

PK results

Mean (SE) Plasma Concentration Time Profiles Following Administration of 40 mg of Pantoprazole to Healthy Adult Subjects (N=24)



Reviewer's comment: *The granules suspended in water with an inactive powder blend were used only in infants younger than 1 year old and the indication for this age group is not pursued for lack of efficacy. The granules suspension with an inactive powder blend* (b) (4) .

The mean AUC for the spheroids, sprinkled in applesauce or administered as a suspension was similar to that for the tablet. For AUC, the 90% CIs for the ratio of the geometric means of the spheroids sprinkled on applesauce to the tablet were from 84.67 to 95.85 and that of the spheroid suspension to the tablet were from 88.14 to 99.78. These 90% CIs for AUC were within the bioequivalence window of 80% to 125%.

Pharmacokinetic Parameters for Pantoprazole

Formulation	Statistic	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (h)	AUC (ng.h/mL)
Tablet	Mean ± SD[a]	2958 ± 927	1.5	2.5	5810± 5287	6073 ± 6146
	Range	1204 – 4826	0.3 – 3.0	1.5 – 4.0	1559 – 29544	1592 – 33978
	Geometric Mean	2810			4870	4982
Spheroids sprinkled on applesauce	Mean ± SD	1865 ± 708	0.2	2.5	5168 ± 4891	5451 ± 5845
	Range	1022 – 3376	0.0 – 2.0	1.5 – 5.0	2305 – 27450	2353 – 32335
	Geometric Mean	1753			4366	4488
Spheroid suspension	Mean ± SD	1929 ± 550	0.3	2.0	5408 ± 4947	5629 ±5653
	Range	1173 – 2001	0.0 – 1.0	1.0 – 4.0	2306 – 27695	2343 – 31335
	Geometric Mean	1855			4574	4672
Geometric Mean Ratio[b]		62.40	---	---	89.63	90.09
Geometric Mean Ratio[c]		66.04			93.91	93.78
90% Log-Transformed CI[b]		55.62 – 70.01	---	---	84.21 – 95.40	84.67 – 95.85
90% Log-Transformed CI[c]		58.86 – 74.08	---	---	88.23 – 99.96	88.14 – 99.78

Abbreviations: C_{max} = peak concentration, t_{lag} = lag time; t_{max} = time peak concentration occurs; AUC_T = area under the concentration-time curve to the last observable concentration (C_T) at time T; AUC = total area under the concentration-time curve ($AUC_T + C_T/\lambda_z$ for single dose; AUC_{0-T} for multiple dose); SD = standard deviation; and CI = confidence interval.

a. Median values reported for t_{lag} and t_{max}.

b. Ratio of tablet to spheroids sprinkled on applesauce.

c. Ratio of tablet to spheroid suspension.

Data source: WR clinical pharmacology department

The mean Cmax was for the spheroids, sprinkled in applesauce or administered as a suspension lower than that of the tablet. For Cmax the 90% CI for the ratio of the geometric means of the spheroids sprinkled on applesauce to the tablet was from 55.62 to 70.01, and that of the spheroid suspension to the tablet was from 58.86 to 74.08. Therefore, both spheroid regimens (sprinkled on applesauce and as suspension) were not within the bioequivalence window with respect to Cmax.

The sponsor explained that the lower Cmax with the spheroid formulation may be because some spheroids can be in the stomach and some in the small intestine, resulting from multiple waves of gastric emptying. On the other hand, once the tablet reaches the small intestine, it dissolves after a lag time and the drug is released over a short time interval.

Reviewer's comments: *A lag time in plasma PK was observed with granules in some pediatric patients.*

Study 119

An open-label, single-dose, randomized, 2-period, crossover, bioequivalence study between the Altana formulation (=Protonix Delayed Release Oral Suspension 40 mg) of pantoprazole delayed-release granules and the Wyeth formulation (=Pediatric formulation) of pantoprazole delayed-release granules in healthy subjects

Note: The Altana formulation is the marketed Protonix® Delayed-Release Oral Suspension 40 mg and the Wyeth formulation is the pediatric granules used in the pediatric program

Study design
This was an open-label, single-dose, randomized, 2-period, 2-sequence crossover, in-patient study in healthy men and women aged 18 to 50 years. Each subject received the test article according to the randomization chart of the study protocol, with 240 mL of room-temperature water after fasting for at least 10 hours. Pantoprazole delayed-release granules (40 mg) in capsule (Wyeth and Altana formulations) were sprinkled over a teaspoonful of applesauce for oral administration. Subjects were to ingest the entire teaspoon of applesauce with the 40-mg pantoprazole delayed release granules at once.
Water was permitted except during the 2 hours before and 2 hours after test article administration. Standard medium-fat meals were served according to the clinic's schedule, starting 4 hours after test article administration.

Blood samples (5 mL) were collected for determination of pantoprazole concentrations at the following times: on day 1, pre-dose (time 0) which may have been collected within 2 hours before test article administration and at 0.33, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after test article administration.

Subject disposition
All subjects (100%) enrolled in this study were males. The majority of the subjects were non-Hispanic (83.33%) and 54.17% were black.

Bioanalytical assay method
Plasma samples were analyzed for pantoprazole concentrations by a validated LC/MS/MS method. The limit of quantitation was 10 ng/mL and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma.

Analytical Summary of Pantoprazole

	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte, ng/mL	Conc.	CV %	Bias %	Conc.	CV %	Bias %	Conc.	CV %	Bias %
Pantoprazole	25	4.1	0.4	2000	2.6	-3.7	4000	2.6	-10.1

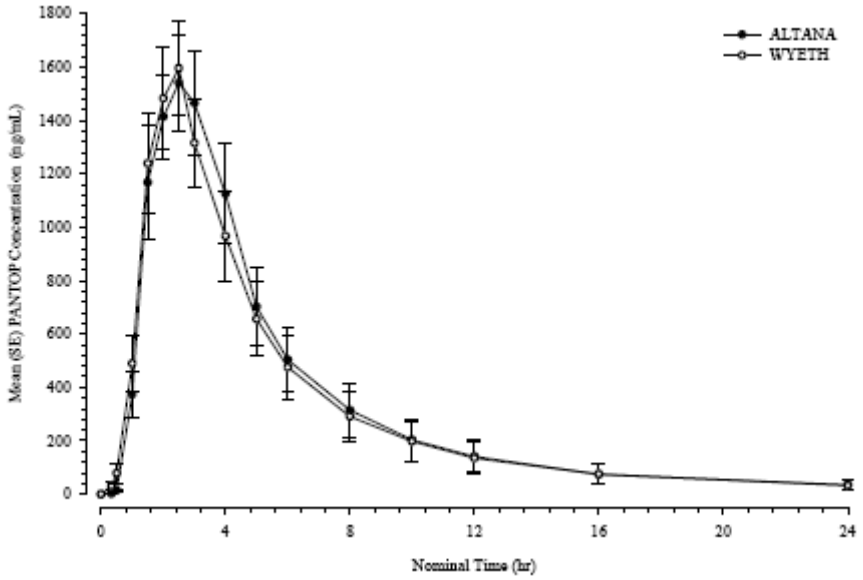
Abbreviations: conc. = concentration; CV = coefficient of variation; QC = quality control sample.

PK results
The Altana and Wyeth treatment formulations were bioequivalent with respect to AUC but not bioequivalent with respect to Cmax.

The mean C_{max}, of pantoprazole with the Altana formulation was about 18% higher compared with Wyeth formulation. For C_{max}, the 90% CI for the ratio of the geometric means between the Altana and the Wyeth granules was from 108% to 129% and did not fall within the bioequivalence window of 80% to 125%.
The mean AUC of pantoprazole with the Altana formulation was about 6% higher compared with the Wyeth formulation. For AUC, the 90% CI for the ratio of the geometric means between the Altana and the Wyeth granules was from 100% to 113% and was within the bioequivalence window of 80% to 125%.

Pharmacokinetic results for three subjects (6, 16 and 19) showed relatively high AUC values with an elimination half-life greater than 6 hours. These data are consistent with the presence of slow metabolizer phenotype for cytochrome P-450 (CYP) 2C19; nonetheless, genotyping was not conducted.

Mean (SE) Plasma Concentration-Time Profiles After Administration of Pantoprazole Sodium Enteric Coated Granules 40 mg to Healthy Adult Subjects (n=24)



- Altlana: Marketed delayed release granules
- Wyeth: Pediatric delayed release granules

Summary of Mean Pharmacokinetic Parameters for Both Treatments

Mean ± SD (CV%) [Geometric Mean]	Treatment			
	ALTANA		WYETH	
C_{max} (ng/mL)	2361 ± 693 [2267]	(29)	2036 ± 705 [1916]	(35)
t_{max} (h)	2.00 (1.50, 4.00)		2.00 (1.50, 5.00)	
$t_{1/2}$ (h)	2.23 ± 1.99 [1.77]	(90)	2.24 ± 1.93 [1.78]	(86)
AUC_T (ng*h/mL)	7821 ± 6983 [5984]	(89)	7597 ± 7135 [5656]	(94)
AUC (ng*h/mL)	8218 ± 7910 [6112]	(96)	7963 ± 8032 [5773]	(101)
t_{lag} (h)	0.50 (0.00, 1.50)		0.50 (0.00, 1.50)	

Summary of Bioequivalence Analysis

	C_{max}	AUC_T	AUC
Ratio of Least Square Geometric Means (%)	118	106	106
90% Confidence Interval around Ratio	108-129	100-112	100-113
Probability <80%	<0.001	<0.001	<0.001
Probability >125%	0.153	<0.001	<0.001
Statistical Power	99.1	100.0	100.0

Abbreviations: AUC_T = area under the concentration-time curve to the last observable concentration (C_T) at time T; AUC = area under the concentration-time curve; C_{max} = peak concentration.

Reviewer's comments: *The AUC and Cmax of slow metabolizers was about 3-6 fold and 1.5-2 fold greater than the geometric mean AUC and the Cmax, respectively.*

Formulation	Altana			Wyeth		
Subject	Cmax	AUCi	$T_{1/2}$	Cmax	AUCi	$T_{1/2}$
6	3266	27808	7.49	2870	27446	7.03
16	3380	22346	6.28	3220	18995	4.81
19	4065	31195	7.74	3800	33300	8.03

Study 115

An open-label, randomized, 2-period crossover study to determine the effect of a high-fat meal on the relative bioavailability of a single 40 mg dose of pantoprazole sodium enteric-coated spheroids administered orally to healthy subjects using two dose regimens.

Note that the term "spheroids" was used for "granules" in this study.

Study design

This was a randomized, open-label, 2-period, 2-sequence crossover, inpatient study in 2 groups of healthy subjects. Each group was assigned to a specific dose regimen (spheroids sprinkled on a teaspoonful of applesauce or suspended in water with an inactive powder blend). Doses were administered with 240 mL of room-temperature, after an overnight fast of at least 10 hours, to subjects who were in the fasting state or immediately after the completion of a standard high-fat breakfast water. The high fat meal was the standard FDA-defined breakfast and was served 30 minutes before dose administration.

PK sampling

Blood samples were collected to measure plasma concentrations of pantoprazole on study day 1 within 2 hours before dose administration and at 0.33, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after test article administration.

Bioanalytical assay method

Plasma samples were analyzed for pantoprazole concentrations by a validated LC-MS-MS method. The limit of quantitation was 10 ng/mL and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma.

Analytical Summary of Pantoprazole

	--- QC 1 ---			--- QC 2 ---			--- QC 3 ---		
Analyte, ng/mL	Conc.	CV %	Bias %	Conc.	CV %	Bias %	Conc.	CV %	Bias %
Pantoprazole	25	7.07	1.94	2500	4.79	3.78	3750	3.95	7.04

Abbreviations: conc. = concentration; CV = coefficient of variation; QC = quality control sample.

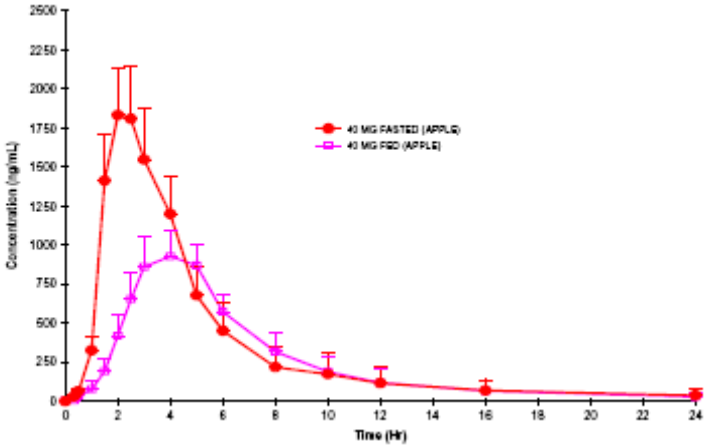
Subject disposition

Subjects in this study were predominantly white (74%) men and women with an average age of 34 years. The 4 treatment groups were comparable; except that the 40 mg fasted/fed (suspension) group

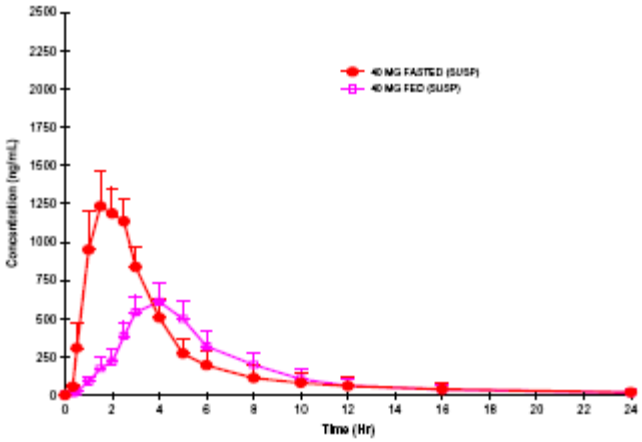
was predominantly men (7 men/8 total) and the 40 mg fed/fasted (apple sauce) group was predominantly women (7 women/9 total). Total 34 subjects completed the study.

Results

Mean (SE) Plasma Concentration Time Profiles Following Administration of 40 mg of Pantoprazole Spheroids in Applesauce to Healthy Adult Subjects (n=17)



Mean (SE) Plasma Concentration Time Profiles Following Administration of 40 mg of Pantoprazole Spheroids in Suspension to Healthy Adult Subjects (n=17)



Pharmacokinetic Parameters for Pantoprazole Spheroids in Applesauce

Treatment	Statistics	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (h)	AUC (ng.h/mL)
Fasted Condition (n=17)	Mean ± SD[a]	2471 ± 1226	0.0	2.0	7961± 10393	8429 ± 12131
	Range	795 – 5994	0.0 – 0.5	1.5 – 4.0	2124 – 47430	2152 – 54764
	Geometric Mean	2218			5788	5881
Fed Condition (n=17)	Mean ± SD	1198 ± 595	0.5	4.0	5698 ± 7455	6087 ± 8805
	Range	506 – 2773	0.0 – 2.0	3.0 – 6.0	1983 – 34098	2048 – 39807
	Geometric Mean	1078			4190	4295
Geometric Mean Ratio		48.33	---	---	72.25	72.87
90% Log-transformed CI		37.07 – 63.00	---	---	60.51 – 86.28	61.23 – 86.73

a: median values reported for t_{lag} and t_{max}

Pharmacokinetic Parameters for Pantoprazole Spheroids in Suspension

Treatment	Statistics	C_{max} (ng/mL)	t_{lag} (h)	t_{max} (h)	AUC_T (h)	AUC (ng.h/mL)
Fasted Condition (n=16)	Mean ± SD[a]	1636 ± 880	0.0	1.5	4845± 5776	5076 ± 6525
	Range	675 – 4126	0.0 – 0.33	1.0 – 2.5	1037 – 25252	1069 – 28441
	Geometric Mean	1463			3481	3549
Fed Condition (n=16)	Mean ± SD	818 ± 491	0.33	4.0	3417 ± 4249	3634 ± 4909
	Range	254 – 1880	0.0 – 1.5	2.5 – 8.0	852 – 18610	964 –21404
	Geometric Mean	677			2365	2445
Geometric Mean Ratio		46.26	---	---	67.94	68.89
90% Log-transformed CI		33.24 – 64.37	---	---	52.45 – 88.00	53.65 – 88.45

a: median values reported for t_{lag} and t_{max}

After a high-fat breakfast the median t_{max} increased by 2 hours for spheroids sprinkled in applesauce and by 2.5 hours for spheroids in suspension. The mean AUC values were 30% and 33% lower in the fed condition compared to the fasting condition for spheroids sprinkled in applesauce and spheroids in suspension, respectively. The mean C_{max} values were 45% and 47% lower in the fed condition compared to the fasting condition for spheroids sprinkled in applesauce and spheroids in suspension, respectively.

