OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA 20-406/S-067 NDA 21-281/S-024 NDA 21-428/S-017	Submission Date(s): April 25, 2008
Brand Name	Prevacid®
Generic Name	lansoprazole
Reviewer	PeiFan Bai, Ph.D., Kristina Estes, Pharm.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Gastroenterology Products
Sponsor	TAP Pharmaceutical Products Inc.
Submission Type; Code	Supplements
Formulation; Strength(s)	NDA 20-406/S-067: PREVACID® (lansoprazole) Delayed-Release Capsules 15 mg, 30 mg NDA 21-281/S-024: PREVACID® (lansoprazole) For Delayed-Release Oral Suspension 15 mg, 30 mg NDA 21-428/S-017: PREVACID® SoluTab™ (lansoprazole) Delayed-Release Orally Disintegrating Tablets, 15 mg, 30 mg
Indication	Symptomatic and/or endoscopically proven Gastroesophageal Reflux Disease (GERD)

Table of Contents

1 Executive Summary

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective. Though the sponsor is not requesting the GERD indication for neonates or infants due to the lack of clinical efficacy in infants, OCP will recommend appropriate description about the PK/PD results in the approved label.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Product: For neonates and infant 0-11 months of age, lansoprazole pediatric suspension is formulated by (b) (4)

[redacted]

Regulatory background:

The Agency issued a Pediatric Written Request for lansoprazole to TAP on August 26, 1999. There were four studies requested in the PWR. TAP submitted Study M97-808 to Supplement 20-406 / SE5-047, which evaluated the PK/PD and efficacy in 1-11 year old patients. Supplement 20-406/SE-047 was approved 07/31/02. To Supplement 20-406/S-057, TAP submitted study M97-640, which determined the PK/PD and efficacy in pediatric patients aged 12-17. Supplement 20-406/S-057 was approved 06/17/04

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To this supplement, TAP submitted study 03-042 and study 03-043, which assess primarily the PK/PD effect in neonates less than 44 weeks of corrected age and infants aged1-11 months, respectively.

The Pediatric Exclusivity Board meeting for NDA 20-406, 21-281 and 21-428 (Prevacid) was held July 15, 2008 and it was concluded that the studies submitted met the PWR requirements. The pediatric exclusivity is granted for PREVACID®.

A separate safety and efficacy study in infants was also submitted, which did not demonstrate efficacy of the studied doses (1.0 and 2.0 mg/kg/day). As such, the sponsor is not pursuing any indication in infants and neonates.

(A) Neonates

Pharmacokinetics:

Single dose and repeated doses: Lansoprazole in neonates showed approximate dose proportionality for both cmax and AUC between 0.5 and 1 mg/kg/day. The 0.5/mg/kg/day group had more physical maturity, and was <1 week older, than the 1 mg/kg/day group. Following repeated dosing, the 2-hr post-dose concentrations were 37% and 34% higher on day 5 than on day 1 for 0.5 mg/kg/day and 1 mg/kg/day, respectively. The 6-hr post dose concentrations were similar on days 1 and 5 for both dose regimens.

Body weight: For the 1 mg/kg/day dose group, dose-normalized AUC and Cmax each showed a positive trend with body weight with a r2 of 0.77 and 0.63, respectively. Pooled data from 0.5 and 1 mg/kg/day groups did not show as strong a trend with body weight as the 1 mg/kg/day group.

Chronological age: Dose-normalized AUC decreased with chronological age up to 6 weeks. Dose-normalized CL/F increased with chronological age with a r2 of 0.48. CL/F did not show an association with body weight when the data of both dose groups were pooled, but showed a small negative trend with body weight with a r2 of 0.34 for the 1 mg/kg/day group.

*Neonaes vs older children, adolescent and adults: A*dults had much lower AUC than neonates based on an equivalent dose per body weight; as did the adolescent group and children ages 1 to 17. Based on an equivalent dose, lansoprazole AUC decreased dramatically from neonates to children ages 1-11 and then slightly to adolescents, and was similar between adolescents to adults. Half-life was 2-3 hrs and longer than those reported for children ages 1-17 and adults. According to the literature 2C19activity is low in the first few weeks of life, reaches the adult level by 6-12 months of age, and then exceeds the adult level between 1 and4 years old and then gradually declines to the adult level by puberty.

CYP2C19 genotype: The limited number of neonates precludes any conclusion about the relationship between 2C19 genotype and lansoprazole.

Gender: It appears that there is no difference in AUC between female and male wt/wt neonates.

Exposure/pharmacodynamic relationship
The number of subject in either dose group was too small for clinically meaningful comparisons.

Exposure/efficacy relationship and exposure/safety relationship
Based on symptom relief and the number of regurgitation/vomiting episodes, there is no exposure/efficacy relationship. Based on treatment-related adverse events, there is no exposure/safety relationship.

(B) Infants

Pharmacokinetics
Single and Multiple Dose PK: On Day 1, C_{max} values for the two dose groups were approximately dose-proportional; however, mean AUC values were higher than dose-proportional between 1 and 2 mg/kg/day. This disproportionate result with regard to AUC was driven by two 6-week-old subjects which, have significantly higher exposure per kg relative to older subjects. There appears to be no accumulation by Day 5, a

finding that is different for infants relative to neonates. The 2-hour (approximate C_{max}), and 6-hour lansoprazole plasma concentrations were similar on Days 1 & 5 for both dose regimens.

Chronological Age:
On Day 1, dose-normalized AUC was greater than 5-fold higher for the three infants ≤ 10 weeks old relative to those > 10 weeks; however, among subjects > 10 weeks of age, no apparent relationship between age and AUC exists. Similarly, apparent clearance was greater than 6-fold lower in the youngest infants; however in patients > 10 weeks of age, no relationship between age and CL/F exists.

CYP 2C19 Genotype: Of the twenty infants who underwent genotype analysis, there were no poor metabolizers and only three heterozygous extensive metabolizers; therefore, no conclusions may be drawn regarding the relationship between genotype and lansoprazole pharmacokinetics.

Infants vs Older Children, Adolescents, and Adults: Infants ≤ 10 weeks old have much higher exposure (dose-normalized to 1 mg/kg/day) relative to all other age groups (3.5- to 8.7-fold higher). Infants > 10 weeks of age (dose-normalized to 1 mg/kg/day) had similar exposure to children who received a weight-based regimen of either 15 or 30mg/day for those children ≤ 30kg or > 30kg, respectively. These infants also have a similar exposure as adolescents and healthy adult subjects who receive 30mg/day. Adolescents who receive only 15mg/day have a lower exposure than infants > 10 weeks of age.

Exposure / Pharmacodynamic Relationship
The high-dose group is no better than the low-dose group when measuring percent time intragastric pH exceeds 3, 4, 5, & 6 over a 24 hour period on either Day 1 or Day 5. Both dose groups see increases in the percent time pH exceeds 3, 4, 5, & 6 on Day 5 relative to Day1. Based on this data, we conclude that there is no exposure/response relationship.

Exposure / Efficacy and Exposure / Safety Relationship
Overall, GERD symptom relief by Day 5 improved in both dose groups; 83% in the 1 mg/kg/day groups and 92% in the 2 mg/kg/day group. The most frequent baseline symptom, regurgitation and vomiting, was not improved in either dose group. There was no difference in the number of adverse events during the dosign period between the two dose groups. We conclude that there may be an exposure / efficacy relationship but there is not an apparent exposure / safety relationship.

Efficacy and safety Trial
A dedicated efficacy and safety study was conducted in infants by the sponsor. Due to lack of clinical efficacy in infants, the sponsor did not propose any additions to the approved labels for the referenced NDAs.

2 Question Based Review

2.1 General Attributes

2.1.1 What is the regulatory background?

The Agency issued a Pediatric Written Request for lansoprazole to TAP on August 26, 1999. There were four studies requested in the Aug-26-1990 PWR. TAP submitted Study M97-808 to Supplement 20-406 / SE5-047, which evaluated the PK/PD effects and efficacy in 1-11 year patients. Supplement 20-406/SE-047 was approved 07/31/02. To Supplement 20-406/S-057, TAP submitted study M97-640, which determined the PK/PD effect and efficacy in pediatric patients aged 12-17. Supplement 20-406/S-057 was approved 06/17/04

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2.1.2 What were the lansoprazole dosage and route of administration studied in neonates and infant?

The formulations of Prevacid® (lansoprazole) Delayed-Release Capsules, Prevacid® (lansoprazole) Delayed-Release Oral Suspension, Prevacid® Solu Tab (lansoprazole) Delayed-Release Orally Disintegrating Tablets are approved for the treatment of Symptomatic GERD and erosive esophagitis in adults as well as in the pediatric patients 1-17 years of age.

For neonates and infant 0-11 months of age, lansoprazole pediatric suspension is formulated by (b) (4)

2.1.3 What is the proposed indication of Prevacid®?

Prevacid® is a proton pump inhibitor. The studies submitted were conducted in neonates and infants (ages 0-11 months) with GERD. Due to failure in demonstrating the clinical efficacy in infants, the sponsor is not seeking an indication in these patients.

2.1.4 What is the proposed mechanism of action of Prevacid®?

Lansoprazole, the active ingredient of Prevacid®, irreversibly binds to, and inactivate, the gastric proton pump, thereby reducing the gastric acid output and elevating the gastric pH.