Under fasting conditions, the C_{max} and AUC for spheroids administered as suspension is 35-40% lower compared to spheroids administered with applesauce. The reason for this observation could be due to the fact that the spheroids were sticking to the sides of the suspension bottle at the time of dose administration, resulting in incomplete dose administration.

Reviewer's comments: *In study 114, the systemic exposure of pantoprazole administered as granules sprinkled on applesauce or suspended in water under fasting condition was comparable.*

Pharmacokinetic parameter estimates for two subjects (9 and 31) showed and the terminal half-life greater than 7 hours in both the periods of the study. These data are consistent with the presence of a slow metabolizer phenotype for cytochrome P-450 (CYP) 2C19; however, genotyping was not conducted.

***Reviewer's comment**: The AUC of pantoprazole in subjects 9 and 31 was about 7-8 folds higher than the geometric mean AUC and Cmax was about 2-3 folds higher than the geometric mean Cmax.*

Study 331

A multicenter, open-label, pharmacokinetic, pharmacodynamic, clinical symptoms, and safety study of pantoprazole delayed-release granules administered as a suspension in neonates and preterm infants with a clinical diagnosis of gastroesophageal reflux disease

Study design

This was a multicenter, open-label, randomized, single-dose and multiple-dose study to assess PK, clinical GERD and respiratory symptoms and safety of 2 dose levels of pantoprazole (1.25 mg and 2.5 mg) and the PD at one dose level (2.5 mg) in neonates and preterm infants with a clinical indication for acid suppression to treat a presumed diagnosis of GERD. Patients were neonates and preterm infants admitted to an NICU or special care nursery at the time of enrollment.

Patients in the study were assigned to 1 of 3 assessment strata, PK, PK/PD, or PD. Patients in the PK and PK/PD strata were randomly assigned to 1.25 or 2.5 mg of pantoprazole delayed-release granules for oral suspension. Patients who participated in the PD stratum (selected sites only) received 2.5 mg of pantoprazole granules for oral suspension. All patients received at least 5 days of treatment.

***Reviewer's comment:** One patient in PK/PD strata was mistakenly assigned to 1.25 mg strata. The sponsor intended to study PD only at 2.5 mg due to the possibility of under dosing in premature infants either due to spitting or possibly malabsorption of the dose due to the immature GI tract. The sponsor concerned that the loss of even 1 or 2 granules at the lowest dose represents a 9-18% of the dose given 1.25 mg represents approximately 11 granules. In 1.25 mg dose cohort, there were five patients who did not have any measurable plasma concentrations of pantoprazole. It is unclear in CRF if this is due to incomplete dosing.*

PK sampling

PK samples after single-dose administration were collected at pre-determined interval divided by two groups. Each patient had 4 blood samples drawn on day 1 at the collection times as shown below.

	Day 1: PK Collection Times						
Group	-2 to 0 h	1 h	2 h	4 h	8 h	12 h	18 h
A	X		X		X		X
B	X	X		X		X	

For multiple dose PK, blood samples after at least 5 consecutive daily doses of pantoprazole were collected at 3 and 6 hours after the last dose. .

Pharmacodynamics

PD assessments were based on pH-metry results. Results were recorded for up to 24 hours during patient screening to obtain baseline pH values and again at steady state after at least5 consecutive doses of pantoprazole. For patients in PD stratum, only multiple-dose PK samples were collected.

Intragastric and intraesophageal pH was assessed during the screening period (baseline evaluation) and after the final dose of pantoprazole after administration of at least 5 consecutive daily doses of

pantoprazole. The patient had an intragastric and intraesophageal pH assessment for up to 24 hours at each of these time points via a 2-channel intragastric and intraesophageal pH probe with an internal reference electrode (supplied by WR) placed transnasally into the stomach.
On each of the pH-metry days, the patients were fed every 3 to 4 hours as appropriate, with each feeding lasting a maximum of 30 minutes. The pH probes were inserted after not feeding for approximately 2 hours. Because of the buffering effects of feeding, data collected during the 30-minute feeding and 30-minute post-feeding periods were excluded from data analysis. Patients who had a total recording time of at least 16 hours of pH-metry were included for PD analysis.

Clinical Symptoms
Secondary parameters for evaluation were changes in the frequency of clinical symptoms of GERD and respiratory symptoms from baseline to steady state. Changes were compared between the 2 dose groups.

Subject disposition
Male and Female term and postterm infants within the neonatal period (≤28 days postnatal age), or preterm infants with a corrected age of less than 44 weeks. Body weight of at least 1500 g was required.

Treatment
Pantoprazole delayed-release granules were provided in an inert powder blend in foil pouches in 1.25- and 2.5-mg dose strengths. At the time of administration, 2.5 mL of water was added to the content of the foil pouch to form a grape-flavored suspension. The appropriate doses were then administered to patients by using an oral syringe approximately 30 minutes before the first feeding each day at approximately the same time as on study day 1.

Bioanalytical assay method
Plasma samples were analyzed for pantoprazole concentrations by a validated LC/MS/MS method. The limit of quantitation was 10 ng/mL, and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma.

Analytical Summary of Pantoprazole

	--------- QC 1 ---------			-------- QC 2 ---------			--------- QC 3 ---------		
Analyte	Conc. (ng/mL)	CV %	Bias %	Conc. (ng/mL)	CV %	Bias %	Conc. (ng/mL)	CV %	Bias %
Pantoprazole	25	5.41	-2.06	2000	3.14	-3.98	4000	3.41	-7.16

Abbreviations: QC=quality control sample; Conc.=concentration; CV%=coefficient of variation.

Patient disposition
The study population consisted of hospitalized preterm infants and neonates. Preterm infants were defined as infants who were born before 37 complete weeks of gestation. Neonates were defined as term or postterm infants in the first 28 days since birth. Term infants were defined as those born after 37 to 42 weeks of gestation, and postterm infants were defined as those born after 42 weeks of gestation.
There were no statistically significant differences between the dose groups. All the patients participating in the study were neonates (aged ≤28 days) or preterm infants with a corrected age of less than 44 weeks. Most (54 of 59; 91.5%) were born prematurely. The median gestational age was 29 weeks. The median corrected age of the infants born prematurely was 37.5 weeks. The mean body-weight was 2673 ± 658 g. The majority (41 of 59; 69.5%) of the patients were male. Race and ethnicity were

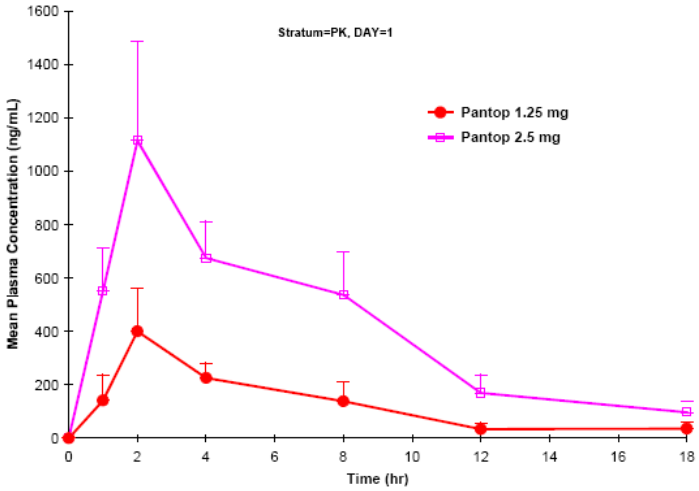
predominantly white, non-Hispanic (46 of 59; 78%) followed by African-American (9 of 59; 15%), other (3 of 59; 5%) and Asian (1 of 59; 1%).

Concomitant medication

All but 1 of the 59 (98.3%) patients received concomitant medication during the study. Iron preparations were the most widely used products and were given to 32 (54.2%) patients. The second most common medications were propulsives (eg, metoclopramide), which were given to 18 (30.5%) patients, indicated for feeding intolerance as well as GERD. At least 12 (20.3%) patients received vitamin supplements, including multivitamin and plain vitamin preparations. Other concomitant products provided to at least 10% of the patients in the study were mydriatics or cycloplegics (11 patients; 18.6%); caffeine for the treatment of apnea (9 patients; 15.3%), nasal decongestants (8 patients; 13.6%); and antifungals for topical use, ascorbic acid, and laxatives (7 patients each; 11.9%).

PK results

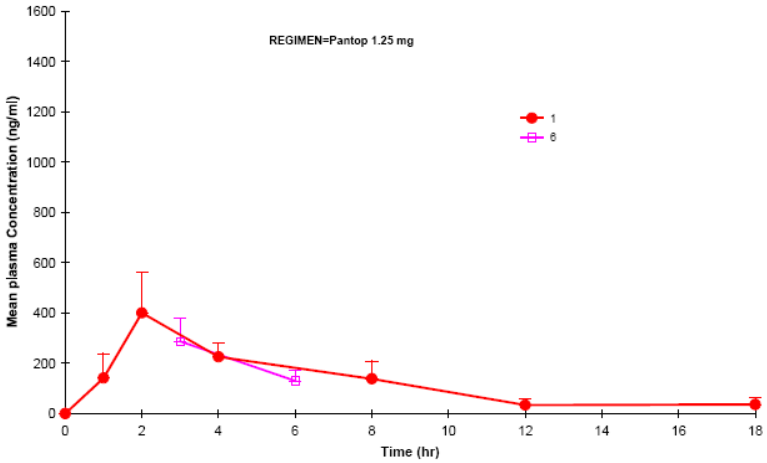
Mean Concentration-Time Profile of Pantoprazole After a Single Oral Dose in Neonates and Preterm Infants



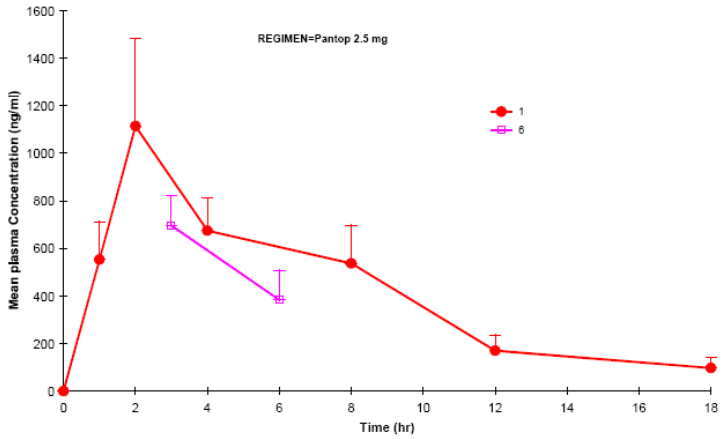
The $t_{1/2}$ calculated from the mean plasma concentration profile was 5.6 hours and 4.2 hours for the 1.25- and 2.5-mg dose groups, respectively. This is longer than the typical $t_{1/2}$ of 1 hour seen in older children and adult subjects. It is probably because of this long $t_{1/2}$ that plasma concentrations are observed even 18 hours postdose. The AUC_T values obtained from the mean plasma concentration profiles were 2251 and 7538 ng•h/mL for the 1.25- and 2.5-mg dose groups, respectively. The AUC_T value at the 2.5-mg dose was higher than that in adults receiving 40-mg dose. The AUC_T values increased with dose, but the increase did not appear to be proportional with dose.

There were 5 patients in the 1.25-mg dose group and 2 patients in the 2.5-mg dose group who had zero concentrations up to 18 hours after dose administration

Pantoprazole Plasma Concentration After Single-Dose and Multiple-Dose Oral Administration of 1.25 mg Daily



Pantoprazole Plasma Concentration After Single-Dose and Multiple-Dose Oral Administration of 2.5 mg Daily



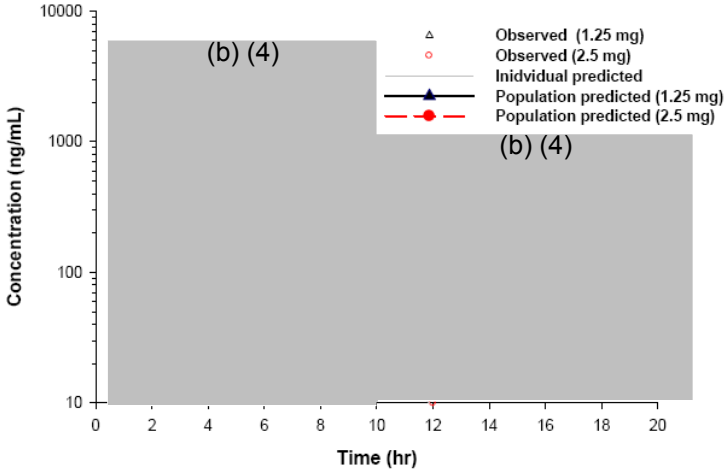
Population PK

A population PK analysis was performed with data obtained after single-dose administration to further characterize the PK in this population. The population PK analysis was done using nonlinear mixed-effects modeling approaches (NONMEM). A one compartment pharmacokinetic model with first order absorption was developed and appeared to best describe the data.

The typical value of apparent oral clearance in this population was estimated to be 0.4 L/h for a patient with weight of 2.5 kg. Similarly, the typical value of apparent oral volume of distribution in this population was estimated to be 1.6 L for a patient with weight of 2.5 kg. The inter-individual variability for Cl/F and V/F were 82.3% and 77.3%, respectively. These %CVs are on the higher side and are expected, given the nature of the data. The residual error was 33%.

Reviewer's comment: *The final population PK model was a two compartment model according to a separate report for population PK analysis.* ***For*** *detailed review of the population PK analysis, please see Pharmacometrics review by Dr. Justin Earp.*

Plot of Observed and Predicted Plasma Concentration



Summary of Pharmacokinetic Results After Single Dose Administration of Pantoprazole (PK and PK/PD Strata) Estimated From Population PK Modeling

	Treatment	
Mean ± SD (CV%) [Geometric Mean]	1.25 mg (n=14)	2.5 mg[a] (n=19)
AUC (ng•hr/mL)	3540 ± 2820 (80) [2785]	7270 ± 5304 (73) [5631]
Cl/F (L/hr/kg)	0.21 ± 0.12(59) [0.17]	0.23 ± 0.21(92) [0.17]

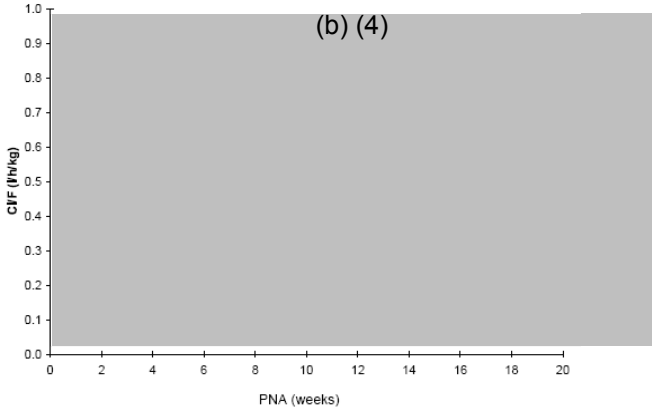
a. Excludes 2 poor metabolizers.
Abbreviations: AUC = area under the concentration-time curve to last time measured; Cl/F = clearance; CV=% = coefficient of variation.