2.2 General Clinical Pharmacology

2.2.1 What were the doses studied and the rationales for the dose selection for neonates and infants?

Neonates: The doses were 0.5 mg/kg/day and 1 mg/kg/day.
Infants: The dose groups were 1 and 2 mg/kg/day.

Dose selection rationales provided by the sponsor: Lansoprazole is approved for use in children 1 to 11 years of age at doses of 15 mg/day for those weighing ≤30 kg and at 30 mg/day for those weighing >30 kg. In a previous TAP Study (M97-808), the mean final dose for 7 children aged 16 to 23 months was 1.4 mg/kg/day. These doses are generally higher than those administered to adults when normalized for body weight (NDA 20-406/S-047). There is PK and PD evidence that orally administered lansoprazole in subjects aged >3 months and in young children has a higher apparent plasma clearance as compared to adults. There are reports in the literature where lansoprazole doses of approximately 0.5 to 1.7 mg/kg were used in children 3 months to approximately 14 years of age. In 23 patients ages 4 months to 13 years with reflux esophagitis, 39% (9/23) of subjects responded to treatment with lansoprazole 0.73 mg/kg/day for 7 days (response was defined as an esophageal pH >3 for >65% of a 24-hour period). An additional 6 patients responded only after the dosage was increased to 1.44 mg/kg/day for the subsequent 7 days, bringing the total number of responders to treatment combined to 15 of the 23 subjects.

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) recommends that infants who require PPIs be given an oral dose of approximately 1.4 mg/kg/day. In addition, after reviewing PK information of orally dosed lansoprazole in children aged 3 months to 13 years, Faure et al have suggested a lansoprazole starting dose of 1.4 mg/kg/day in children 3 months to 13 years of age.

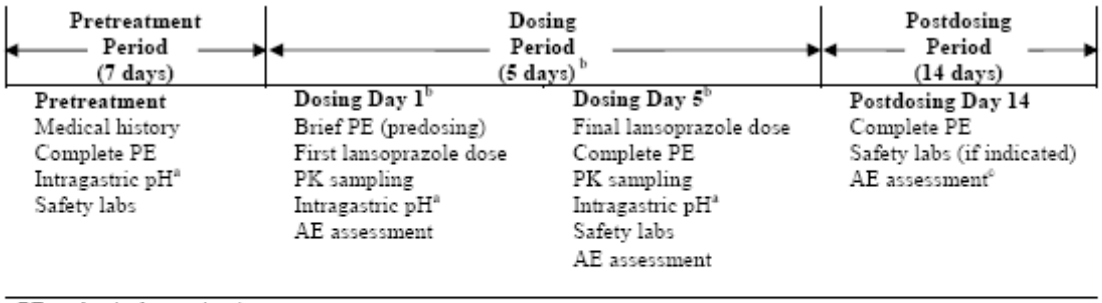
The sponsor's rationales for dose selection in neonates and infants are considered acceptable.

2.2.2 What are the design features of the submitted studies for neonates and infants?

Neonates:
This was a Phase 1, single- and repeated-dose, randomized, parallel group, open-label, 2-country, multicenter study. The study was designed to characterize the pharmacokinetic and pharmacodynamic profiles and to assess the safety of lansoprazole pediatric suspension (0.5 or 1.0 mg/kg/day) following 5 days of oral administration in neonates (chronological age <28 days for term/postterm infants or corrected age <44 weeks for preterm infants) with clinically evident GERD. The study evaluated the PD profile of lansoprazole by measuring intragastric and intraesophageal pH in a subset of 6 of the 24 neonates enrolled in the study. Twelve subjects were preterm (gestational age <38 weeks), and 12 subjects were term (gestational age 38-42 weeks). No subject was postterm (i.e. gestational age >42 weeks).

The study consisted of 3 periods as shown below. Any adverse event (AE) that occurred up to 30 days after the last dose of study drug was also recorded.

Study Design for Subjects Undergoing pH Evaluations



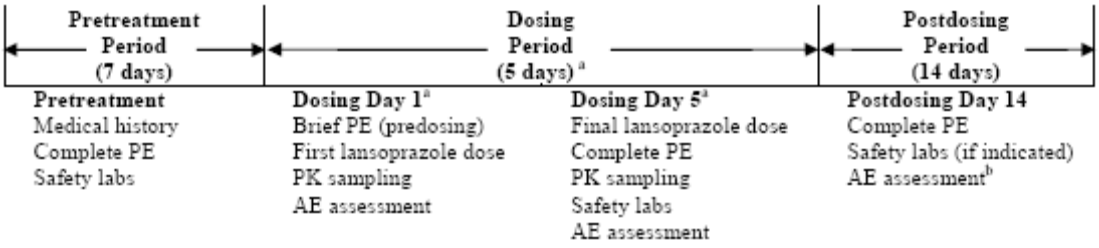
PE = physical examination.

a Intraesophageal pH could be done in addition to intragastric pH, at the discretion of the investigator.

b If a subject vomited within 1 hour postdose on Dosing Days 1 or 5, study procedures for that day were stopped and the schedule of procedures was shifted accordingly to the following day.

c AEs and serious adverse events (SAEs) continued to be captured for 30 days after the last dose of study drug.

Study Design for Subjects Not Undergoing pH Evaluations



PE = physical examination.

a If a subject vomited within 1 hour postdose on Dosing Days 1 or 5, study procedures for that day were stopped and the schedule of procedures was shifted accordingly to the following day.

b AEs and SAEs continued to be captured for 30 days after the last dose of study drug.

Infants:

Study C03-043 was a Phase 1, single- and repeated-dose, parallel group, multicenter, 2-country, randomized, open-label study in 24 infants 1 to 11 months of age with clinically evident GERD. Infants were treated with either 1 or 2 mg/kg/day for five days. Blood was drawn on Days 1 & 5 in order to characterize the single- and multiple-dose pharmacokinetics of lansoprazole. Intragastric and intraesophageal pH were measured for 24 hours postdose in a subset of 6 patients. Infants were also assessed for symptoms of GERD at baseline and during the dosing period. The study consisted of three periods as shown for the neonate study.

Summary: Both study designs met the requirements set forth in PWR in terms of the number of subjects (≥ 12 per treatment group for pharmacokinetics and ≥ 6 for pharmacodynamics), two dose levels, single-dose and multiple-dose pharmacokinetics, and pharmacodynamic measurements.

2.2.3 What are the patient demographics at baseline?

Neonates:

As shown below, the subjects involved are equally distributed between males and females. The majority of subjects were non-Hispanic Whites.

Table 1. Demographics of neonates

Demographic Variable	Lansoprazole 0.5 mg/kg/day (n=12)	Lansoprazole 1.0 mg/kg/day (n=12)
Gender	6M, 6F	5M, 7 F
Race	White: 12	White: 11, Black: 1
Chronological age weeks Mean (SD)	4.1 (4.87)	3.3 (3.11)
Weight (g)	3339 (763)	2690 (926)
Length (cm)	53 (3.8)	49 (5.7)
Head Circumference (cm)	34.2 (2.1)	33.1 (2.6)

Mean (SD)

The 0.5 mg/kg/ day group was less than 1 week older than the 1.0mg/kg/day group and showed more mature physical appearance (weight, length and head circumference).

Infants:

Table 2. Infant study demographics:

Variable		Lansoprazole 1 mg/kg/day (n=12)	Lansoprazole 2 mg/kg/day (n=12)
Gender	Male	8 (66.7%)	6 (50%)
	Female	4 (33.3%)	6 (50%)
Race	Black or AA	5 (41.7%)	7 (58.3%)
	White	7 (58.3%)	5 (41.7%)
Ethnicity	Hispanic	3 (25%)	3 (25%)
	Not Hispanic	9 (75%)	9 (75%)
Chronological Age (SD)		24 (13.44) Range 6-54	24.2 (13.59) Range 6-50
Corrected Age (SD)		59.5 (12.1)	59.8 (12.88)

The 1 mg/kg/day group included more males and white infants. The 2 mg/kg/day group included 2 infants aged 6 weeks old while the lower dose group had only one such infant.

2.2.4 What are the pharmacokinetic characteristics in neonates?

Table 2. Mean Plasma Concentrations of Lansoprazole Following Oral Administration of 0.5- or 1.0-mg/kg/day Dose of Lansoprazole Pediatric Suspension on Dosing Days 1 or 5 in 24 Neonates with GERD

	0 hr	1 hr	2 hr	3 hr	4 hr	6hr	8 hr	12 hr
0.5 mg day 1	0	412.2 (128)	571.8 (86)	581.1 (63)	537.1 (55)	382 (48)	270.5 (57)	166.3 (67)
0.5 mg day 5	17.6 (157)	-	783.7 (51)	--	--	416.8 (40)	--	--
1 mg day 1	0	540.2 (114)	1099 (95)	1029.8 (76)	1015.4 (75)	761.5 (81)	527.5 (80)	240.9 (76)
1 mg	22.78	--	1471.9	--	--	690.4	--	--

day 5	(158)		(51)			(58)		

Mean (CV%)

For both dose regimens, there was carryover from the previous dose, resulting in non-zero concentrations at time zero before dosing on day 5. The observed non-zero concentrations at time zero are considered acceptable since they are <10% of the respective 2-hr post-dose concentrations. For multiple dosing, it is acceptable that the sponsor only collected blood samples at 2 and 6 hrs post dose considering the patients were neonates, where the 2-hr post-dose was close to Tmax and the 6-hr post-dose was approximately two half-lives after dosing. For each of 0.5 mg/kg/day and 1 mg/kg/day dose regimens, the day-5 concentration at 2 hrs post dose was higher than the corresponding day-1 concentration; likewise for the 6-hr post dose concentration from the 0.5 mg/kg/day regimen. In the 1mg/kg/day group, the 6-hr post dose concentrations on days 1 and 5 were similar.

Table 3. Mean plasma lansoprazole pharmacokinetic parameters estimates in neonates

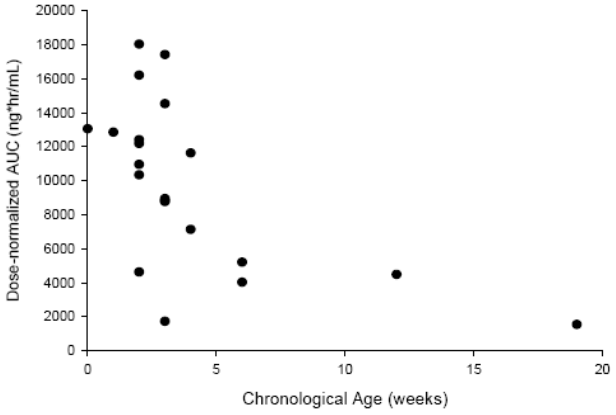
	Tmax (hr)	Cmax (ng/ml)	AUC (ng*h/ml)	T1/2[a] (hr)	CL/F (L/h/kg)
0.5 mg/kg/day[b]	3.1 (70)	831 (46)	5086 (51)	2.76	0.16 (111)
1 mg/kg/day[c]	2.6 (58)	1672 (48)	9372 (51)	1.97	0.16 (92)

Mean (CV%) a: harmonic mean; b: corrected age 35-43 weeks; c: corrected age 30-44 weeks

Oral absorption of lansoprazole in neonates reached was relatively rapid with tmax less than 3.5 hrs. Based on the coefficients of variation, lansoprazole is a highly variable drug. The AUC and Cmax showed approximate dose proportionality over the two doses studied, as evidenced by the same apparent oral clearance.

Dose-normalized AUC

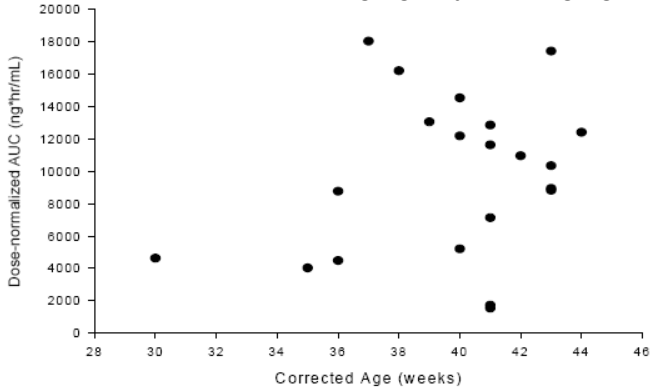
Fig 1. Lansoprazole Dose-normalized AUC vs. Chronological Age in Neonates Following Oral Administration of 0.5 mg/kg/day or 1 mg/kg /day Lansoprazole



The dose-normalized AUC seemed to decrease sharply with chronological age (weeks) until 6 weeks and then remained relatively constant up to 19 weeks. The

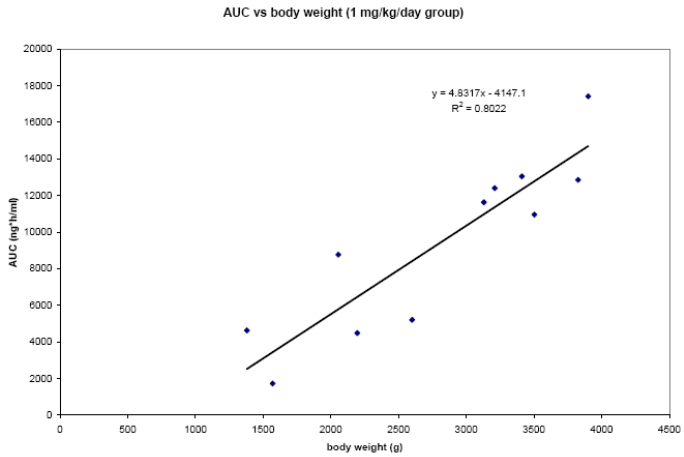
sponsor concluded that due to the limited number of subjects, it is difficult to determine whether age had an effect on the pharmacokinetic parameters of lansoprazole in neonates.

Fig 2. Lansoprazole Dose-normalized AUC vs. Corrected Age in Neonates Following Oral Administration of 0.5 mg/kg/day or 1 mg/kg /day Lansoprazole



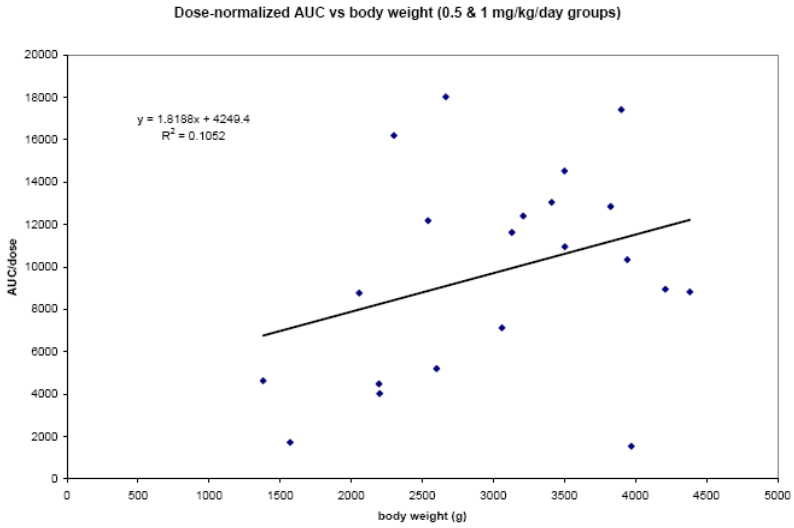
The dose-normalized AUC did not show strong association with corrected age.

Fig 3. Lansoprazole Dose-normalized AUC vs. Body Weight in Neonates Following Oral Administration of 1 mg/kg/day Lansoprazole



The dose-normalized AUC showed a positive trend with body weight for the 1 mg/kg/day group with a r2 of 0.80, but there was a slight negative trend for the 0.5 mg/kg/day group with a r2 of 0.1 (plot not shown).

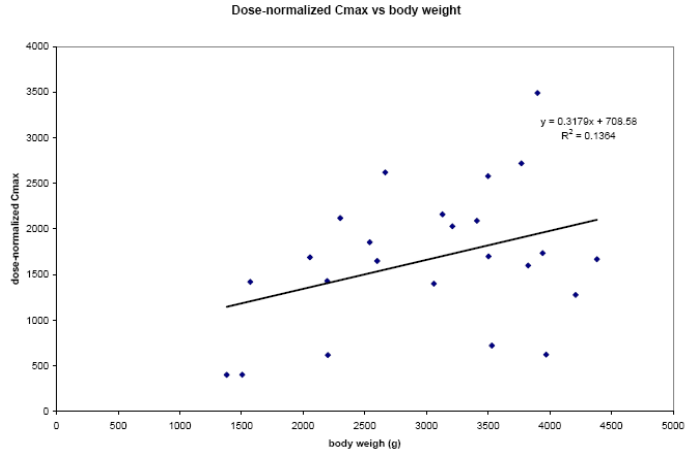
Fig 4. Lansoprazole Dose-normalized AUC vs. Body Weight in Neonates Following Oral Administration of 0.5 mg/kg/day or 1 mg/kg/day Lansoprazole



When the data from both dose groups are pooled, there is only a very small positive trend between dose-normalized AUC and body weight with a r2 of 0.11.

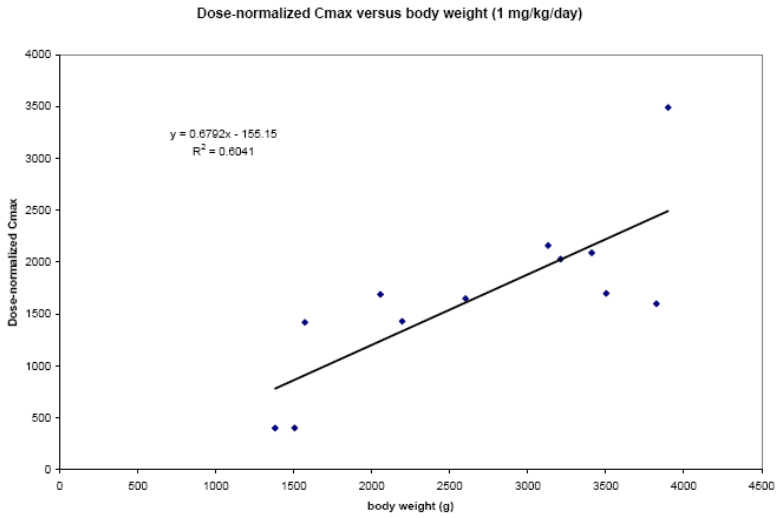
Dose-normalized Cmax

Fig 5. Lansoprazole Dose-normalized Cmax vs. Body Weight in Neonates Following Oral Administration of 0.5 mg/kg/day or 1 mg/kg/day Lansoprazole



The dose-normalized Cmax shows a small positive trend with body weight in neonates. The correlation coefficient is 0.14 when the 0.5 mg/kg/day and 1 mg/kg/day data are pooled.