The mean (± SD) half-life ($t_{1/2}$) estimated from the population PK modeling was 3.1 hours (± 1.5) and 2.7 hours (± 1.1) for the 1.25- and 2.5-mg dose groups, respectively.

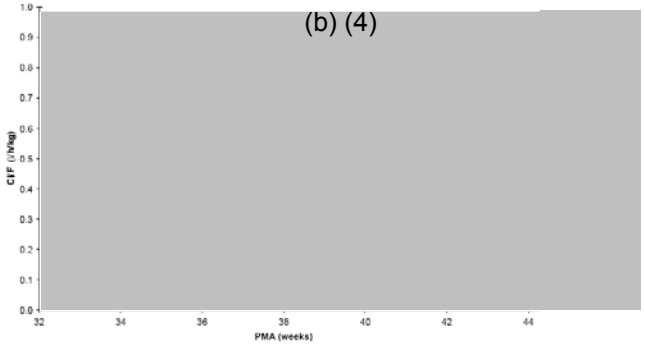
Reviewer's comment: *The $t_{1/2}$ calculated from the mean plasma concentration profile was 5.6 hours and 4.2 hours for the 1.25- and 2.5-mg dose groups, respectively.*

No apparent trends were observed between AUC and weight normalized CL/F with corrected age. There appeared to be a trend towards decrease in AUC and increase in oral clearance with increase in postnatal age.

Model-Estimated Individual Weight-Normalized Clearance Values versus Postnatal Age



Model-Estimated Individual Weight-Normalized Clearance Values Versus Corrected Age



Abbreviation: PMA=postmenstrual (ie, corrected) age.

Pharmacogenomics

Two (2) patients were identified as poor metabolizers of CYP2C19. With only 2 patients identified as poor metabolizers, no clear pattern can be discerned on the effect of genotype on the AUC of pantoprazole. Among the 40 PK and PK/PD patients, 10 were heterozygous for CYP2C19*1/*2, 6 were heterozygous for CYP3A4*1/*B, 2 were heterozygous for CYP3A4*1/*3, and 3 were homozygous for CYP3A4*B/*B. There were few patients with plasma concentration data who were heterozygous for CYP3A4 or CYP2C19 within each treatment group, making it difficult to draw meaningful conclusions on their effect on the AUC of pantoprazole.

Pharmacodynamics

Please, see QBR.

Summary of intragastric pH related PD Parameters in preterm infants/neonates

Parameter	Preterm infants/neonates	
Dose	2.5 mg (n=16)	
Mean ± SD	Baseline	Steady State
Initial Stomach pH	2.61 ± 2.12	4.13 ± 1.68*
Mean Intragastric pH	4.3 ± 0.9	5.2 ± 1.0*
% time intragastric pH>4	59.8 ± 20.7	79.3 ± 20.5*
% time intragastric pH >3	72.79 ± 19.35	86.24 ± 17.48*

The initial stomach pH at start of pH-metry increased significantly from 2.61 ± 2.12 to 4.13 ± 1.68 during the treatment period of the study. The patients' mean and median intragastric pH levels increased significantly from baseline at steady state. Moreover, the percentage of time that intragastric pH was >3 and >4 also significantly increased.

Reviewer's comment: *There were four patients whose % time gastric pH >4 was greater than 70%.*

Intraesophageal pH in preterm infants/neonates after at least 5 days of treatment

	Dose mg	Baseline (b) Mean ± SD	Steady-state (s)	Change from baseline Mean ± SD	P-value
Mean intraesophageal pH over 24 h	2.5	5.06 ± 0.28	4.91 ± 0.31	-0.16 ± 0.31	0.060
% time Intraesophageal pH <4 (reflux index)	2.5	8.65 ± 8.93	7.34 ± 8.63	-1.31 ± 12.34	0.676
Esophageal Reflux Area (pH•min) (time-pH area under pH <4)	2.5	73.86 ± 131.12	23.58 ± 34.36	-50.29 ± 139.54	0.170
AUC of esophgeal H+ activity (H*mmol/L)	2.5	5.84 ± 12.08	0.91 ± 0.70	-4.92 ± 12.17	0.126
Number of Reflux episode	2.5	124.00 ± 77.47	184.38 ± 189.85	60.38 ± 182.54	0.206

However, there was no intraesophageal pH parameters that resulted in statistically significant change after multiple dosing of pantoprazole. The intraesophageal pH-metry parameters had large interindividual variability and did not show consistent results. The inconsistent results were attributed to 1) 50% increase in number of reflux episode at steady-state from baseline; 2) the majority of patients had a normal % time of intraesophageal pH <4 e.g. <10%. Because of the increased number of reflux episode, the sponsor claims that even with an increase gastric pH the increased exposure time of esophagus to refluxant would have contributed to the decreased mean intraesophageal pH.

Reviewer's comment: *It is unknown if pantoprazole had any effect on the increase in reflux episode. It was noted that the % patients whose % time of intraesophageal pH <4 (reflux index) was considered abnormal (e.g.>10%) decreased from 25% at baseline to 18.8% at steady-state while no consistent trend was observed for the majority of patients who had normal % time of intraesophageal pH <4. However, in infants 1-11 months old, the % patients whose reflux index was abnormal increased after treatment.*

Clinical evaluation

Total Daily GERD Symptom Scores

Descriptive statistics for the total daily GERD symptom score, a sum of 5 selected GERD symptoms, are presented from baseline through the last day on therapy. Because this clinical evaluation was exploratory in nature under a short-term treatment, detailed review was not conducted. Please, see Clinical Review by Dr. Il-Lun Chen.

PK conclusion

The concentration values were highly variable after single and multiple doses of pantoprazole in this study population; however, further PK analysis was still possible. The $t_{1/2}$ of pantoprazole appeared to be

longer in neonates and preterm infants compared with that seen in adults and children aged 1 through 16 years. This finding was expected and consistent with literature reports. Pantoprazole is primarily metabolized by the CYP2C19 enzyme and to a limited extent by CYP3A4. These enzymes are not completely developed in neonates and preterm infants and appear to be activated by a mechanism associated by birth but independent of gestational age. This is probably the reason for the longer $t_{1/2}$ observed in this population. The trend toward increased apparent oral clearance with increase in postnatal age is probably a result of activation of CYP enzymes after birth.

Reviewer's comments: For a detailed review, please see Pharmacometrics review in Appendix.

Study 333

A multicenter, randomized, open-label, single-dose and multiple dose study of the pharmacokinetics and pharmacodynamics of 2 dose levels of pantoprazole sodium enteric-coated spheroid suspension in infants aged 1 through 11 months with presumed GERD

Study design

This was a Phase 3, multicenter, randomized, open-label, single-dose and multiple-dose PK and safety, in infants aged 1 month through 11 months with presumed GERD. Hospitalized patients or outpatients participated in 1 of 2 strata: PK or PD. Approximately 56 patients were to be enrolled in the study; 32 patients in the PK portion of the study and 24 patients in the PD portion of the study.

After screening, patients whose weight was 2.5 kg to < 7 kg were randomly assigned in a 1:1 fashion to receive either a 5-mg (high) daily dose or a 2.5-mg (low) daily dose of pantoprazole, and patients whose weight was at least 7 kg but not more than 15 kg were randomly assigned in a 1:1 fashion to receive either a 10-mg (high) daily dose or a 5-mg (low) daily dose of pantoprazole.

Pantoprazole Dose Strength Based Upon Weight Group

	Dose Group	
Weight[a]	Low	High
2.5 to < 7 kg	2.5 mg	5 mg
≥ 7 kg to ≤ 15 kg	5 mg	10 mg

a. Baseline Weight

Source: 3001B3-333-WW Study Protocol

For patients in the PK stratum, single-dose PK analysis was performed after the first dose of pantoprazole. Multiple-dose PK values were assessed after at least 5 (but not more than 10) consecutive daily doses of pantoprazole. For patients in the PD stratum, PD assessments were made by using 24-hour pH-metry at baseline and at steady state after at least 5 (but not more than 10) consecutive daily doses of pantoprazole to measure the intragastric and intraesophageal pH for up to 24 hours. All PD patients participated in the multiple-dose PK assessment, but PD patients did not participate in the single-dose PK assessments.

Reviewer's comment: *PK/PD relationship was not analyzed.*

Treatment

The test article was pantoprazole sodium enteric-coated spheroids (granules) in an inactive powder blend, provided in 3 strengths (2.5 mg, 5 mg, and 10 mg) for administration to patients in the low (0.6 mg/kg) and high (1.2 mg/kg) dose groups. The contents of the pouch were reconstituted with 5 mL of

water to produce a grape-flavored oral suspension. Dosing with an oral syringe or small spoon occurred approximately 30 minutes before the morning feeding.

PK sampling

Blood samples for single-dose PK assessments were collected on study day 1 at 2 hours before and at 0.5, 1, 2, 4, 6, and 12 hours after pantoprazole administration. PK samples were collected at 2 and 4 hours after multiple dose pantoprazole administration. PK plasma samples for PD patients were collected on the morning of study day 1, at hour -2 (predose), and on study day 7 ± 2 (final study evaluation) at 3 hours after pantoprazole administration.

Bioanalytical assay method

Plasma samples were analyzed for pantoprazole concentrations by a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method. The limit of quantitation was 10 ng/mL and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma.

Analytical Summary of Pantoprazole

	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte	Conc. (ng/mL)	CV%	Bias %	Conc. (ng/mL)	CV%	Bias %	Conc. (ng/mL)	CV%	Bias %
Pantoprazole	25	9.19	-1.0	2000	2.2	-2.92	4000	4.67	-7.73

Abbreviations: Conc. = concentration; CV% = coefficient of variation; QC = quality control sample.

Disposition of patients

Eighty-one (81) patients were enrolled in the study. Fourteen (14) patients were screen failures. Sixty-seven (67) were randomly assigned to treatment and received at least 1 dose of pantoprazole. Thirty-three (33) patients were randomly assigned in a 1:1 fashion to receive the low dose (0.6 mg/kg), and 34 patients were randomly assigned to the high-dose (1.2 mg/kg) group.

PK results

Summary of Pharmacokinetic Parameter Estimates- Day 1

	---------- Treatment ----------	
Mean ± SD (CV%) [Geometric Mean]	Pantoprazole 0.6 mg/kg (n=17)	Pantoprazole 1.2 mg/kg (n=18)
C_{max} (ng/mL)	567 ± 534 (94%) [341]	1527 ± 1298 (85%) [1009]
t_{max} (hr)[a]	1.03 (1.00, 4.00)	1.02 (0.5, 4.08)
t_{lag} (hr) [a]	0.5 (0.00, 1.03)	0.0 (0.00, 1.0)
$t_{1/2}$ (hr)	1.78 ± 1.30 (73%) [1.63][b]	1.42 ± 0.78 (93%) [1.30][b]
AUC_T (ng•hr/mL)	949 ± 969 (102%) [605]	3513 ± 3267 (93%) [2107]
AUC (ng•hr/mL)	1046 ± 1043 (100%) [671]	3602 ± 3269 (91%) [2202]
CL/F (L/hr/kg)	1.54 ± 2.35 (153%) [0.89]	0.87 ± 1.36 (156%) [0.48]

a. Values for t_{lag} and t_{max} are median (minimum, maximum).
b. Median value.

Reviewer's comment: *The systemic exposure of pantoprazole was highly variable (CV >80%). The PK sampling was not sufficient for some subjects as there was no sample collected between 6-12 hours post-dose and a few patients had substantial plasma concentration at 6 hours post-dose. For six patients (two in 0.6 mg/kg and four in 1.2 mg/kg group) did not have at least 2 measurable concentrations after Cmax thus were excluded from the AUC_{inf} estimation. Subjects for whom % AUCext was greater than 20% were excluded from AUC_{inf} estimation.*

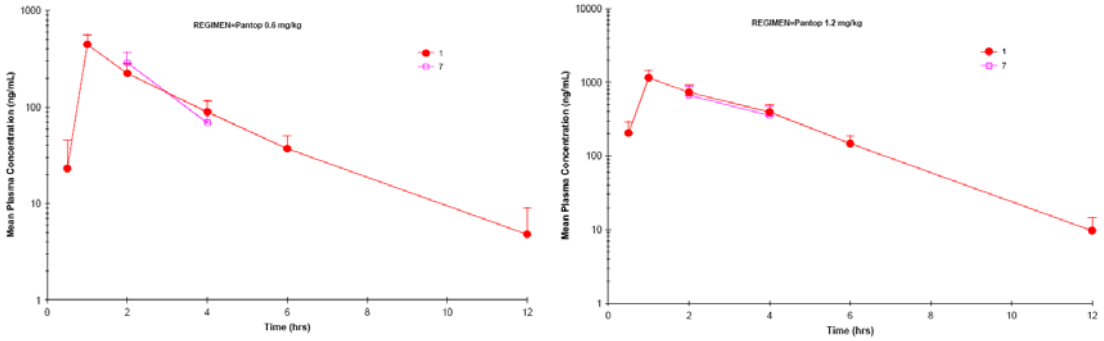
The exposures observed with the 1.2-mg/kg dose regimen were similar to those seen in adults receiving 40 mg of pantoprazole, although variable.

There was no evidence of accumulation of pantoprazole after multiple-dose administration judged based on mean plasma concentration time profiles after single dose and plasma concentrations at two time points after multiple dose administration.

Reviewer's comments: *Apparently blood samples were collected beyond expected tmax after multiple dosing. The accumulation of pantoprazole after multiple-dose was not adequately addressed although the current data appears to be consistent with what was observed in adults e.g. no accumulation after multiple doses (Protonix label).*

Mean Plasma Concentration-Time Profiles of Pantoprazole After Single-Dose and Multiple-Dose Oral Administration of Pantoprazole Suspension All PK Population

0.6 mg/kg **1.2 mg/kg**



Pharmacogenomics

Two (2) of the PD patients were poor metabolizers based on their CYP2C19 genotype but one blood sample was collected only after multiple doses. As such they were not included for a single dose PK analysis. Ten (10) patients were heterozygous for CYP2C19*1/*2, 12 patients were heterozygous for CYP3A4*1/*1B, and 3 patients were homozygous for CYP3A4*1B/*1B.

Results for PD parameters

There was statistically significant increase at steady-state from baseline in mean gastric pH, median gastric pH, and percentages of time that gastric pH was > 4 and > 3, while corresponding changes following the low dose (0.6 mg/kg) were not statistically significant.

Reviewer's comments: *It was noted that the mean intragastric pH at baseline was elevated in 0.6 mg/kg dose group from initial stomach pH. Consistently, the % time intragastirc pH>4 and >3 was higher at baseline for 0.6 mg/kg dose group compared to that for 1.2 mg/kg dose group. Moreover, mean gastric pH % time gastric pH>4 at baseline for 0.6 mg/kg dose cohort was comparable with those at steady-*

state after 1.2 mg/kg dosing. As such the dose-response relationship based on mean change from baseline appears to be confounded by difference at baseline. This may be reflective of difficulty in collecting reliable pH measurements in this age group and difficulty in identifying patients in this age group who would need acid suppression based on clinical symptom.

Descriptive Summary of Intragastric pH related Pharmacodynamic Parameters in infants 1-11 months old

Parameter	Infants 1-11 months			
Dose	0.6 mg/kg (n=11)		1.2 mg/kg (n=10)	
Mean ± SD	Baseline	Steady State	Baseline	Steady State
Initial Stomach pH	2.4 ± 1.5	2.6 ± 1.3	2.8 ± 1.9	2.8 ± 2.5
Mean Intragastric pH	4.2 ± 1.4	4.8 ± 1.3	3.1 ± 1.4	4.2 ± 1.5*
% time intragastric pH>4	55.5 ± 28.6	68.5 ± 28.3	32.2 ±24.1	56.6 ± 31.1*
% time intragastric pH >3	68.4 ± 26.3	76.9 ± 24.5	43.5 ± 29.8	66.3 ± 30.5*

There was significant decrease in mean intraesophageal pH over 24 h and AUC of esophgeal H+ activity (H*mmol/L) after 1.2 mg/kg treatment. Except them there was no statistically significant change in most of esophageal pH parameters after either treatment . Notably, the number of reflux episode also increased at steady-state similarly in preterm infants.