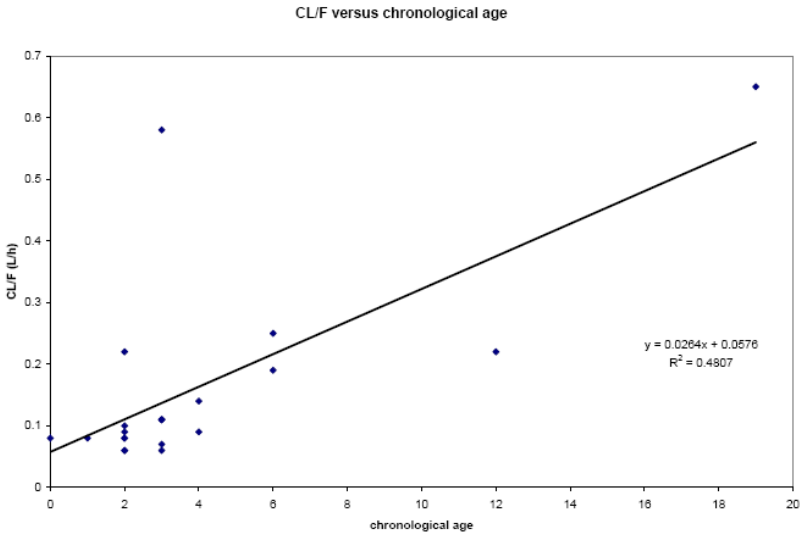
Fig 6. Lansoprazole Dose-normalized Cmax vs. Body Weight in Neonates Following Oral Administration of 1 mg/kg/day Lansoprazole



The dose-normalized Cmax shows a positive trend with body weight in neonates following 1 mg/kg/day, with a correlation coefficient of 0.60.

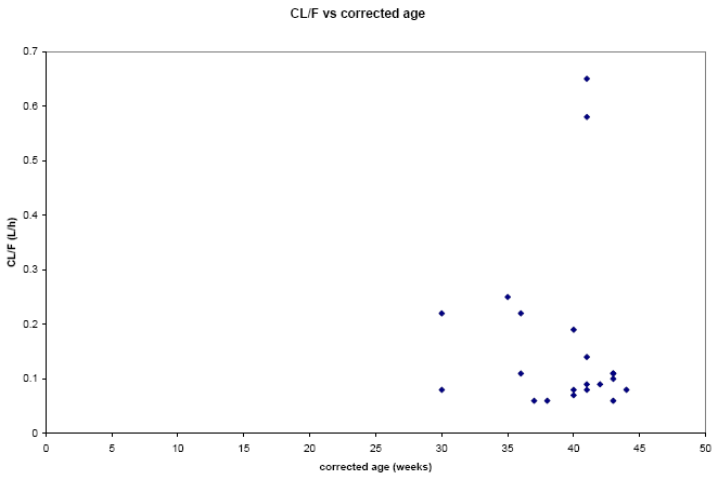
Apparent clearance CL/F

Fig 7. Lansoprazole Apparent Clearance (CL/F) vs. Chronological Age in Neonates Following Oral Administration of 0.5 mg/kg/day or 1 mg/kg /day Lansoprazole



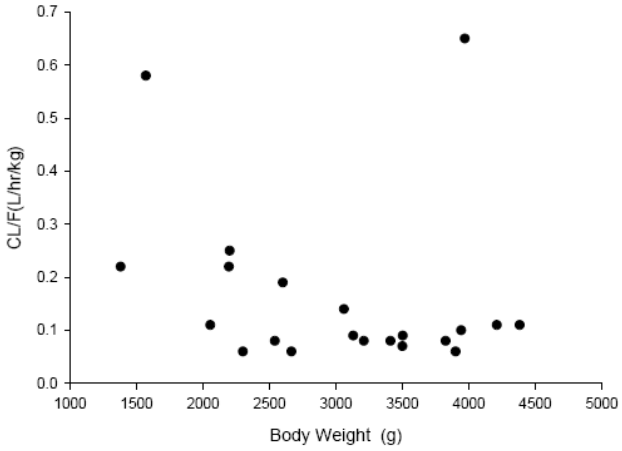
Apparent oral clearance showed a trend of increase with chronological age with a r2 of 0.48.

Fig 8. Lansoprazole Apparent Clearance (CL/F) vs. Corrected Age in Neonates Following Oral Administration of 0.5 mg/kg/day or 1 mg/kg /day Lansoprazole



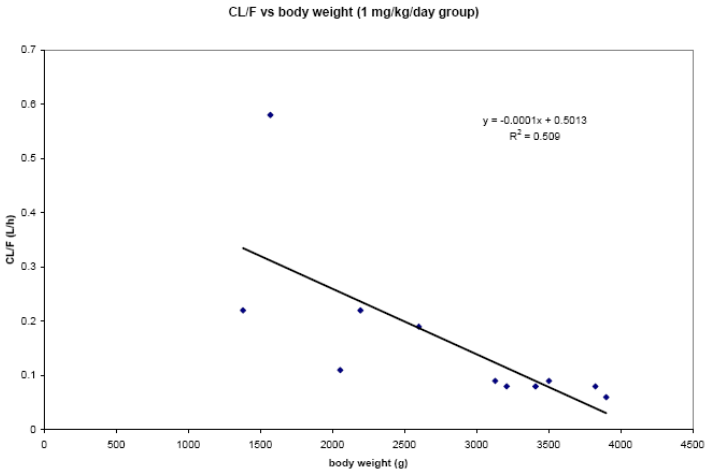
Apparent oral clearance did not show a trend of increase with corrected age.

Fig 9. Lansoprazole Apparent Clearance (CL/F) vs. Body Weight in Neonates Following Oral Administration of 0.5 mg/kg/day or 1 mg/kg/day Lansoprazole



Apparent oral clearance did not show a trend of increase with body weight.

Fig 10. Lansoprazole Apparent Clearance (CL/F) vs. Body Weight in Neonates Following Oral Administration of 1 mg/kg/day Lansoprazole



CL/F decreased slightly with body weight for the 1 mg/kg/day group with a r2 of 0.34 (shown above) but did not show a trend for the 0.5 mg/kg/day group. As shown above the dose-normalized AUC showed a positive trend with body weight for the 1mg/kg/day group, it is not surprising that CL/F showed a negative association.

Reviewer's comments: The number of subjects is limited, a general conclusion about the relations between lansoprazole pharmacokinetic in neonates with body weight and chronological age is unlikely meaningful. The results of 1 mg/kg/day group however seemed to show some relations between pharmacokinetic parameters and body weight or chronological age, but those of the 0.5 mg/kg/day group did not. The average body weight of the 0.5 mg/kg/day group was 3155 g and that of the 1 mg/kg/day group was 2564 g; and other physical appearances also demonstrate that the lower dose group was more mature. One possible explanation for the lack of such relations in the lower dose group is that lower dose might be more prone to analytical error and to the impact of dose lost to vomiting.

2.2.4.1 What are the pharmacokinetic characteristics of lansoprazole in infants?

In contrast to the neonate study, there appears to be no evidence of accumulation in infants on Day 5. Though only sparse sampling was conducted on Day 5, the pharmacokinetic parameters do not seem to be altered with multiple doses of lansoprazole relative to single dose administration.

Mean plasma concentrations on Days 1 & 5 for both the 1 and 2 mg/kg/day dose groups.

Time	Plasma Lansoprazole Concentration (ng/mL)							
	0 h	1 h	2 h	3 h	4 h	6 h	8 h	12 h
1.0 mg/kg/day (Dosing Day 1)								
Mean	0.00	682.63	510.62	290.61	219.56	85.11	42.42	15.16
%CV	U	81	96	142	151	216	298	307
1.0 mg/kg/day (Dosing Day 5)								
Mean	0.00	NP	484.18	NP	NP	186.64	NP	NP
%CV	U	NP	94	NP	NP	283	NP	NP
2.0 mg/kg/day (Dosing Day 1)								
Mean	0.00	1747.26	1482.58	986.96	567.99	195.41	72.35	6.33
%CV	U	99	94	112	115	142	164	240
2.0 mg/kg/day (Dosing Day 5)								
Mean	0.00	NP	1190.59	NP	NP	241.91	NP	NP
%CV	U	NP	85	NP	NP	147	NP	NP

U=undefined; NP=not performed.

Oral absorption in infants is fast with a t_{max} of around 2 hours in both groups. C_{max} values for the two dose groups were approximately dose-proportional; however, mean AUC values were higher than dose-proportional. This disproportionate result with regard to AUC was driven by two 6-week-old subjects which have significantly higher exposure per kg relative to older subjects (see second table below). Half-life and apparent clearance are similar between dose groups.

Pharmacokinetic parameter estimates for lansoprazole in infants by ***dose*** group.