Intraesophageal pH in infants aged 1-11 months

PD parameter	Dose mg/kg	Baseline Mean ± SD	Steady-state Mean ± SD	P-value
Mean intraesophageal pH over 24 h	0.6	5.7 ± 0.7	5.6 ± 0.8	0.347
	1.2	5.2 ± 0.4	4.9 ± 0.3	0.012
% time Intraesophageal pH <4 (reflux index)	0.6	4.6 ± 3.9	4.6 ± 5.6	0.982
	1.2	8.0 ± 5.6	9.4 ± 5.8	0.534
Esophageal Reflux Area (pH•min) (time-pH area under pH <4)	0.6	33.4 ± 25.2	24.5 ± 36.7	0.423
	1.2	57.5 ± 39.3	31.3 ± 13.3	0.066
AUC of esophgeal H+ activity (H*mmol/L)	0.6	2.1 ± 1.6	1.5 ± 2.4	0.387
	1.2	3.5 ± 2.3	1.5 ± 0.6	0.021
Number of Reflux episode	0.6	87.4 ± 59.9	109.1 ± 121.0	0.410
	1.2	143.2 ± 48.3	212.6 ± 112.6	0.144

Based on the PK and PD from this study the 1.2-mg/kg daily dose was selected for the efficacy study 3001B3-329-WW, which was conducted in infants aged 1 month through 11 months.

Study 334

A multicenter, randomized, open label, single and multiple dose study of the safety and pharmacokinetics of 2 dose levels of pantoprazole sodium in children aged 1 through 11 years with endoscopically proven GERD

Note that the term "spheroid" was used for "granules" in this study.

Study design

This study was a multicenter, randomized, open-label, single-dose and multiple-dose PK study in children ages 1 through 11 years with endoscopically proven GERD at 2 dose levels (0.6 mg/kg [low dose] and 1.2 mg/kg [high dose] to assess the safety and tolerability in this population.

For children ages 1 through 5 years, the 2 dosage levels (low and high) of pantoprazole spheroids were provided in 4 strengths: 5, 10, 15 and 20 mg, according to the patient's weight, for administration as a sprinkle on applesauce or in apple juice. For patients ages 6 through 11 years, the low and high dosage levels were achieved using pantoprazole tablets in strengths of 20 and 40 mg.

Dose Strength Based on Weight Group (Age <6 Years/Spheroid)

	Dose Group	
Weight (kg)	Low	High
≤12.5	5.0 mg	15 mg
>12.5 to <25	10 mg	20 mg

Dose Strength Based on Weight Group (Age <6 Years/Spheroid)

	Dose Group	
Weight (kg)	Low	High
≥25	20 mg	40 mg

Reviewer's comment: *It was noted that two patients were randomly assigned to a lower dose group, 0.6 mg/kg but based on the patient's body weight, the investigators were given permission to treat the patients with a highest dose (1.2 mg/kg).*

PK sampling

Samples for PK analysis was taken up to 2 hours before dose administration, and at 0.5, 1, 2, 4, 6 and 12 hours after a single- dose administration and at 2 and 4 hours after at least 5 consecutive dose administrations.

Reviewer's comments: *For six subjects aged less than 5 years, apparently Cmax was achieved at 6 hours post-dose; however, there was no sampling done until 12 hours. As such PK sampling was not sufficient to capture a full PK profile for these subjects.*

Patient disposition

Plasma from the PK blood samples was analyzed for pantoprazole by a validated liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) assay. The lower limit of quantitation (LLQ) was 10 ng/mL and the assay was linear up to 5000 ng/mL using 0.1 mL of human plasma.

Bioanalytical Summary of Pantoprazole

	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte	Conc. (ng/mL)	CV%	Bias %	Conc. (ng/mL)	CV%	Bias %	Conc. (ng/mL)	CV%	Bias %
Pantoprazole	25	4.93	-1.94	2000	2.68	-3.82	4000	3.62	-8.00

Abbreviations: Conc.=concentration; CV%=coefficient of variation; QC=quality control sample.

PK results

Summary of Pharmacokinetic Results: Day 1 (Age <6 Years/Spheroid)

Age	1-5 years old	
Dose	0.6 mg/kg (n=7)[1]	1.2 mg/kg (n=10)[2]
Cmax (ng/ml)	181 (85) [166]	653 (99) [406]
Tmax (hr) (min-max)	5.8 (1-6)	3 (1-6)
AUCt (ng*hr/ml)	563 (76) [377]	1920 (89) [1205]
Number of subjects [3]	(n=2)	(n=6)
AUC_∞ (ng*hr/ml)	294 (70) [266]	1840 (87) [1194]
t1/2 (h) (± SD)	1.1 ±0.1	1.5 ±0.5
CL/F (L/h/kg)	2.4 (67)	1.46 (79)

[1] included four subjects whose tmax was 6 hours

[2] included two subjects whose tmax was 6 hours

[3] when λ-extrapolation was not reliable, patients were excluded.

Reviewer's comments*: In six subjects: four in 0.6 mg/kg and two in 1.2 mg/kg, tmax was delayed to 6 hours. Because there were no PK samples collected between 6 to 12 hours, it is unclear if this is true tmax. Subjects whose % AUCext is greater than 20% was excluded from AUC_∞ calculation.*

Clearance versus age across ages 1 year through 11 years shows a trend toward decreased clearance with increasing age. However, this may result in part from the difference in formulation between the 2 age groups and the extent of absorption. There was considerable variability observed in the lag time after single-dose and after multiple-dose administration of pantoprazole. Therefore, pantoprazole concentrations at each time point on day 1 and at steady state could not be compared.

Pharmacogenomics

There were no poor metabolizers of CYP2C19. Out of the 41 subjects who received pantoprazole, there were 11 patients heterozygous for CYP2C19 * 1/ *2, 2 heterozygous for CYP3A4 * 1/ *B, 1 heterozygous for CYP3A4 *1/ *3, and 1 was homozygous for CYP3A4 *B/*B.

Conclusion

A total of 17 subjects in the age group 1 through < 6 years and 21 subjects in the age group 6 through 11 years contributed to the PK evaluations of pantoprazole spheroid and tablet formulations. The plasma concentrations and the PK parameters were in general highly variable in the age group 1 through < 6 years. Less variability was observed in the age group 6 to 11 years with the tablet formulation. It is

unclear if this higher variability in the younger patients is due to the nature of this patient population or a result of the spheroid formulation used in this group. The C_{max} and AUC increased with increasing doses of pantoprazole. Probably due to the large variability and the small number of subjects within each group, the increase in C_{max} and AUC did not appear to be exactly dose proportional.

Summary of Pharmacokinetic Parameter Estimates: Age ≥6 Years/Tablet

Mean±SD (CV%) [Geometric Mean]	Treatment: Pantoprazole 0.6 mg/kg (n=10)	Treatment: Pantoprazole 1.2 mg/kg (n=11)
C_{max} (ng/mL)	1643±1229 (75%) [1351]	2429±1073 (44%) [2223]
t_{max} (h)[a]	2.00 (1.00, 4.00)	2.00 (1.00, 2.27)
t_{lag} (h)[a]	1.00 (0.50, 2.0)	1.00 (0.00, 1.00)
$t_{1/2}$ (h)	0.77±0.22 (28) [0.71][b]	0.7±0.16 (23) [0.68][b]
AUC_T (ng•h/mL)	2448.61±2007.21 (82%) [1945.64]	3748.45±1805.39 (48%) [3376.87]
AUC (ng•h/mL)	2497.13±2099.64 (84%) [1971.62]	3782.49±1837.42 (49%) [3402.96]
CL/F (L/h/kg)	0.41±0.3 (74%) [0.32]	0.40±0.22 (55%) [0.36]
Vz/F (L/h/kg)	0.43±0.3 (69%) [0.35]	0.40±0.27 (66%) [0.35]

Abbreviations: AUC=area under the concentration-time curve; AUCT=area under the concentration-time curve to last time measured; Cmax=peak concentration; CL/F=apparent oral-dose clearance; CV%=coefficient of variation; t1/2=terminal-phase disposition half-life; tlag=lag time; tmax=time to peak concentration; Vz/F=apparent terminal-phase volume of distribution.

a. Values for tlag and tmax are median (minimum, maximum).

b. Median.

Source: Supportive Tables 15.63 and 15.64.

Study 337

A multicenter, randomized, open-label, single- and multiple-dose study of the pharmacokinetics and safety of 2 dose levels of pantoprazole sodium tablets in adolescents aged 12 through 16 years with a clinical diagnosis of gastroesophageal reflux disease

Study design

This was a multicenter, randomized, open-label, single- and multiple-dose PK study in adolescents aged 12 through 16 years with GERD. There were 2 dose groups (20-mg and 40-mg tablets), with each subject receiving 5 to 11 doses of pantoprazole. Patients were randomly assigned in a 1:1 fashion to the 20- or 40-mg treatment groups. Single-dose PK analysis was performed after the first dose of pantoprazole. Multiple-dose PK values were assessed on day 8 (± 3 days) of pantoprazole administration after the last of at least 5 consecutive doses. Because patients were to be provided with a 14-day supply of pantoprazole, if a patient missed a dose, that patient could restart accumulating a run of 5 consecutive doses.

PK sampling
Two (2) hours before dose administration, and at 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, and 12.0 hours after oral dose administration on study day 1. Patient took a minimum of 5 consecutive doses (no missed doses) before this PK determination at 2 and 4 hours after the dose on day 8 ± 3 days.

Bioanalytical assay method
Plasma samples were analyzed for pantoprazole concentrations by a validated liquid chromatography/tandem mass spectroscopy (LC/MS/MS) method. The limit of quantitation was 10 ng/mL and the assay was linear up to 5000 mg/mL using 0.1 mL of human plasma.

Analytical Summary of Pantoprazole

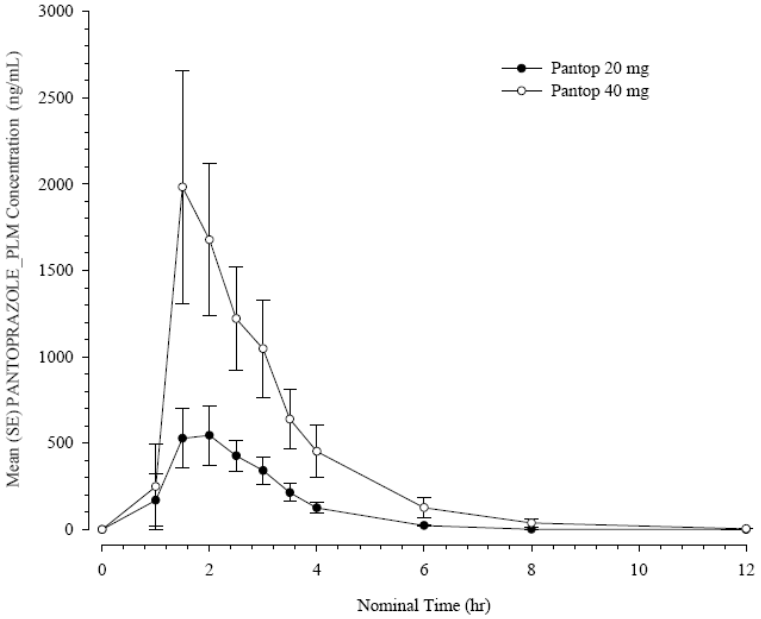
	----- QC 1 -----			----- QC 2 -----			----- QC 3 -----		
Analyte	Conc. (ng/mL)	CV%	Bias %	Conc. (ng/mL)	CV%	Bias %	Conc. (ng/mL)	CV%	Bias %
Pantoprazole	25	4.75	-3.86	2000	2.03	-3.56	4000	3.40	-4.91

Abbreviations: Conc. = concentration; CV% = coefficient of variation; QC = quality control sample.

Patient disposition
All patients entered the study with clinical signs and symptoms of GERD including 4 patients with a diagnosis of EE by endoscopy, 4 patients with a diagnosis of reflux esophagitis established by biopsy, 4 patients with abnormal pH-metry that was consistent with reflux esophagitis, and 4 patients with other objective testing consistent with GERD. Adolescents aged 12 through 16 years with a clinical diagnosis of GERD. Patients of both sexes (10 male and 12 female adolescents) were enrolled in this single- and multiple-dose study.

PK results

Mean Plasma Concentration Time Profiles Following Single-Dose Oral Administration of Pantoprazole Delayed-Release Tablet

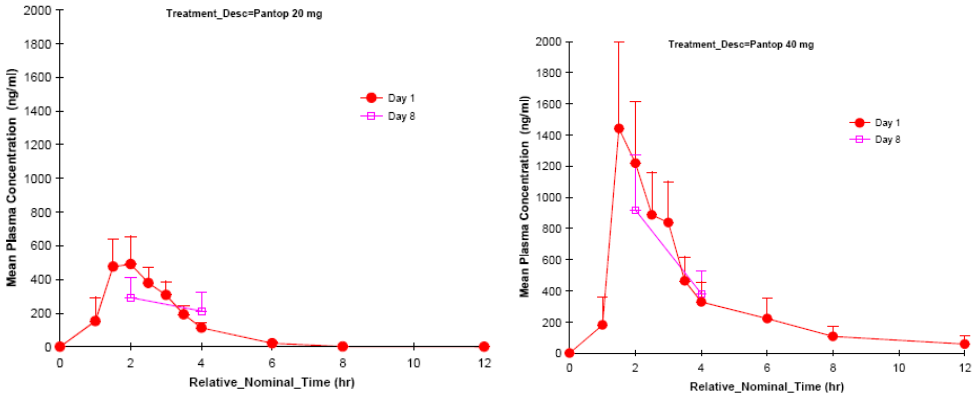


Summary of Pharmacokinetic Results - Day 1

Mean ± SD (CV%) [Geometric Mean]	Treatment: Pantoprazole 20 mg (n=9)	Treatment: Pantoprazole 40 mg (n=8)
C_{max} (ng/mL)	987 ± 390 (39) [924]	2690 ± 1338 (50) [2423]
t_{max} (hr)[a]	1.52 (1.00, 3.00)	1.50 (1.03, 3.02)
t_{lag} (hr)[a]	1.03 (0.00, 2.50)	1.00 (0.00, 2.00)
$t_{1/2}$ (hr)	0.83 ± 0.29 (34) [0.79]	0.93 ± 0.30 (32) [0.89]
AUC_T (ng•hr/mL)	1264 ± 625 (49) [1146]	4223 ± 3072 (73) [3472]
AUC (ng•hr/mL)	1305 ± 620 (48) [1194]	4262 ± 3087 (72) [3510]
CL/F (L/hr/kg)	0.28 ± 0.17 (59) [0.24]	0.18 ± 0.08 (46) [0.16]
Vz/F (L/hr/kg)	0.32 ± 0.22 (68) [0.28]	0.21 ± 0.06 (28) [0.21]

Abbreviations: AUC = area under the concentration-time curve; AUC_T = area under the concentration-time curve to last time measured; C_{max} = peak concentration; CL/F = apparent oral-dose clearance; CV% = coefficient of variation; $t_{1/2}$ = terminal-phase disposition half-life; t_{lag} = lag time; t_{max} = time to peak concentration; Vz/F = apparent terminal-phase volume of distribution.
a. Values for t_{lag} and t_{max} are median (minimum, maximum).
Source: Supportive Tables 14.18 and 14.19.

Mean Plasma Concentration-Time Profiles After Single- and Multiple-Dose Oral Administration of 40 mg of Pantoprazole Delayed-Release Tablet – All-Patient PK Population



Pharmacogenomics

There were no poor metabolizers of CYP2C19. There appeared to be no clear pattern for C_{max} and AUC of pantoprazole based on the genotype. For patients who were heterozygous for CYP2C19 or had a variant of CYP3A4, there were too few patients per treatment group to make any meaningful conclusion about the effect of these polymorphisms.