Dose Group	T_{max} (hr)	C_{max} (ng/mL)	AUC_{∞} (ng*h/mL)	$T_{1/2}$ (hr)*	CL/F (L/hr/kg)
1 mg/kg/day (SD)	1.83 (1.19)	959.08 (472)	2202.83 (2301)	1.14 (0.79)	0.71 (0.40)
2 mg/kg/day (SD)	1.76 (1.06)	2086.83 (1558)	5794.35 (5618)	1.22 (1.35)	0.61 (0.38)

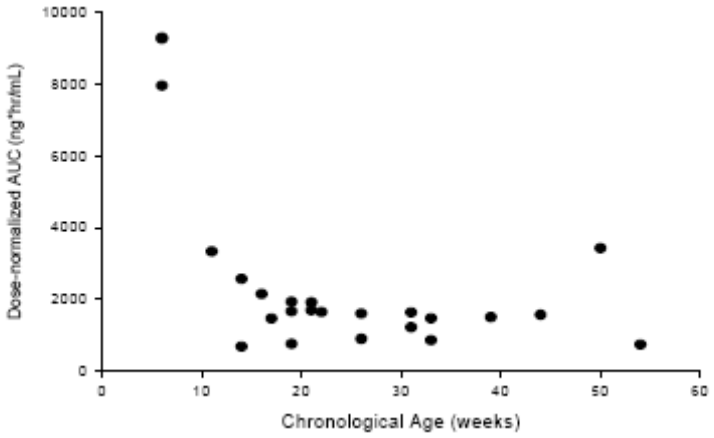
*harmonic mean

There are some notable differences in pharmacokinetic parameters when comparing patients > 10 weeks of age to those patients ≤ 10 weeks of age. The three subjects < 10 weeks old had a six-fold lower apparent clearance, more than double the dose-normalized C_{max}, and six-fold higher AUC than subjects > 10 weeks old. Though there were only three subjects in the lower age group relative to the 21 subjects in the upper age group, these differences tend to support the conclusion that there is a significant difference in the pharmacokinetics between older and younger infants. Indeed, the three 6-week old infants had a mean dose-adjusted AUC and CL/F that was very similar to neonates

Pharmacokinetic parameter estimates for lansoprazole in infants by ***age***.

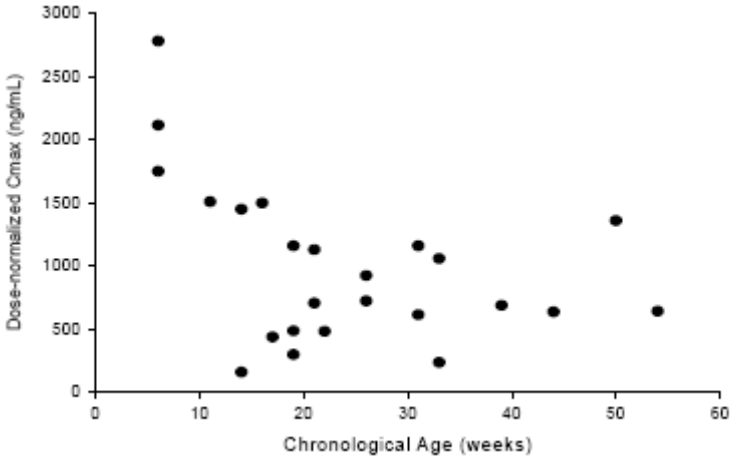
Age Group	T_{max} (hr)	C_{max} (ng/mL)	AUC_{∞} (ng*h/mL)	AUC_{∞} /Dose (ng*h/mL/mg/kg)	CL/F (L/hr/kg)
> 10 weeks (SD)	1.86 (1.15)	1191 (735)	2487.45 (1642)	1651.88 (751)	0.74 (0.35)
≤ 10 weeks (SD)	1.33 (0.58)	3846.67 (1933)	14576.58 (4759)	8836.89 (762)	0.11 (0.01)

Dose-normalized AUC vs. chronological age in infants receiving 1 or 2 mg/kg/day lansoprazole.



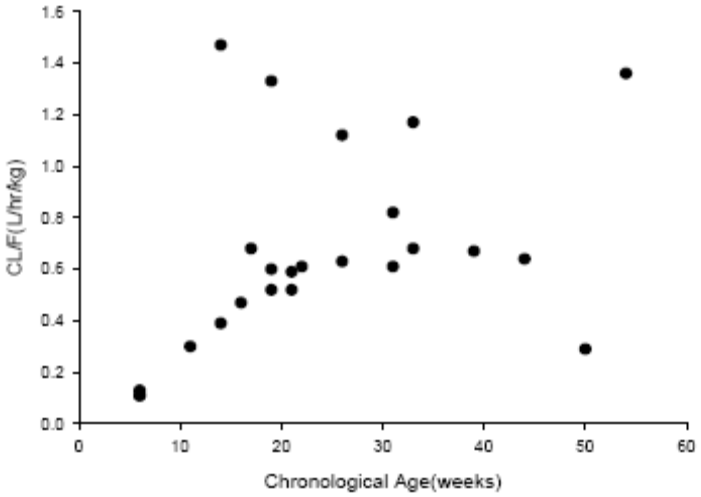
There appears to be no relationship between dose-normalized AUC and chronological age with the exception of the youngest patients who have a much higher exposure relative to the older patients. The distribution is very similar for dose-normalized AUC vs. corrected age and is not presented here.

Dose-normalized C_{max} vs. chronological age in infants receiving 1 or 2 mg/kg/day lansoprazole.



Similar to the relationship between dose-normalized AUC and chronological age, there appears to be no relationship between dose-normalized C_{max} and chronological age except in the youngest patients.

Lansoprazole apparent clearance vs. chronological age in infants receiving 1 or 2 mg/kg/day lansoprazole.



Lansoprazole clearance in infants is highly variable as indicated by the figure above. Although the data shows that the youngest patients have the lowest apparent clearance, no clear relationship is present when looking at the group as a whole.

Reviewer's comments: The youngest patients in this study (three patients were 6-weeks of age) have a higher exposure and lower apparent clearance relative to the older patients but very similar to neonates with regard to doase-adjusted AUC and CL/F.. These differences tend to support the conclusion that there is a significant difference in the pharmacokinetics between older and younger infants.

2.2.5 How does CYP 2C19 genotype affect lansoprazole exposure in neonates?

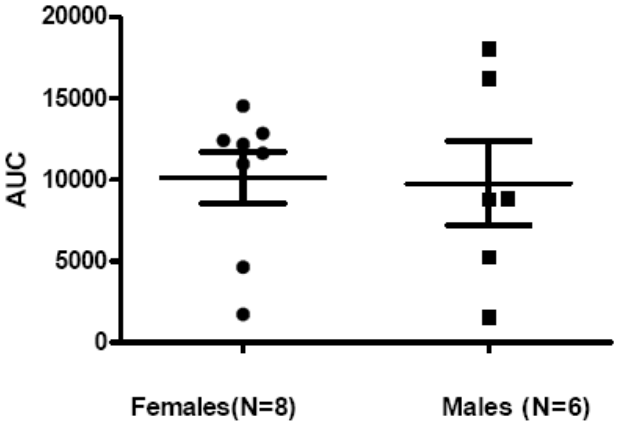
Table 4. Comparison of lansoprazole pharmacokinetics following a single administration of 0.5 or 1.0 mg/kg/day lansoprazole pediatric suspension in CYP2C19 homozygous extensive metabolizer and heterozygous extensive metabolizer

CYP2C19 Genotype	Statistic	Chronological Age (weeks)	Corrected Age (weeks)	Body Weight (g)	C_{max}/D (ng/mL/mg/kg)	AUC_{∞}/D (ng-h/mL/mg/kg)	CL/F (L/hr/kg)	Vz/F (L/kg)
Hom EM, (CYP2C19, wt/wt) (n=16)	Mean	4	40	2996	1722.50	9959.88	0.18	0.53
	SD	4	3	876	686.29	5116.62	0.19	0.31
	%CV	120	8	29	40	51	109	59
Het EM, (CYP2C19, *2/wt) (n=6)	Mean	5	38	2800	1512.83	8677.52	0.15	0.56
	SD	4	5	998	1096.45	5495.43	0.08	0.21
	%CV	79	13	36	73	63	53	37

Hom EM = CYP2C19 homozygous extensive metabolizer; Het EM = CYP2C19 heterozygous extensive metabolizer.