Sponsor's discussion

The plasma concentrations and the PK parameters C_{max} and AUC increased with increasing doses of pantoprazole. The Cl/F and Vz/F normalized to body weight did not show any trend across ages 12 to

16 years. These parameters are in general highly variable, presumably due to the uncertainty of the bioavailability factor (F).

There was considerable variability observed in the lag time after single-dose and after multiple-dose administration of pantoprazole. Therefore, pantoprazole concentrations at each time point on day 1 and at steady state could not be compared. As expected, there was no appreciable accumulation after multiple doses of pantoprazole, which is consistent with the short half-life of pantoprazole.

After single dose administration of 40 mg, 3 patients had an unusually long lag time (4-8 hours) and 1 patient had no measurable concentration up to 12 hours postdose. Two (2) patients did not have any measurable concentrations after multiple doses of pantoprazole. The dosing records for the patients with zero concentrations were verified to ensure that the patients did take the protocol-specified dose. The above phenomenon can be attributed to either delayed gastric emptying of the tablet or failure of dissolution of the enteric coating. If the tablet did not pass the pylorus for a long time (up to 8 or 12 hours postdose) then it would not have been possible to capture the PK profile within the specified window of measurement.

4.4. Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

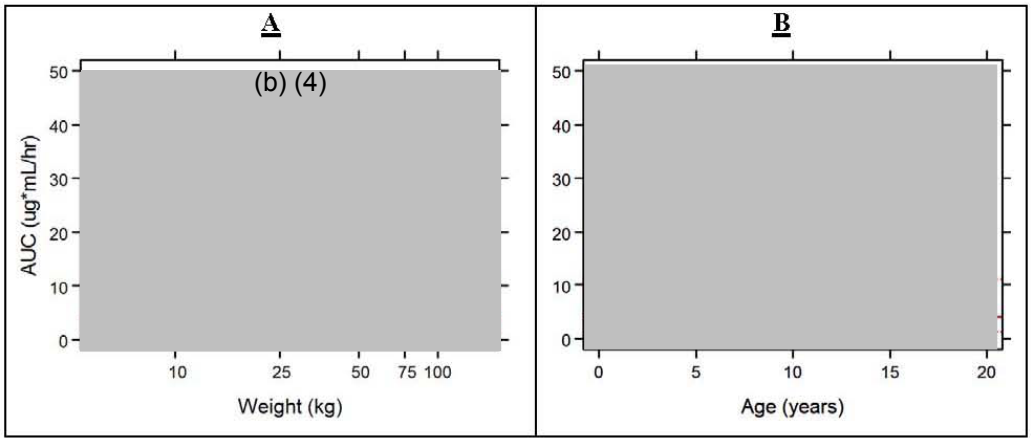
1.1 Key Review Questions

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

1.1.1 Does the proposed dosing regimen produce exposures in pediatrics that are comparable to adults?

No, the mean AUC values in the pediatric population exceed the mean AUC in the adult range by approximately 26% (Figure 1 and Table 1) when dosing 20 mg to pediatric patients 1-5 years of age and 40 mg to pediatric patients 6-17 years. The highest exposure is seen in pediatric patients with the lowest body weight in each dose group. The observations that 1) AUC increases with decreasing body weight and 2) AUC does not change significantly with age suggest that dosing by body weight will better match adult exposure consistently across pediatric patients.

Figure 1. AUC increases with decreasing weight in each dose group. Solid and dashed red lines represent the mean and range (minimum and maximum observed values) of the adult exposures. The symbols × and • indicate individual AUC estimates for the 20 and 40 mg dose groups (i.e. age < 6 yr receives 20 mg, age ≥ 6 yr receives 40 mg). Green, black and orange symbols indicate poor, extensive, or unknown CYP2C19 metabolizer status.



1.1.2 Should the pediatric dosing be weight-based?

Yes, in the pediatric population it is evident that the sponsor's proposed regimen based on age yields exposures that are 26-31% higher than observed in adults. Whereas the dosing regimen based on weight matches the adult exposures more closely (Figure 2 and Table 1).

Figure 2. Dosing By Weight Matches Adult Exposures. Solid and dashed red lines represent the mean and range (minimum and maximum observed values) of the adult exposures. The symbols ×, •, and, Δ indicate individual AUC estimates for the 10, 20, and 40 mg dose groups (i.e. body weight < 15 kg receives 10 mg, 15 kg ≤ body weight <40 kg receives 20 mg, and body weight ≥ 40 kg receives 40 mg). Green, black and orange symbols indicate poor, extensive, or unknown CYP2C19 metabolizer status.

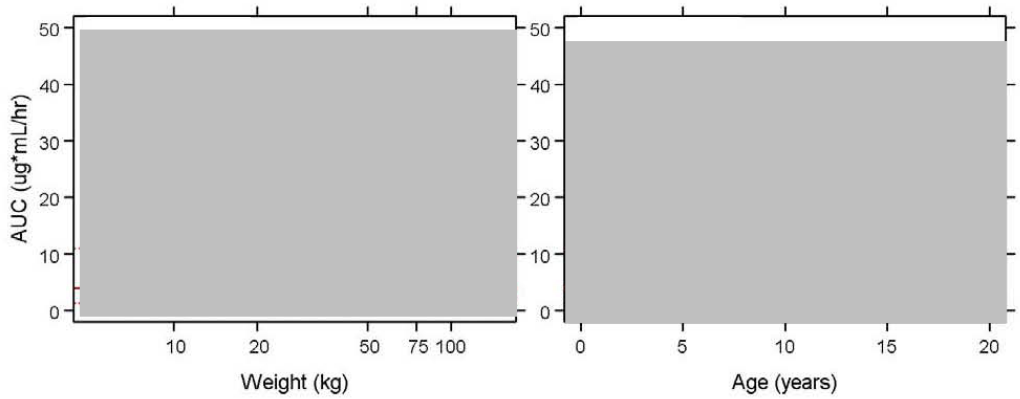


Table 1. FDA and Sponsor's Proposed Pediatric Dosing. **Results are presented as geometric mean (Range: minimum – maximum). Poor metabolizers are excluded from this analysis.**

(b) (4)

Dosing by body weight is further supported by the similar results of effectiveness for the 10, 20, and 40 mg doses. No loss of effectiveness is anticipated with reducing the dose for the youngest patients, even if this yields reduced exposures for some patients. Subjects who received the 10 mg dose performed equally well in reducing the composite symptom score at 8 weeks (primary endpoint) to those who received 20 mg or the 40 mg doses.

1.1.3 Should there be dose reduction for CYP2C19 poor-metabolizers?

Yes, ideally the dose should be reduced to ¼ the recommended dose for individuals with poor CYP2C19 metabolizer status. Clearance is estimated to be reduced by 95% in poor metabolizers. However, genotyping for the sole purpose of dose adjustment may not be necessary. Pantoprazole sodium does not have a narrow therapeutic index and safety issues were not identified in the poor metabolizers who received the 20 or 40 mg doses. Further, there is a low prevalence in the Caucasian population (3%).

1.1.4 Are the pharmacokinetics of the granule and tablet formulations comparable without dosage adjustment?

The C_{max} of the oral suspension formulation is 38% lower than the C_{max} of the tablet formulation. However, the AUC's are within 10% of each other. Based on the similarity of the pharmacokinetic profiles it is not anticipated that dose adjustment will be required when switching between formulations.

1.1.5 Do the pharmacokinetic parameter values from the population model agree with the parameter values presented in the label?

No, the population model predicts higher exposures than reported in the label. The pharmacokinetic sampling for 1-11 year olds was insufficient to capture the entire elimination time course of the drug. Pantoprazole sodium concentrations decline in a biexponential manner. Samples after 8 hrs post dose were not collected. In many patients the second terminal elimination phase is not present or obscured due to variation in the data. The values provided in the label were determined by non-compartmental analysis. This approach uses the last sampled data points to determine the remaining AUC area. Since the last sampled concentration-time points in this study (334) may not be reflective of the terminal decline and are highly variable, the values in the label are not reliable for this population (i.e. study 334). In study 334 the residual variation was higher than that of other PK studies in pediatric patients. Using non-compartmental approaches for estimating AUC is not as reliable as the population pharmacokinetic model which takes all the data into consideration.

1.2 Recommendations

The Office of Clinical Pharmacology finds that there are adequate data in pediatrics to provide dosing recommendations in pediatric patients 1 year to 16 years of age.

Table 2. **Dosage and Administration in Pediatrics.**

(b) (4)

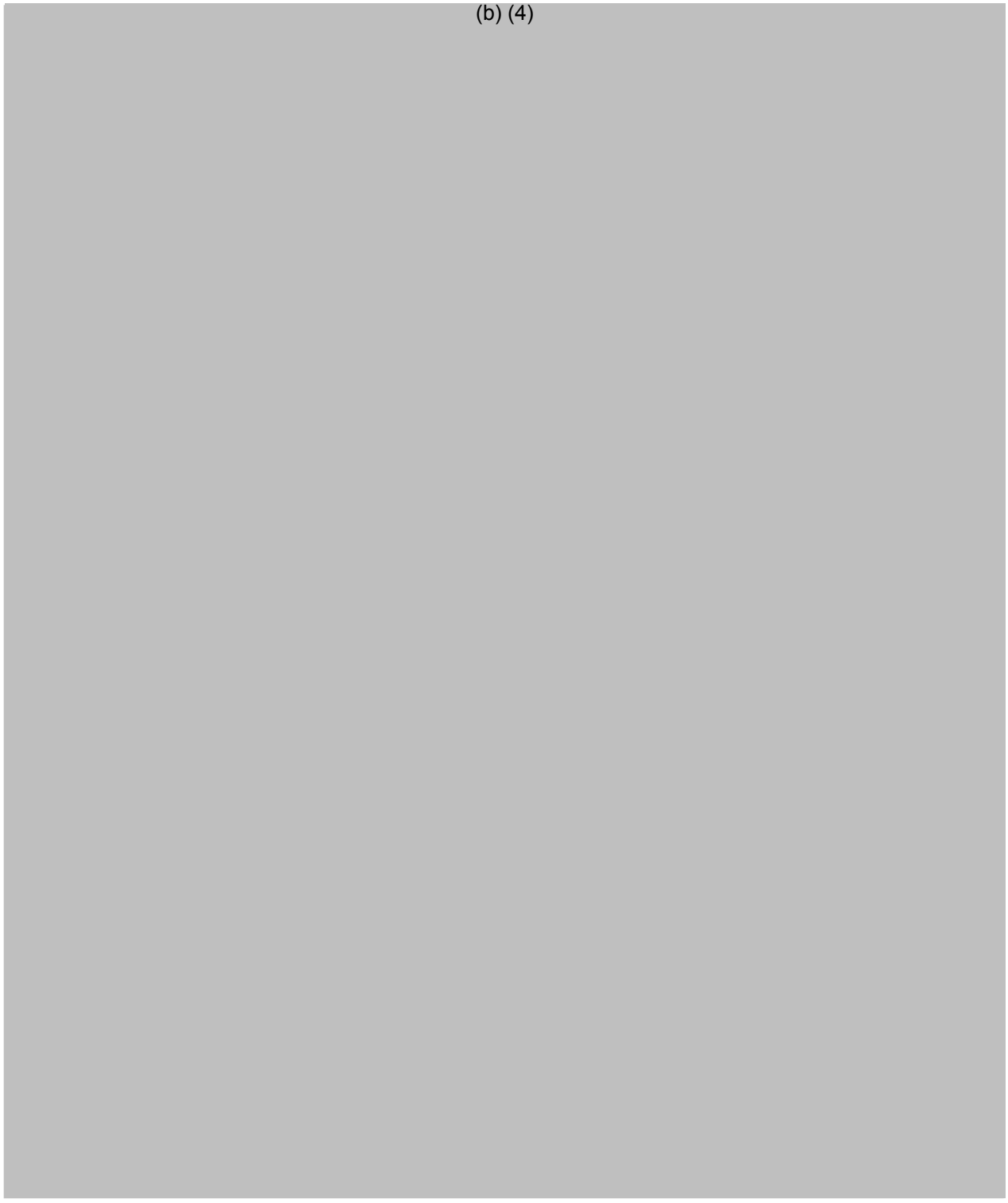
Protonix is not recommended for use in children less than one year of age. The efficacy of protonix has not been established for this age group. No differences between treatment groups were observed for the primary efficacy endpoint (rate of withdrawal due to lack of efficacy).

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

(b) (4)

(b) (4)



2 PERTINENT REGULATORY BACKGROUND

History of Pantoprazole Sodium Pediatric Program:

"Pantoprazole sodium was originally discovered by ALTANA Pharma in Konstanz, Germany and is currently under further development in the United States by Wyeth Research (WR). Pantoprazole (oral formulation tablet form) was first approved for marketing in 1994 in South Africa. As of 31 January 2006, the 40-mg tablet had received regulatory approval in 92 countries and marketing authorization in 75 countries. Sixty-eight (68) countries have granted marketing authorization for the intravenous (IV) formulation of pantoprazole by this date. The use of oral pantoprazole for short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis (EE) (New Drug Application [NDA] 20-987) was approved in the United States on 02 Feb 2000, its use for maintenance of healing of EE and control of daytime and nighttime heartburn symptoms in subjects with gastroesophageal reflux disease (GERD) (NDA 20-987/S-001) was approved on 12 Jun 2001, and its use for pathological hypersecretory conditions including Zollinger-Ellison syndrome (ZES) (NDA 20-987/S-007) was approved on 19 April 2002."

(Source: Introduction to Common Technical Document Summaries, Response to Pediatric Written Request)

3 RESULTS OF SPONSOR'S ANALYSIS

The results of sponsor's analysis are summarized below.

3.1 Population Pharmacokinetic Modeling of Pantoprazole in Pediatric Patients

3.1.1 Methods

Data from six clinical trials (3001A3-337-US, 3001B3-334-US, 3001B3-333-WW, 3001B3-331-WW, 3001K1-110-US, 3001K1-117-US) comprised the final population PK database. The clinical trials included single and multiple-dose data from pediatric patients with presumed or endoscopically proven gastroesophageal reflux disease GERD.

Data were analyzed using nonlinear mixed-effects modeling with the NONMEM® software system, Version VI (ICON Development Solutions). Model selection was guided by various goodness-of-fit criteria, including diagnostic scatter plots, convergence with at least 2 significant digits, plausibility of parameter estimates, precision of parameter estimates, and correlation between model parameter estimation errors < 0.95. Final model parameter estimates were reported with a measure of estimation uncertainty based on non-parametric bootstrap 95% confidence intervals.

A covariate modeling approach emphasizing parameter estimation rather than stepwise hypothesis testing was implemented for this population PK analysis. A full model was constructed, with care to avoid correlation or co linearity in predictors. Model parameters were estimated and assessment of any remaining trends was conducted by graphical inspection of all covariate effects. Inferences about clinical relevance of parameters were based on the resulting parameter estimates of the full model and measures of estimation precision. A predictive check model evaluation step was performed to assess the performance of the final model and parameters.

3.1.2 Results and Discussion

The pantoprazole pediatric population PK database was comprised of 202 patients contributing a total of 922 plasma pantoprazole concentrations. The study population consisted of 121 males and 81 females with ages ranging from 0.3 to 192 months (0.025 – 16 years) and weights ranging from 1.6 to 127 kg. There were 77 preterm (gestational age less than 38 weeks) infants ranging from 1 to 15 weeks preterm. Caucasians (72%) were the predominant race in the PK database, followed by African Americans (19%), with Asian, Hispanic, and other accounting for the remaining 9%. There were 4 poor metabolizers, 165 extensive metabolizers, and 33 with unknown cytochrome P450 (CYP) 2C19 metabolizer status.

The PK of pantoprazole in pediatric patients was described by a two-compartment model with first order absorption parameterized in terms of CL, V2, Q, V3, Ka, and F1 (Table 3). The median beta half-life estimate based on the final model was 2.3 hr with a range of 1.3 to 11 hours in subjects classified as CYP2C19 extensive/unknown metabolizers, with all but one subject having a beta half-life less than 7.5 hours. The four CYP2C19 poor metabolizers had beta half-lives ranging from 7.5 – 64 hours. Goodness-of-fit criteria indicated the final model did not demonstrate any systematic bias.

Table 3. Sponsor's Final Population PK Model Parameter Estimates.

Population parameter point-estimates, percent standard errors (%SE) and 95% CI from a non-parametric bootstrap are presented for the final full population model (Run 414; 414.lst and WyethPantoPKBoot414_997.csv).

Parameter	Fixed Effect Parameter Estimate (%SE)	Bootstrap 95% CI's
CL (L/hr)	1.93 (13%)	1.53, 2.61
*(WT/10)$^{\Theta 10}$	0.75 (fixed)	NA
$Hill_{CL}$	1.48 (13%)	0.979, 1.9
AG50 (yr)	0.153 (32%)	0.0896, 0.554
$AG50P_{preterm}$	1.38 (24%)	0.805, 2.08
*Θ15SEX	1.06 (12%)	0.832, 1.34
*Θ16CPH1	0.0716 (41%)	0.0274, 0.199
*Θ17RACE2	1.29 (12%)	0.995, 1.63
V2 (L)	1.3 (9%)	0.925, 1.56
*(WT/10)$^{\Theta 11}$	1 (fixed)	NA
Q (L/hr)	0.23 (23%)	0.155, 0.953
*(WT/10)$^{\Theta 10}$	0.75 (fixed)	NA
V3 (L)	0.596 (31%)	0.297, 0.974
*(WT/10)$^{\Theta 11}$	1 (fixed)	NA
Ka tablet (hr^{-1})	1.32 (9%)	1.05, 1.92
Lag Time (hr)	0.444 (3%)	0.4, 0.491
F1 tablet	1 (fixed)	NA
F1 spheroid	0.295 (17%)	0.175, 0.405
Ka spheroid (hr^{-1})	0.613 (18%)	0.428, 1.4
	Interindividual Variance (%SE)	
$\Omega^{1,1}$CL	0.412 (18%) CV%=64.2	0.242, 0.573
$\Omega^{1,2}COV_{CL-V2}$	0.0898 (115%) r=0.28	-0.234, 0.292
$\Omega^{2,2}$V2	0.25 (31%) CV%=50	0.113, 0.897
$\Omega^{3,3}$Ka	0.586 (32%) CV%=76.5	1.3e-11, 1.42
$\Omega^{4,4}F1_{IOV-spheroid}$	0.321 (27%) CV%=56.7	0.142, 0.519
	Residual variance (%SE)	
$\sigma^{1,1}$proIV	0.0678 (23%) CV%=26	0.0275, 0.101
$\sigma^{2,2}$proTAB	0.344 (17%) CV%=58.6	0.241, 0.476
$\sigma^{3,3}$addTAB-SPH	37 (58%) SD=6.08	8.27, 1940
$\sigma^{4,4}$proSPH	0.314 (10%) CV%=56	0.244, 0.377

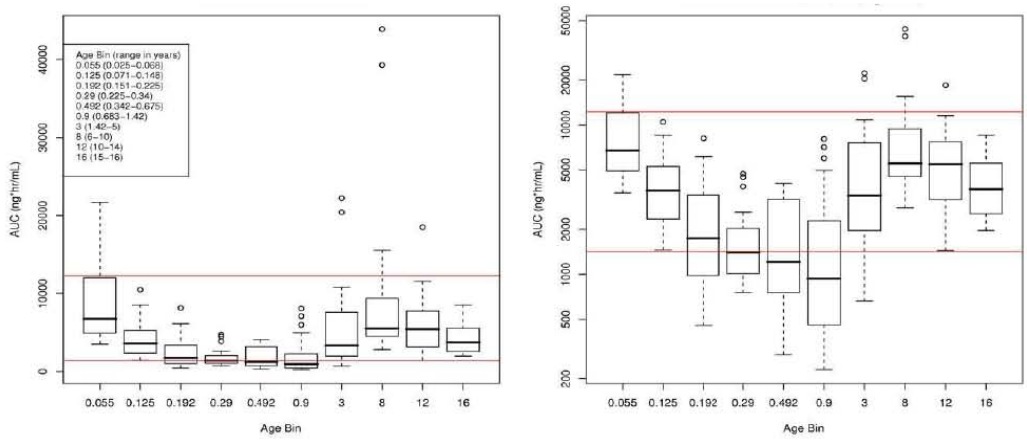
The model indicated the spheroid dosage form demonstrated decreased bioavailability and a slower absorption rate constant, as evidenced by typical population PK estimates for F1 and Ka (Table 3). The median age of the subjects receiving the spheroid in the studies available for this analysis was 0.3 years with the majority of subjects (116 out of 137) less than one year old. Physiologically, there is no reason for the bioavailability to be markedly lower in the youngest pediatric subjects. It is more likely that the decreased bioavailability estimated in this analysis is a result of incomplete intake of dose, due to the difficulty of administering a syringe or spoon of liquid to a child under one year of age, rather than a decreased bioavailability of the spheroid dosage form. Unfortunately, the available data does not allow this hypothesis to be tested. Studies in adults have estimated the absolute bioavailability of the tablet at 77%. The current dataset was not designed to estimate tablet bioavailability.

Variability in pantoprazole CL was partially explained by weight, age, and CYP2C19 metabolizer status. CL, V2, Q, and V3 were allometrically scaled to account for the physiology

of the pediatric population in this analysis. The effect of age was best described by a sigmoid Emax model that allowed the effect of age to represent up to 100% of the total allometrically scaled CL with the effect due to age decreasing as age increased. Infants less than one year of age were characterized by a decreased allometrically scaled CL, but the age effect reached an asymptote approximately equal to the adult allometrically scaled CL by 1 year of age. The effect of CYP2C19 poor metabolizer status on allometrically scaled CL resulted in a point estimate and 95% CI that were more than 70% lower than the typical value. The effect of African American race yielded an allometrically scaled CL point estimate greater than 25% of the typical value but a 95% CI that was wide and included one, which indicated the covariate may play a role in the prediction of pantoprazole CL but the current dataset does not contain enough information to determine if it is clinically relevant. The effect of sex on allometrically scaled CL contained the null value of one and its 95% CI was wide and fell primarily within the clinically unimportant range, but poor estimation precision precludes any definitive determination of clinical relevance.

The typical CL and Vss (V2 + V3) for a 70 kg adult, who was not a CYP2C19 poor metabolizer, based on the final model would be 8.3 L/hr and 13.3 L, respectively. This is in good agreement with the results (8 L/hr for CL and 11 L for V) presented in the NDA submission for pantoprazole. Individual CL estimates from the final model, and the associated subject-specific weight and age, were utilized to assess the effects of three different dosing scenarios on pediatric pantoprazole exposure. Scenario 1 (1.2 mg/kg) provided the best match to the adult AUC range with the majority of simulated AUCss falling within the adult range across all of the age bins except the 0.492 and 0.9 year age bins. Scenario 3 (highest fixed dose tested in each age group) provided similar results for the youngest (age bin: 0.192 years) and oldest (age bin: 3 years) children but resulted in simulated AUCss estimates for 50% or more of the individuals below the lower adult AUC range for the age bins from 0.29 to 0.9 years (Figure 3). Selection of pediatric dosing rules should be made while considering the PK results in the context of safety and efficacy findings, which were not included in these analyses.

Figure 3: Simulated AUC_{SS} for Highest Weight-Based and Fixed Dosing Without CYP2C19 Poor Metabolizers. The red line represents the range of values for Adults who received 40 mg tablets.



(Source: Sponsor's Population Pharmacokinetic Report Synopsis)

***Reviewer's comments on sponsor's population PK analysis**: The sponsor's population pharmacokinetic model takes into account as many factors as practical to improve the overall fitting of the model to the data. This was done in a manner that is both physiologically relevent and statistically significant. Body weight is relevant to volume of distribution and clearance, regardless of the age. Age is relevant for maturation of the liver CYP protein expression and its effect on the individual's clearance reaches the adult level after 1 year. Clearance is reduced 95% for poor metabolizers. However, the impact of gender and race on the model are small and not defined to be clinically meaningful. It is likely that these two factors are not critical for dosing recommendations.*

4 REVIEWER'S ANALYSIS

4.1 Objectives

Analysis objectives are:

1. To determine the major intrinsic factors (body weight, age, gender, race, and CYP2C19 metabolizer status) and extrinsic factors (administration with food) that influence the pharmacokinetics of pantoprazole sodium.
2. To use the results from the first objective to determine if the proposed regimen produces exposures in pediatric patients that match the adult range.
3. If the proposed regimen does not match exposures in adults, propose a new dosing regimen based on the relevant intrinsic factors (i.e body weight, age, metabolizer status) that match the pediatric exposures with the adult pantoprazole exposures.

4.2 Methods

4.2.1 Data Sets

Data sets used are summarized in Table 4.

Table 4. Analysis Data Sets

Study Number	Name	Link to EDR
PopPK	panto-all1r1.txt	\\Cdsesub1\evsprod\NDA022020\0020\m5\datasets\rpt-74378\analysis

4.2.2 Software

NONMEM IV was used to generate the final individual pharmacokinetic parameters. S-plus was used to compile and analyze the sponsor's provided data.

4.2.3 Models

The sponsor's pharmacokinetic model was reviewed to determine if all included covariates were significant and whether or not they are relevant to the dosing of pantoprazole. The final model was reconstructed sequentially from the covariates the sponsor included in the model (Table 5). Plots of clearance estimates against each intrinsic factor (body weight, age, gender, metabolizer status, and race), the magnitude of the intrinsic factor parameter estimates on clearance, the reduction in the IIV, physiological understanding, and the objective function value (OFV) were considered in determining the impact each covariate had on the individual's clearance estimate.

Table 5. Individual estimates of clearance are more precise when considering body weight, age, and metabolizer status.

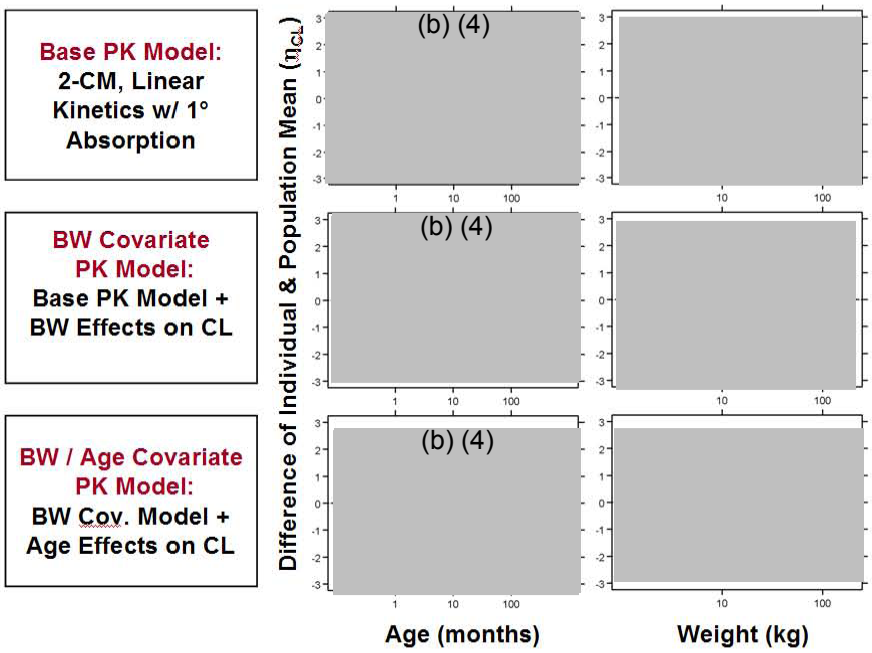
Model	Description	IIV of CL CV%	OFV
Base	BWT on CL, Q, Vc, Vd	34.9	11,567***
Cov1	Base + Age factor on CL (Age/(Age+A_{50})	29.1	11,499***
Cov2*	Cov1 + Gender on CL	N/A	11,499

Cov3	Cov2 + Metabolizer on CL	26.9	11,478***
Full	Cov3 + Race on CL	N/A	11,475
Final**	Cov1 + Metabolizer Status on CL	26.7	11,468***

* Model Cov2 did not converge successfully.
** The final fit was modified to allow the allometric scaling exponent for the BW covariate to be estimated. This improved model fitting and the covariance step was successful.
*** The covariance step completed successfully.

Figure 2 shows the reduction in the inter-individual variation of pantoprazole clearance (CL) as a function of age or body weight (BW) after 1) the inclusion of body weight as a covariate and 2) the subsequent inclusion of age as a covariate. Visual inspection of the difference between the base model (Figure 4, 1st row, 3rd column) and body weight covariate model by weight (Figure 4, 2nd row, 3rd column) indicates that the BW model corrects under-prediction of the clearance. However, there still appears to be a correlation between age and inter-individual variation of clearance for the youngest population (i.e. less than three years of age; Figure 4, 2nd row, 2nd column). Incorporating age as a factor on clearance eliminates the majority of the remaining bias in the model prediction as seen from the near symmetrical distribution about zero in the panels on the 3rd row of Figure 4.

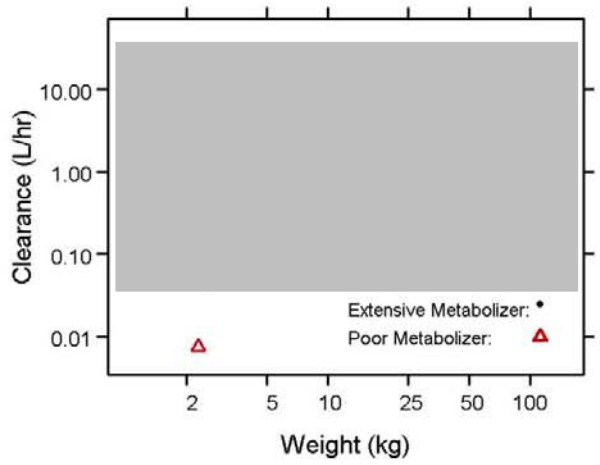
Figure 4. Including body weight and age as covariates on clearance significantly reduce the inter-individual variation of the clearance estimates.



Model development indicated that body weight is the key covariate on clearance (Figure 5) causing increased clearance with increasing body weight regardless of metabolizer status.

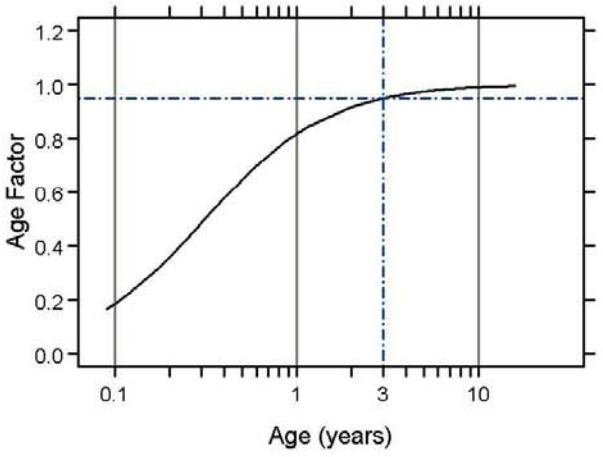
However, poor metabolizer status indicated a 96% reduction in clearance when compared to extensive metabolizers (Figure 5: open, red triangles).

Figure 5. Body weight is the key covariate affecting pantoprazole clearance in pediatrics >3 years of age.



The green line in Figure 5 is the prediction of clearance based on the effect of all the covariates except metabolizer status (body weight and age) excluding the contribution of the random IIV component. The line appears jagged at the lower weights as age is important in determining clearance of individuals less than 1-3 years of age (Figure 6). At 1 year the age factor reduces clearance 20%, i.e. to 80% of the adult value. At 3 years of age the age factor reduces clearance 5% (Figure 6, blue dashed lines). This diminished effect of age on clearance can be seen in Figure 5 where the green line becomes smooth.