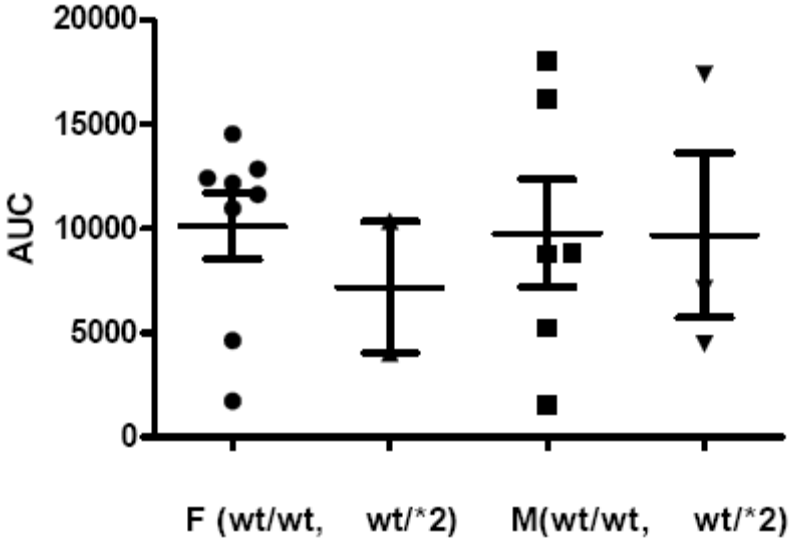
Homozygous extensive metabolizers (EMs) had slightly higher mean dose-normalized Cmax and AUC than heterozygous EMs, but not significantly higher. According to the literature, it is expected that homozygous EMs have higher CYP 2C19 activity than heterozygous EMs since the *2 allele has no 2C19 functional activity. The observed results which contradict the general scientific understanding of 2C19 genotypes and phenotypes might have resulted from a limited number of subjects involved.

Fig 11. Dose-normalized AUC in females and males with CYP 2C19 wt/wt genotype



Female neonates showed slightly higher mean AUC than male neonates. It appears that there is no statistical difference in AUC between female and male wt/wt neonates. In the figure below, the female (F) and male (M) carrying wt/*2 genotype are also included. There are only two female neonates and three male neonates who are heterozygous EMs.

Fig 12. Dose-normalized AUC in females and males



The limited number of neonates precludes any conclusion about the relationship between 2C19 genotype and lansoprazole.

2.2.5.1 How does CYP 2C19 genotype affect lansoprazole exposure in infants?

Comparison of pharmacokinetic parameters in homozygous and heterozygous extensive metabolizers.

CYP 2C19	Cmax / Dose	AUC_{∞} / Dose	CL / F

Genotype			
wt / wt (N = 17)	888.47 (632)	1944.47 (1996)	0.77 (0.39)
*2 / wt (N = 3)	1149.00 (445)	2519.59 (928)	0.44 (0.18)

Though there appears to be an increase in dose-normalized Cmax and AUC and a decrease in apparent clearance, the small number of heterozygotes (N=3) and the complete absence of any poor metabolizers precludes drawing any conclusions regarding the impact of 2C19 genotype on plasma exposure in infants.

2.2.6 How does the pharmacokinetics of lansoprazole in neonates compare to those in children, adolescents, and healthy adults?

Table 5. Mean Plasma Lansoprazole Pharmacokinetic Parameter Estimates in Neonates, Children, Adolescents, and Healthy Adults

Variable	t_{max} (h)	C_{max} (ng/mL)	AUC (ng·h/mL)	$t_{1/2}$ (h)[a]	CL/F (L/hr/kg)
Neonates (Age 0-19 Weeks)[b] (0.5 mg/kg/day) (n=12)					
Mean	3.1	831	5086	2.76	0.16
%CV	70	46	51	–	111
Neonates (Age 0-12 Weeks)[c] (1.0 mg/kg/day) (n=12)					
Mean	2.6	1672	9372	1.97	0.16
%CV	58	48	51	–	92
Children ≤30 kg (Aged 1 to 11 Years) (15 mg QD) (n=28)					
Mean	1.5	791	1707	0.68	–
%CV	45	55	99	–	–
Children >30 kg (Aged 1 to 11 Years) (30 mg QD) (n=31)					
Mean	1.7	899	1883	0.71	–
%CV	42	49	62	–	–
Adolescents (Aged 12 to 17 Years) (15 mg QD) (n=30)					
Mean	1.6	415	1017	0.84	–
%CV	44	52	171	–	–
Adolescents (Aged 12 to 17 Years) (30 mg QD) (n=29)					
Mean	1.7	1005	2490	0.95	–
%CV	42	60	101	–	–
Healthy Adult Subjects (Aged ≥18 Years) (30 mg)					
Mean	1.7[d]	824[e]	2133[f]	1.19[g]	–
%CV	48	51	84	–	–

Note: Data values listed in this table for age groups are from the following sources: Neonates (Study C03-042), Children (Study M97-808),[9] Adolescents (Study M97-640),[20] and Healthy Adults (pooled data across Phase 1 studies).[21]

Note: "–" indicates no data collected/available.

a Harmonic mean.

b Corrected age 35 to 43 weeks.

c Corrected age 30 to 44 weeks.

d n=345.

e n=515.

f n=513.

g n=285.

QD = once daily.

With75 kg as the average body weight of healthy adults, adults showed much lower AUC than neonates for an equivalent dose per body weight. The adolescent group also exhibits lower AUC than neonates based on an equivalent dose per body weight

administered. Children ages 1 to 17 had lower AUC than neonates based on an equivalent dose per body weight. Examining the data of 0.5 mg/kg/day across all age groups (neonates, children (body weight ≤30 kg) as well as in adolescents taking 15mg, and adults), it is clear that lansoprazole AUC decreased dramatically from neonates to children ages 1-11 and then slightly to adolescents, but was similar between adolescents and adults.

According to the literature about the ontogenic development of 2C19 (Clin Pharmacokinet 2005; 44 (5):441 & Pediatr Clin North Am 1997; 44: 55-77), its activity is low in the first few weeks of life, reached the adult level by 6-12 months of age, and then exceeds the adult level between 1 and4 years old and then gradually declines to the adult level by puberty. The results shown above are in agreement with the literature.

2.2.6.1 How does the pharmacokinetics of lansoprazole in infants compare to those in children, adolescents, and healthy adults?

Pharmacokinetic parameter estimates in infants, children, adolescents, and healthy adults.

Table 13.1.a Mean Plasma Lansoprazole Pharmacokinetic Parameter Estimates in Infants, Children, Adolescents, and Healthy Adults

Variable	t_{max} (h)	C_{max} (ng/mL)	AUC (ng·h/mL)	$t_{1/2}$ (h)[a]	CL/F (L/hr/kg)
Infants (Age ≤10 Weeks) (Dose-Normalized to 1.0 mg/kg/day) (n=3)					
Mean	1.3	2215	8837	1.61	0.11
%CV	43	24	9	–	9
Infants (Age >10 Weeks) (Dose-Normalized to 1.0 mg/kg/day) (n=21)					
Mean	1.9	828	1652	0.76	0.74
%CV	62	51	46	–	47
Children ≤30 kg (Aged 1 to 11 Years) (15 mg QD) (n=28)					
Mean	1.5	791	1707	0.68	–
%CV	45	55	99	–	–
Children >30 kg (Aged 1 to 11 Years) (30 mg QD) (n=31)					
Mean	1.7	899	1883	0.71	–
%CV	42	49	62	–	–
Adolescents (Aged 12 to 17 Years) (15 mg QD) (n=30)					
Mean	1.6	415	1017	0.84	–
%CV	44	52	171	–	–
Adolescents (Aged 12 to 17 Years) (30 mg QD) (n=29)					
Mean	1.7	1005	2490	0.95	–
%CV	42	60	101	–	–
Healthy Adult Subjects (Aged ≥18 Years) (30 mg)					
Mean	1.7[b]	824[c]	2133[d]	1.19[e]	–
%CV	48	51	84	–	–

Infants > 10 weeks of age (dose-normalized to 1 mg/kg/day) had similar exposure to children who received a weight-based regimen of either 15 or 30mg/day for those children ≤ 30kg or > 30kg, respectively. These infants also have a simialr exposure as adolescents and healthy adult subjects who receive 30mg/day. Adolescents who receive only 15mg/day have a lower exposure than infants > 10 weeks of age.

Infants ≤ 10 weeks of age had significantly higher exposure than all other groups; however, there were only three patients in this age range.

2.2.7 What is the exposure/pharmacodynamic relationship?

Neonates

Intragastric and Intraesophageal pHs

The baseline, day 1, and day 5 intragastric pHs over time following lansoprazole 0.5 mg/kg/day and 1 mg/kg/day are shown in figures 1.a and 1.b. Both dose regimens raised intragastric pH substantially. The 0.5 mg/kg/day dose group had less baseline pH fluctuations than the 1 mg/kg/day dose group, and had more data points of pH>6 on day 5 than on day 1, while the latter had more data points of pH>6 on day 1 than on day 5. The 1 mg/kg/day group had higher magnitude of baseline pH fluctuation than the 0.5 mg/kg/day group.