Figure 6. Age factor (Age/(Age+A_{50})) vs. age. Age does not significantly influence clearance for pediatric patients older than 1-3 years of age.



The final model parameters and CV% are presented in Table 6. The effect of gender and race were removed from the sponsor's full model and the effect of body weight on clearance was estimated.

Table 6. Final Reviewer's PK Model Estimates and % Standard Errors.

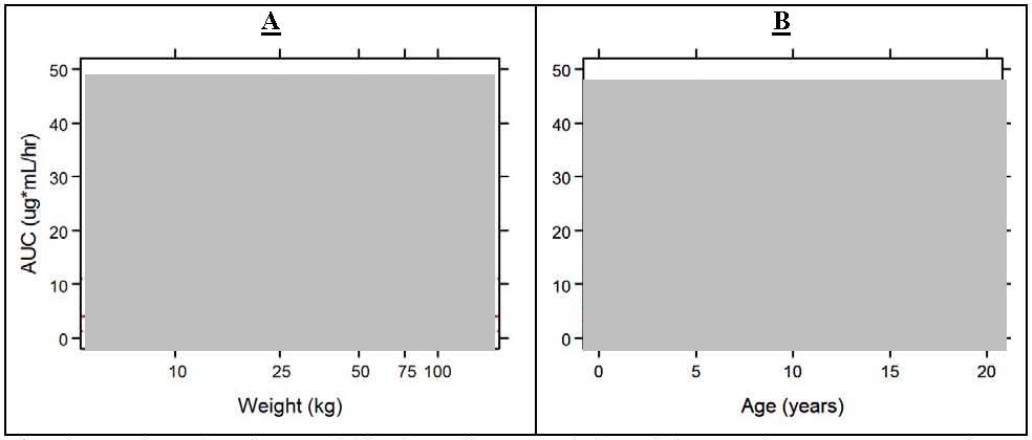
Parameter (units)	Description	Sponsor's Estimate	Final Estimate	Final RSE %
CL (L/hr)	Clearance	1.93	3.08	30.4
$*(WT/10)^{\theta 10}$	Exponent for BW Effect on CL & Q	0.75 (fixed)	0.457	32.0
$Hill_{CL}$	Hill Coefficient for Age Factor on CL	1.48	1.29	22.9
AG_{50} (yr)	Age at which Age Factor has ½-Maximal Effect	0.153	0.315	82.9
$AG_{50}P_{Preterm}$	Age for ½-Maximal Age Effect Preterm Infants	1.38	1.31	24.0
$*\theta_{16,CPH1}$	Effect of poor metabolizer on CL	0.0716	0.0682	30.4
V_2 (L)	Central Volume of Distribution	1.3	1.41	10.1
$*(WT/10)^{\theta 11}$	Effect of Body Weight on V_2 & V_3	1	1	FIXED
Q (L/hr)	Intercompartmental Clearance	0.23	0.307	32.0
V_3 (L)	Peripheral Volume of Distribution	0.596	0.916	44.5
$k_{a,tablet}$ (hr^{-1})	1st-order Absorption Rate Constant for Tablet	1.32	1.47	38.9
lag time (hr)	Delay in Absorption Relevant to Tablet	0.444	0.447	2.2
$F1_{tablet}$	Bioavailability of Tablet (Reference for dataset)	1	1	FIXED
$F1_{granule}$	Bioavailability of Granule Relative to Tablet	0.295	0.370	21.8
$k_{a,granule}$ (hr^{-1})	1st-order Absorption Rate Constant for Granule	0.613	0.63	20.3
Interindividual Variance (%SE)				
$\Omega^{1,1}CL$		CV%= 64.2	CV%= 64.9	2.96
$\Omega^{1,2}COV_{CL-V2}$	Covariance between CL and V_2	r = 0.28	r = 0.27	0.46
$\Omega^{2,2}V_2$		CV%= 50	CV%= 43.0	1.28
$\Omega^{3,3}k_a$		CV%= 76.5	CV%= 85.4	0.58
$\Omega^{4,4}F1_{IOV-Granule}$	Interoccasion Variation of Granule Formulation	CV%= 56.7	CV%= 54.7	1.60
Residual Variance (%SE)				
$\sigma^{1,1}$ proIV	proportional error model component: IV	CV%= 26	CV%= 26.6	5.90
$\sigma^{2,2}$ proTablet	proportional error model component: Tablet	CV%= 58.6	CV%= 57.0	11.0
$\sigma^{3,3}$ addTab-Gran	Additive error component: Tablet & Granules	SD = 6.08	SD = 5.16	2.56
$\sigma^{4,4}$ proGranule	proportional error model component: Granules	CV%= 56	CV%= 55.9	5.52

4.3 Results

4.3.1 Does the proposed dosing regimen produce exposures in pediatrics that are comparable to adults?

The final clearance estimates for each individual in the study population were used to predict their AUC's based on the sponsors proposed dosing regimen. These exposures were plotted against weight (Figure 7, Panel A) and age (Figure 7, Panel B) to further inform about the decision to dose based on age instead of weight. The AUC values in the pediatric population exceed those identified in the adult range by 29%. Further, increasing body weight appears to indicate a decrease in exposure within each dose group.

Figure 7. AUC increases with decreasing weight in each dose group. **Solid and dashed red lines represent the mean and range (minimum and maximum observed values) of the adult exposures. The symbols × and • indicate individual AUC estimates for the 20 and 40 mg dose groups (i.e. age < 6 yr receives 20 mg, age ≥ 6 yr receives 40 mg). Green, black and orange symbols indicate poor, extensive, or unknown CYP2C19 metabolizer status.**



The observations that 1) AUC shifts depending on weight and 2) AUC does not appear to change with age would suggest that dosing by body weight would better match adult exposures. In either case the poor metabolizers AUC values were much greater than the adult exposures (see section 4.3.3 for dosing recommendations based on metabolizer status).

4.3.2 Should the pediatric dosing be weight-based?

The final individual clearance estimates were also used to determine AUC values for an adjusted regimen based on body weight (Figure 8). The adjusted regimen included a 10 mg dose for the patients with the lowest body weight in addition to the 20 mg and 40 mg doses. Cutoffs by weight for each dose group were determined to match the pediatric exposures with the adult mean and range. Under the adjusted dosing regimen pediatrics < 15 kg would receive 10 mg oral suspension once-daily, pediatrics ≥ 15kg and < 40 kg would receive 20 mg of oral suspension or tablet depending on the age group (oral suspension for patients less than 5 years of age), and pediatrics ≥ 40 kg would receive the 40 mg tablet once-daily.

Figure 8. Dosing By Weight Matches Adult Exposures. **Solid and dashed red lines represent the mean and range (minimum and maximum observed values) of the adult exposures. The symbols ×, •, and, Δ indicate individual AUC estimates for the 10, 20, and 40 mg dose groups (i.e. body weight < 15 kg receives 10 mg, 15 kg ≤ body weight <40 kg receives 20 mg, and body weight ≥ 40 kg receives 40 mg). Green, black and orange symbols indicate poor, extensive, or unknown CYP2C19 metabolizer status.**

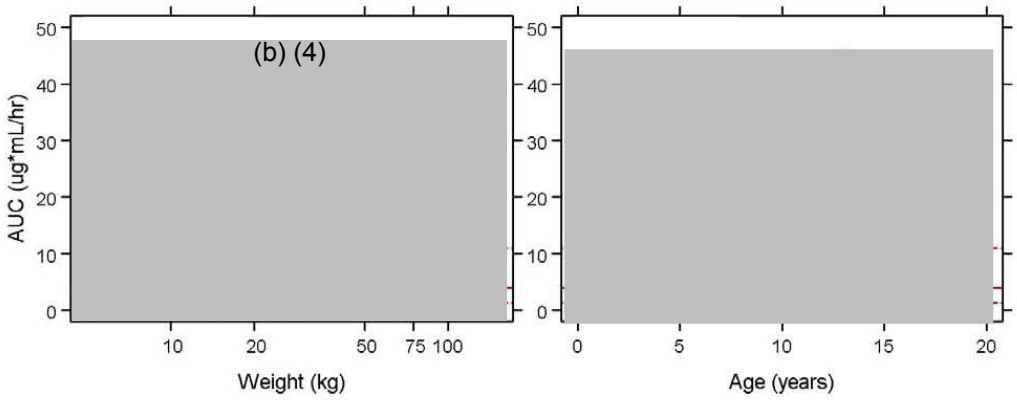


Table 7 shows the sponsor's and the FDA proposed dosing regimens and the exposures that correlate with these doses. In the pediatric population it is evident that the sponsor's proposed regimen (b) (4) Whereas the dosing regiment based on weight by FDA matches the adult exposures more closely.

Table 7. FDA proposed doses match adult exposures. **Results are presented as mean (Range: minimum – maximum). Poor metabolizers are excluded from this analysis.**

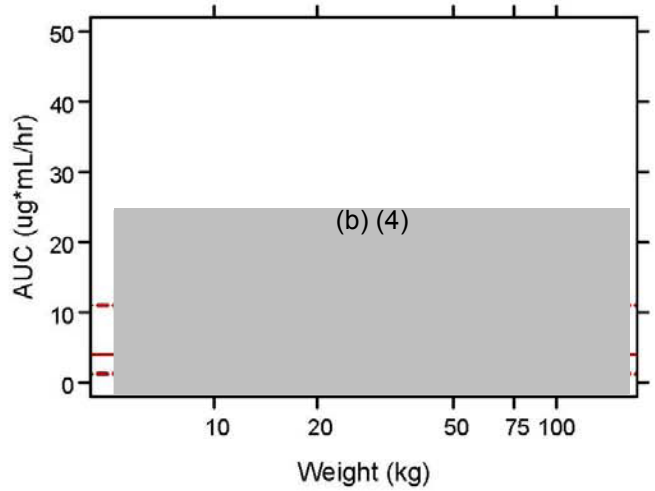
(b) (4)

Dosing by body weight is further supported by the similar results of effectiveness for the 10, 20, and 40 mg doses. No loss of effectiveness is anticipated with reducing the dose for the youngest patients, even if this yields reduced exposures for some patients. Subjects who received the 10 mg dose performed equally well in reducing the composite symptom score at 8 weeks (primary endpoint) to those who received 20 mg or the 40 mg doses.

4.3.3 Should there be dose reduction for CYP2C19 poor-metabolizers?

There should ideally be dose reduction to ¼ the recommended dose for individuals with poor CYP2C19 metabolizer status. The higher exposures can clearly be seen by the green symbols in Figure 7 and Figure 8. Further, clearance is reduced 95% by poor metabolizer status in the population pharmacokinetic model. In order to match exposures for extensive and poor CYP2C19 metabolizers, the poor metabolizer's dose should be reduced to ¼ the recommended dose across all weight groups. Exposures for the studied poor metabolizers after this dose reduction are depicted as green blocks in Figure 9.

Figure 9. Dose reduction to ¼ the proposed dose matches adult exposures for subjects with the poor metabolizer genotype. **Solid and dashed red lines represent the mean and range (minimum and maximum observed values) of the adult exposures. The symbols ×, •, and, Δ indicate individual AUC estimates for the 10, 20, and 40 mg dose groups (i.e. age < 6 yr receives 20 mg, age ≥ 6 yr receives 40 mg). Green, black and orange symbols indicate poor, extensive, or unknown CYP2C19 metabolizer status. Solid squares also denote poor metabolizer status.**



Genotyping for the sole purpose of dose adjustment may not be necessary. Pantoprazole sodium does not have a narrow therapeutic index and safety issues were not identified in the poor metabolizers who received the 20 or 40 mg doses. Further, there is a low prevalence in the Caucasian population (3%). However, the number of poor metabolizers is small and it is not possible to conclude that adverse events are not increased in this population.

4.3.4 Are the granule and tablet formulations comparable without dosage adjustment?

The table titled "Single-dose PK parameters for pantoprazole in healthy adult volunteers after administration of 40 mg pantoprazole under fasted condition (study 114)" in page 77 under

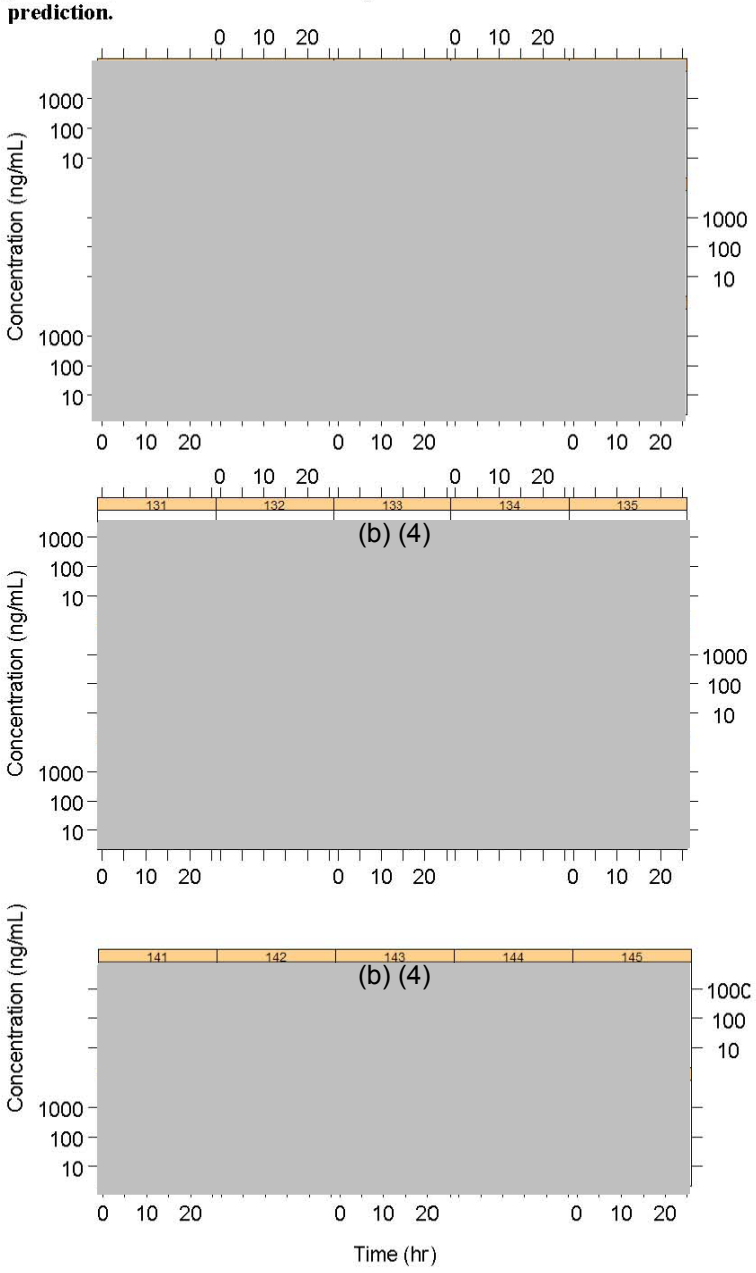
section 4.2. Individual Study Review indicates the pharmacokinetic profiles of the table and oral granule formulations almost entirely superimpose with the absorption phase being the exception. The C_{max} of the oral suspension formulation is 38% lower than the C_{max} of the tablet formulation. However, the AUC's are within 10% of each other. Based on the similarity of the pharmacokinetic profiles it is not anticipated that dose adjustment will be required when switching between formulations.

4.3.5 Do the pharmacokinetic parameter values from the population model agree with the parameter values presented in the label?

No, the population model predicts higher exposures than reported in the label. The pharmacokinetic sampling for 1-11 year olds was insufficient to capture the entire elimination time course of the drug (Figure 10). Pantoprazole sodium concentrations decline in a biexponential manner. Samples after 8 hrs post dose were not collected. In many patients the second terminal elimination phase is not present or obscured due to variation in the data. The values provided in the label were determined by non-compartmental analysis. This approach uses the last sampled data points to determine the remaining AUC area. Since the last sampled concentration-time points in this study (334) may not be reflective of the terminal decline and are highly variable, the values in the label are not reliable for this population (i.e. study 334). In study 334 the residual variation was higher than that of other pk studies in pediatric patients. Using non-compartmental approaches for estimating AUC is not as reliable as the population pharmacokinetic model which takes all the data into consideration.

The values in the label have been adjusted to reflect the model predictions for the respective patient demographics.

Figure 10. Individual model predictions for pantoprazole sodium concentrations in 1-11 year-old patients. Solid circles represent observed concentrations. The solid line indicates the model prediction.



5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
r414FinalBWest.ctl	Final PK Model Control Stream	Pantoprazole sodium\pk\
r414FinalBWest.lst	Final PK Model Output	Pantoprazole sodium\pk\NONMEM\ modelfit_dir30\
ModelCLEtaDist.ssc	S-plus code to produce Figure 4	Pantoprazole sodium\pk\
Pantoprazole_Covariates_Plots2.ss	S-plus code for remaining figures	Pantoprazole sodium\pk\
PKCheck.ssc	S-plus code for Figure 10	Pantoprazole sodium\pk\

4.4. Pharmacogenomics Review

Pharmacogenomics Review

NDA 22,020

PDUFA Date:	May 21, 2009
Drug Name:	PROTONIX (pantoprazole sodium) Delayed-Release Tablets and For Delayed-Release Oral Suspension
Pharmacogenomic Reviewer:	Li Zhang
Applicant:	Wyeth Pharmaceuticals Inc.

Indication:
1) Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)
2) Maintenance of Healing of Erosive Esophagitis
3) Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Review Date:	March 10, 2009

Metabolism Gene

The active ingredient in PROTONIX® (pantoprazole sodium) Delayed-Release Tablets and PROTONIX® (pantoprazole sodium) For Delayed-Release Oral Suspension is a compound that inhibits gastric acid secretion.

Pantoprazole is metabolized in the liver by the cytochrome P450 system. Metabolism mainly consists of demethylation by CYP2C19 followed by sulfation. Another metabolic pathway is oxidation by CYP3A4 (minor role). Pantoprazole metabolites are not thought to have any pharmacological significance. Pantoprazole is relatively free of drug interactions; however it may alter the absorption of other medications that depend on the amount of acid in the stomach, such as ketoconazole or digoxin.

CYP2C19 is located within a cluster of cytochrome P450 genes on chromosome 10 q24 (OMIM). Polymorphism within this gene is associated with variable ability to metabolize mephenytoin, known as the poor metabolizer (PM) and extensive metabolizer (EM) phenotypes. Genetic polymorphism (mainly CYP2C19*2, CYP2C19*3 and CYP2C19*17) exists for CYP2C19 expression, with approximately 3–5% of Caucasian and 15–20% of Asian populations being poor metabolisers with no CYP2C19 function [1]. Although these sub-populations of slow

pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (≤23%) with once daily dosing.

CYP3A4 is located on chromosome 7 q22 (OMIM), most abundant in liver and intestine. CYP3A4*1B allele was more common in Ghanaians and African Americans (gene frequency more than 50%) than in Caucasians (less than 10%), and was apparently nonexistent in Asians [2]. Desta(2002) [1] demonstrated in EMs, approximately 80% of doses of the proton pump inhibitors (PPIs) such as pantoprazole seem to be cleared by CYP2C19, whereas CYP3A is more important in PMs. In this submission, whether 3A4 mutations were associated with any metabolism phenotypes was not reported.

In the published literatures, several scientific findings were made.

1. As this enzyme is mainly responsible for the metabolism (hepatic elimination rate) of pantoprazole, AUC and pharmacodynamic response are much more dependent on the genotype/phenotype of CYP2C19 compared with esomeprazole (metabolic contribution by CYP3A4) or rabeprazole (eliminated mainly by a nonenzymatic pathway).
2. Proton-pump inhibitors interact with and are metabolized by several human CYP450, but only pantoprazole is also metabolized by a sulfotransferase. This may partly explain why, in this group of proton-pump inhibitors, pantoprazole has the lowest potential for interactions with other drugs.
3. In groups of patients at 2 to 16Y, statistically significant differences were observed for dose-normalized pantoprazole area under the plasma concentration-time curve when compared between CYP2C19 EM with 1 versus 2 functional alleles.
4. PM experience higher pantoprazole AUC compared with both heterozygous and homozygous EM, for whom there is a substantial overlap.

Genotyping Assay

The purpose of the genotyping validation in this PG review is to examine the accuracy, precision, specificity, and robustness of the methods to detect CYP polymorphisms. The following table demonstrates sponsor's genotyping method in each study.

Sample Size	Genotyping Method
Study 109: 24	PCR-RFLP (CYP2C19 *2, *3, *2B, *4, *5, *6, *7, *8)
Study 334: 59	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 333: 67	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 331: 59	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 337: 22	PCR-RFLP (CYP2C19 *2, *3, *4, *5; 3A4 *2, *3), ASA-PCR(3A4*1B)
Study 117: 4	PCR-RFLP (CYP2C19 *2, *3, *4, *5)

1) PCR-RFLP

A restriction fragment length polymorphism is a variation in the DNA sequence of a genome that can be detected by breaking the DNA into pieces with restriction enzymes and analyzing the size of the resulting fragments by gel electrophoresis. PCR-RFLP is a technique fragmenting a sample of DNA by a restriction enzyme, which can recognize and cut DNA wherever a specific

short sequence occurs, in a process known as a restriction digest. The resulting DNA fragments are then separated by length through a process known as gel electrophoresis, and transferred to a membrane via the Southern blot procedure. Hybridization of the membrane to a labeled DNA probe then determines the length of the fragments which are complementary to the probe. A RFLP occurs when the length of a detected fragment varies between individuals. Each fragment length is considered an allele, and can be used in genetic analysis. Analysis of RFLP variation is an important tool in genome mapping and genetic disease analysis.

CYP2C19 Genotype in Pediatric Pantoprazole Study Subjects:

- *2 allele: mutation in exon 5 creating an aberrant splice site and truncated protein and destroying a SmaI digestion site
- *3 allele: mutation in exon 4 creating a premature stop codon and destroying a BamHI digestion site

Defective *2 and *3 account for most of the PM alleles.

Additional assays for *2B, *4, *5, *6, *7, *8 alleles were also conducted.

- *2B allele: enzyme at BsmBI restriction site
- *4 allele: an adenine (A) to guanine (G) mutation creating the initiation codon. Enzyme at PstI restriction site.
- *5 allele: a cytosine (C) to thymine (T) mutation in exon 9. Enzymes at BstXI restriction site.
- *6 allele: enzyme at PstI restriction site.
- *7 allele: enzyme at MaeIII restriction site.
- *8 allele: enzyme at BsmBI restriction site.

CYP3A4 Genotype in Pediatric Pantoprazole Study Subjects:

- *2 allele: a thymine (T) to cytosine (C) base transition in exon 7 leading to a serine to proline substitution. Enzyme at XcmI restriction site.
- *3 allele: a thymine (T) to cytosine (C) base transition in exon 12 leading to a methionine to threonine substitution. Enzyme at BssSI restriction site.
-

2) ASA-PCR (Allele-Specific Amplification PCR)

This diagnostic or cloning technique is used to identify or utilize single-nucleotide polymorphisms (SNPs). It requires prior knowledge of a DNA sequence, including differences between alleles, and uses primers whose 3' ends encompass the SNP. PCR amplification under stringent conditions is much less efficient in the presence of a mismatch between template and primer, so successful amplification with an SNP-specific primer signals presence of the specific SNP in a sequence [3].

CYP3A4 Genotype in Pediatric Pantoprazole Study Subjects:

- *1B allele: an adenine (A) to guanine (G) mutation in the promoter region, altering 5' regulatory element.

3) Assay Validation: PCR-RFLP assay (CYP3A4*2, *3) and ASA-PCR assay (CYP3A4*1B)

i) Intra-Assay Precision

The testing was completed by the three scientists. Upon re-amplification and sample testing in duplicate, all repeat samples passed interpretation and matched with expected results.

ii) Inter-Assay Precision
The final genotypes from each sample run in triplicate, in tests performed by three scientists were identical. All samples amplified successfully during repeat testing.

iii) Accuracy
The genotypes determined by sequencing were identical to the genotypes detected by the PCR-RFLP.

iv) Specificity
The generated sequences aligned with the sequence found in Genbank.

v) Conclusion
The performances of assays resulted in definitive and unambiguous result interpretation on the test samples and controls. The performance of the assays successfully met all pre-determined acceptance criteria. Post validation monitoring procedures are also applied.

4) Genomic Analysis Results:
i) CYP2C19

In 6 genotyping studies, 6/226 individuals are identified as PM, 220/226 individuals are identified as EM. The *1 frequency across total datasets is 0.8054, *2 frequency across total datasets is 0.1902 and *4 frequency across total datasets is 0.0044. The frequencies of the CYP2C19 *1 and *2 in this analysis are in the range of the frequencies observed in American adult populations (0.775-0.871 for *1, and 0.129-0.198 for *2).

CYP2C19 genotyping in study #3001A1-109-US shows: 16/24 individuals are identified as *1/*1 homozygous EM, 5/24 individuals are identified as heterozygous *1*2, 1/24 individuals are identified as heterozygous *1*4 and 2/24 individuals are identified as *2/*2 homozygous PM. Therefore, *1 allele frequency is 0.792 (38/48), *2 allele frequency is 0.188(9/48), and *4 allele frequency is 0.021 (1/48).

CYP2C19 genotyping in study #3001B3-334-WW shows: 58/58 individuals are identified as *1/*1 homozygous EM. 1 individual failed to pass the genotyping. Therefore, *1 allele frequency is 0.853 (99/116), and *2 allele frequency is 0.147(17/116).

CYP2C19 genotyping in study #3001B3-333-WW shows: 51/63 individuals are identified as *1/*1 homozygous EM, 10/63 individuals are identified as heterozygous and 2/63 individuals are identified as *2/*2 homozygous PM. 4 individuals failed to pass the genotyping. Therefore, *1 allele frequency is 0.889 (112/126), and *2 allele frequency is 0.111(14/126).

CYP2C19 genotyping in study #3001B3-331-WW shows: 42/56 individuals are identified as *1/*1 homozygous EM, 12/56 individuals are identified as heterozygous and 2/56 individuals are

identified as *2/*2 homozygous PM. 3 individuals failed to pass the genotyping. Therefore, *1 allele frequency is 0.857 (96/112), and *2 allele frequency is 0.143(16/112).

CYP2C19 genotyping in study #3001A3-337-US shows: 17/21 individuals are identified as *1/*1 homozygous EM, 4/21 individuals are identified as heterozygous *1*2. 1 individual failed to pass the genotyping. Therefore, *1 allele frequency is 0.905 (38/42), and *2 allele frequency is 0.095(4/42).

CYP2C19 genotyping in study #3001K1-117-US shows: 4/4 individuals are identified as *1/*1 homozygous EM. Therefore, *1 allele frequency is 1.0(8/8).

ii) CYP3A4

The *1 frequency across total datasets is 0.727, *1B frequency across total datasets is 0.262, and *3 frequency across total datasets is 0.011.

CYP3A4 genotyping in study #3001B3-334-WW shows: 40/50 individuals are identified as *1/*1, 7/50 individuals are identified as heterozygous *1*1B, 2/50 individuals are identified as heterozygous *1*3, and 1/50 individuals are identified as *1B/*1B. 9 individuals failed to pass the genotyping. Therefore, *1 allele frequency is 0.89 (89/100), *1B allele frequency is 0.09(9/100), and *3 allele frequency is 0.02(2/100).

CYP3A4 genotyping in study #3001B3-333-WW shows: 45/60 individuals are identified as *1/*1, 13/60 individuals are identified as heterozygous and 2/60 individuals are identified as *1B/*1B. 7 individuals failed to pass the genotyping. Therefore, *1 allele frequency is 0.858 (103/120), and *1B allele frequency is 0.142(17/120).
CYP3A4 genotyping in study #3001B3-331-WW shows: 45/56 individuals are identified as *1/*1, 8/56 individuals are identified as heterozygous and 3/56 individuals are identified as *1B/*1B. 3individuals failed to pass the genotyping. Therefore, *1 allele frequency is 0.875 (98/112), and *1B allele frequency is 0.125(14/112).

CYP3A4 genotyping in study #3001A3-337-US shows: 13/21 individuals are identified as *1/*1, 7/21 individuals are identified as heterozygous and 1/21 individuals are identified as *1B/*1B. 1 individual failed to pass the genotyping. Therefore, *1 allele frequency is 0.786 (33/42), and *1B allele frequency is 0.214(9/42).

Pharmacogenetic Comments

Pantoprazole exhibited a variable acid inhibition that was significantly dependent on the CYP2C19 genotype. As there is a significantly positive relationship between the extent and duration of elevated intragastric pH and the clinical efficacy of pantoprazole, we can anticipate CYP2C19 genotype has a significant impact on the therapeutic outcome and a genotype-adjusted dosage regimen may improve therapeutic efficacy. We recommend sponsor's efficacy studies to include genotyping data investigation.

Reference:

1) Desta Z, Zhao X, Shin JG et al. (2002). "Clinical significance of the cytochrome P450 2C19 genetic polymorphism". Clin Pharmacokinet 41 (12): 913–58. PMID 12222994
2) Zeigler-Johnson, C. M.; Walker, A. H.; Mancke, B et al. (2002). "Ethnic differences in the frequency of prostate cancer susceptibility alleles at SRD5A2 and CYP3A4". Hum. Hered. 54: 13-21. PMID : 12446983
3) Newton CR, Graham A, Heptinstall LE, Powell SJ, Summers C, et al. (1989). "Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS)". *Nucleic Acids Research* **17** (7): 2503–2516. PMID 2785681

4.5. OCP Filing Form

Office of Clinical Pharmacology

w Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-020**	**Brand Name**	**Protonix**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Pantoprazole sodium**
Medical Division	**DGP**	**Drug Class**	**PPI**
OCP Reviewer	**Insook Kim, Ph.D.**	**Indication(s)**	**GERD**
OCP Team Leader	**Sue-Chih Lee, Ph.D.**	**Dosage Form**	**Granules for oral suspension** **Oral tablet**
Pharmacometrics Reviewer	**Justin Earp, Ph.D.**	**Dosing Regimen**	**20 mg QD** **40 mg QD**
Date of Submission	**11/21/2008**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**March 24, 2009**	**Sponsor**	**Wyeth**
Medical Division Due Date	**April 1, 2009**	**Priority Classification**	**Priority**
PDUFA Due Date	**5/21/2009**		

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**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:		**3**		
multiple dose:		**4**		
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:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:		**1**		
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:		**2**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:		**1**		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:		**1**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies		**2**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**11**		

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?			n/a	
2	Has the applicant provided metabolism and drug-drug interaction information?			n/a	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	y			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	y			
5	Has a rationale for dose selection been submitted?	y			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	y			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	y			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	y			
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)?	y			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	y			
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)?	y			Dose-ranging studies
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	y			Dose-response relationship
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			n/a	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?				Pending review
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	y			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	y			
	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?	y			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			n/a	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ____yes___

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.

The sponsor stated that the commercially available 40 mg delayed-release granules formulation (co-developed with Nycomed, formerly ALTANA Pharma) was not selected because it is not bioequivalent to the pediatric formulation. Please, guide the reviewer to the study report if submitted.

Insook Kim, Ph.D. 1/14/2009

Reviewing Clinical Pharmacologist Date

Sue-Chih Lee, Ph.D. 1/14/2009

Team Leader/Supervisor Date

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20987	SUPPL 36		PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
NDA 20987	SUPPL 36		PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
NDA 20987	SUPPL 37		PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 2		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 2		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 2		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 2		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 2		PROTONIX DELAYED RELEASE GRANULES

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

/s/

INSOOK KIM
08/13/2009

JUSTIN C EARP
08/13/2009

LI ZHANG
08/13/2009

ISSAM ZINEH
08/13/2009

CHRISTOFFER W TORNOE
08/13/2009

SUE CHIH H LEE
08/13/2009