Fig. 13 Mean of 15-minute median intragastric pH over time following lansoprazole 0.5 mg/kg/day

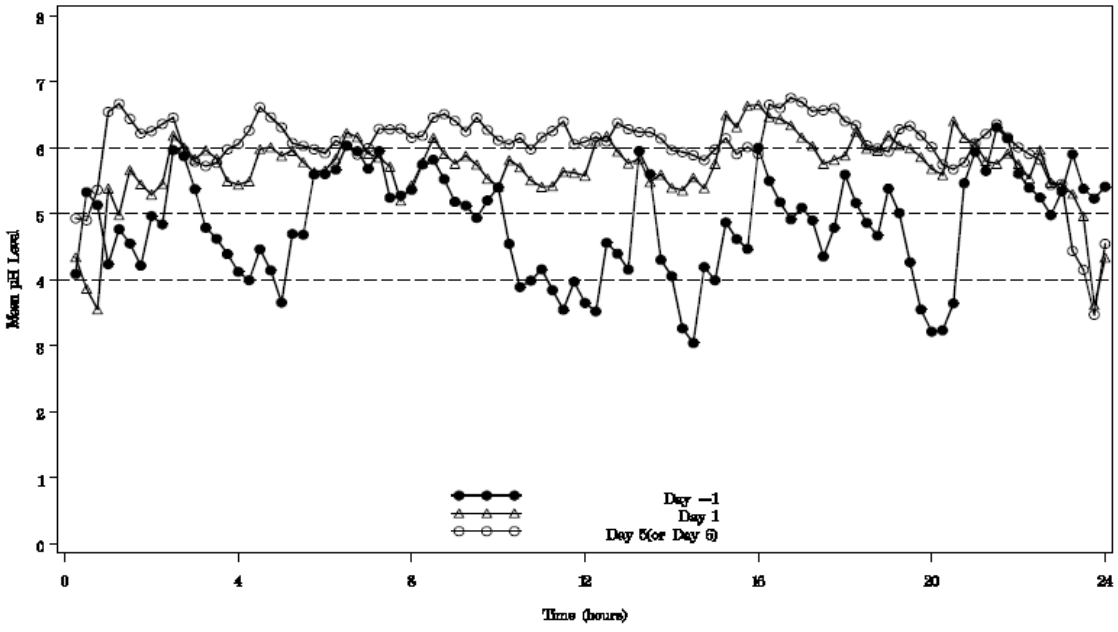
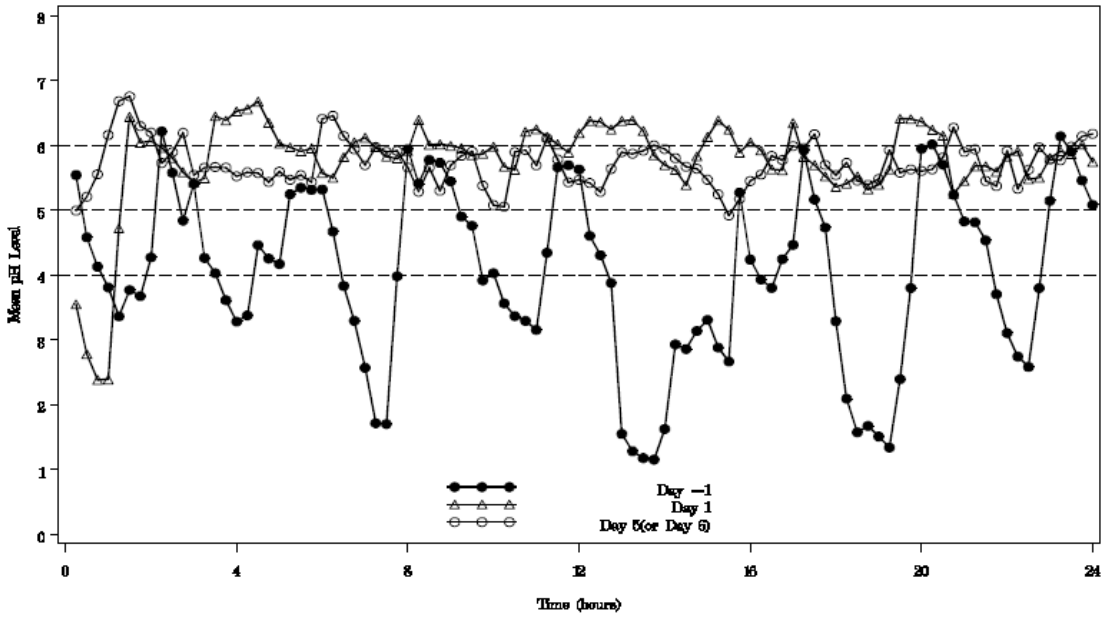


Fig. 14 Mean of 15-minute median intragastric pH over time following lansoprazole 1 mg/kg/day



At baseline, the 0.5 mg/kg/day group had higher mean percentages of time intragastric pH> 4, > 5 and > 6 than the 1.0 mg/kg/day dose group. The mean percentages time pH> 4 and > 5 increased from baseline to day 1 in both dose groups with the 1.0 mg/kg/day group showing a higher mean percent time pH> 4 or >5.

Table 6 Mean Percentages of Time Intragastric pH >3, >4, >5, and >6 Over 24-Hour Postdose Period

	Lansoprazole 0.5 mg/kg/day (n=4)[a]				Lansoprazole 1.0 mg/kg/day (n=2)[b]			
Visit Day	pH >3	pH >4	pH >5	pH >6	pH >3	pH >4	pH >5	pH >6
Day -1	83.6	76.6	60.9	24.5	66.1	58.8	42.7	14.6
Dosing Day 1	98.7	90.1	76.5	47.8	98.4	95.3	88.5	51.0
Dosing Day 5	98.7	96.6	91.9	56.3	100.0	99.0	84.4	39.6

a Subjects 185, 189, 192, 193.
b Subjects 188, 194.

The 1.0 mg/kg/day dose group exhibited higher changes from baseline values in the mean percentages time pH> 4 and pH > 5 on day 5 than the 0.5 mg/kg/day group. The number of subject in either dose group was too small for clinically meaningful comparisons. For both dose regimens, the AUC (integrated gastric acidity) of proton concentration are summarized below. Both dose groups showed a great extent of decrease in the integrated gastric acidity.

Table 7 Mean 24-Hour Integrated Gastric Acidity (mmol*hr/L)

Visit Day	Lansoprazole 0.5 mg/kg/day (n=4)[a]	Lansoprazole 1.0 mg/kg/day (n=2)[b]
Day -1	115.1 ± 109.2	251.8 ± 32.9
Dosing Day 1	4.1 ± 6.4	13.6 ± 18.6
Dosing Day 5	1.0 ± 1.1	0.2 ± 0.2

Note: Data are mean integrated gastric acidity ± SD.
a Subjects 185, 189, 192, 193.
b Subjects 188, 194.

The day 1 results showed that the mean percent time intraesophageal pH < 4 over a 24-hr post-dose period increased from baseline in both dose groups. On Day 5, the mean percent time intraesophageal pH< 4 was similar to the baseline for the 0.5 mg/kg/day dose group but was lower than the baseline for the 1 mg/kg/day dose group. Both dose groups showed comparable results on day 5.

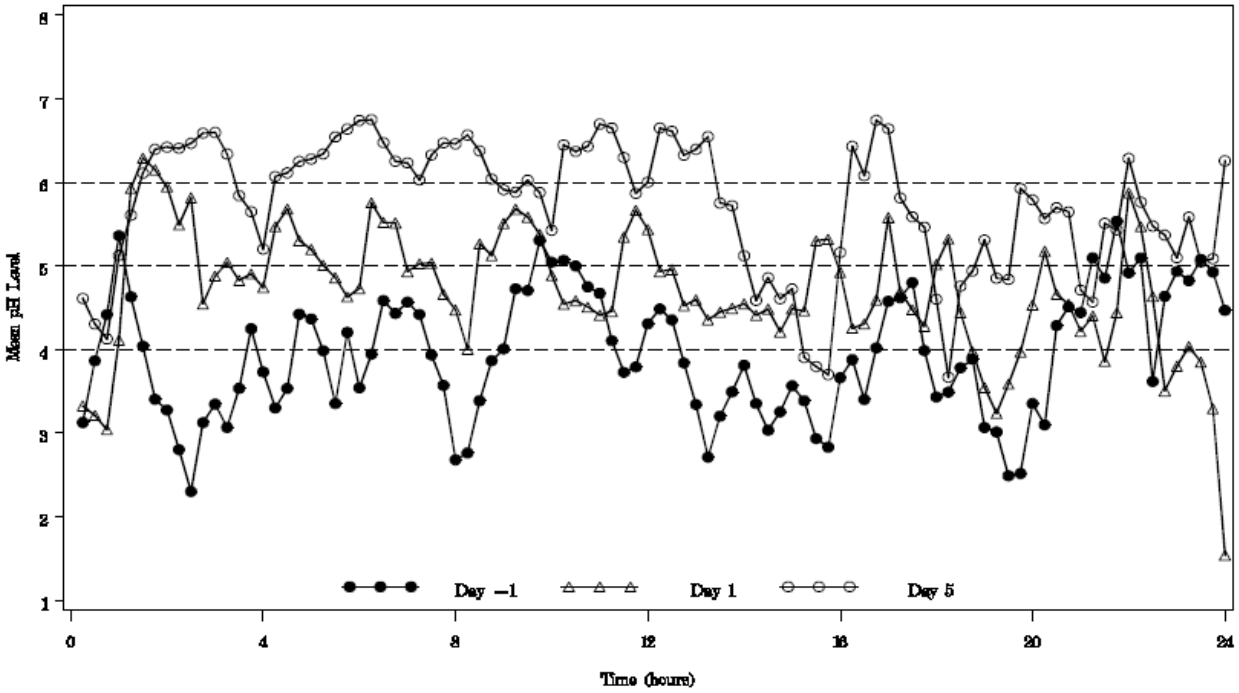
Table 8 Mean Percentages of Time Intraesophageal pH <4 Over a 24-Hour Postdose Period

Visit Day	Lansoprazole 0.5 mg/kg/day (n=4)[a]	Lansoprazole 1.0 mg/kg/day (n=2)[b]
Day -1	21.6 ± 17.4	27.1 ± 5.9
Dosing Day 1	32.7 ± 28.6	35.4 ± 20.6
Dosing Day 5	21.6 ± 10.0	22.4 ± 3.7

Note: Data values are mean percentages of time ± SD intraesophageal pH <4.
a Subjects 185, 189, 192, 193.
b Subjects 188, 194.

Reviewer's comments: Considering that AUC showed approximate dose proportionality between 0.5 and 1 mg/kg/day and the pharmacodynamic profiles of both dosing regimen, there is no response/exposure relationship for the percentage of time intragastric pH > 4 or pH > 5 or for the percentage of time intraesophageal pH < 4. Comparison of the integrated gastric acidity between 0.5 and 1 mg/kg/day, higher exposure resulted in better outcome. According to Dr. Ali Niak (medical officer), gastric acid secretion is highly influenced by environmental factors which impact neonates' mood. It is concerning whether pH measurements truly reflect the therapeutic effect of lansoprazole or could be the results of external manipulation.

Infants: The mean intragastric pH improves from Baseline to Day 1 and from Day 1 to Day5 (see figure below); however, there is no apparent dose-response (see tables below). However, the sample size was small (only 6 subjects were included in the PD subset) which makes a dose-response relationship difficult to establish.



The high-dose group is no better than the low-dose group when measuring percent time intragastric pH exceeds 3, 4, 5, & 6 over a 24 hour period. In addition, both dose groups see increases by Day 5 relative to Day1 at all pH ranges.

Percentage of time intragastric pH exceeded 3, 4, 5, & 6 over a 24-hour period by dose.

	Lansoprazole 1.0 mg/kg/day[a] (n=3)				Lansoprazole 2.0 mg/kg/day[b] (n=3)			
Study Day	pH>3	pH>4	pH>5	pH>6	pH>3	pH>4	pH>5	pH>6
Day -1	62.5	50.0	27.4	12.1	67.0	52.4	34.0	24.0
Dosing Day 1	81.1	71.5	60.2	34.0	64.2	60.0	55.1	41.7
Dosing Day 5	89.8	84.9	76.5	53.8	88.8	83.9	75.9	53.2

When analyzing the intragastric pH by age subgroup, some differences are noted. The youngest subjects have higher baseline pH and have similar response on Days 1 & 5. The older infants have a significantly better response on Day 5 relative to Day 1 but have lower baseline pH.

Percentage of time intragastric pH exceeded 3, 4, 5, & 6 over a 24-hour period by age.

	Subjects ≤10 Weeks of Age[a] (n=3)				Subjects >10 Weeks of Age[b] (n=3)			
Study Day	pH>3	pH>4	pH>5	pH>6	pH>3	pH>4	pH>5	pH>6
Day -1	71.5	58.3	39.2	25.7	58.0	44.1	22.2	10.4
Dosing Day 1	94.4	88.4	80.0	56.8	50.9	43.1	35.2	18.9
Dosing Day 5	92.3	88.8	83.9	66.7	86.3	80.0	68.5	40.2

Consistent with the pH results, the integrated gastric acidity does not appear to be dose-dependent.

Mean integrated gastric acidity over the 24-hour postdose period by dose.

Study Day	Lansoprazole 1.0 mg/kg/day[a] (n=3)	Lansoprazole 2.0 mg/kg/day[b] (n=3)
Day -1	319.4 ± 338.9	161.1 ± 90.2
Dosing Day 1	197.3 ± 222.3	284.4 ± 466.6
Dosing Day 5	76.6 ± 117.0	71.3 ± 72.5

Reviewer's comment: There is no exposure-response between the two dose groups in the infant study. The effect is time-dependent as pH increases consistently between Days 1 and 5 in the older infants.

2.2.8 What is the exposure/efficacy relationship?

Neonates:

Regurgitation/vomiting

Decreases in the occurrence of regurgitation/vomiting were similar for both dose groups. In the lansoprazole 0.5 mg/kg/day group, regurgitation/vomiting was observed in 92% (11/12) of subjects at Baseline and in 75% (9/12) of subjects on Dosing Day 5. In the lansoprazole 1.0 mg/kg/day dose group, regurgitation/vomiting was observed in 92% (11/12) of subjects at Baseline and in 67% (8/12) of subjects on Dosing Day 5.

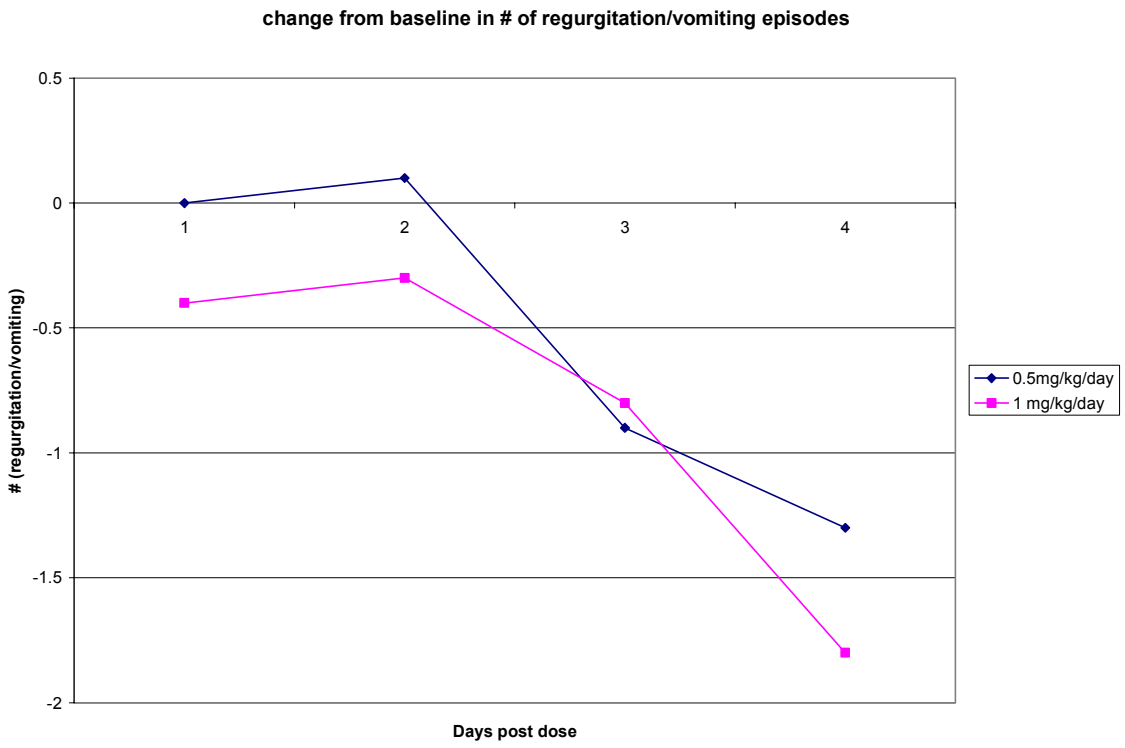
The mean number of episodes of regurgitation/vomiting per 24-hour period was 3.4 at Baseline and 2.1 on Dosing Day 5 for the lansoprazole 0.5 mg/kg/day dose group. For the lansoprazole 1.0 mg/kg/day dose group, the mean number of episodes of regurgitation/vomiting per 24-hour period was 3.3 at Baseline and 1.5 on Dosing Day 5.

Table 9. Change from Baseline in the Number of Episodes of Regurgitation/Vomiting

Evaluation/ Timepoint	Lansoprazole 0.5 mg/kg/day (N=12) n	Mean	SD	Median	Min	Max	Lansoprazole 1.0 mg/kg/day (N=12) n	Mean	SD	Median	Min	Max
Actual Value												
Baseline	12	3.4	1.43	3.67	0	6	12	3.3	1.11	3.33	0	4
Day 2	12	3.4	2.47	2.00	0	9	12	2.8	1.95	3.00	0	8
Day 3	12	3.5	2.58	3.00	0	8	12	3.0	1.60	3.50	0	5
Day 4	12	2.5	2.32	2.00	0	8	12	2.4	1.73	2.00	0	6
Day 5 (or 6)	12	2.1	1.93	2.00	0	7	12	1.5	1.24	2.00	0	3
Change from Baseline												
Day 2	12	0.0	2.05	-0.83	-2	5	12	-0.4	1.69	-0.75	-2	4
Day 3	12	0.1	2.40	-0.33	-3	5	12	-0.3	1.30	0.25	-2	1
Day 4	12	-0.9	2.16	-1.67	-3	4	12	-0.8	1.48	-0.92	-3	2
Day 5 (or 6)	12	-1.3	1.91	-1.83	-4	3	12	-1.8	1.22	-1.67	-3	0

The baseline value is the average of the 24 hour counts over the 3 days prior to dosing Day 1.
Per protocol, subjects were to receive the first dose of study drug on Dosing Day 1 at approximately 10:00 am.
Symptoms were analyzed for this table starting on Day 2, the first full 24-hour day of treatment.

Fig 15. Change from baseline in the numbers of regurgitation/vomiting episodes



In terms of the number of regurgitation/vomiting episodes, the 1 mg/kg/day group exhibited a slightly better outcome than the 0.5 mg/kg/day group.

Symptom relief
Overall GERD symptom relief on Dosing Day 5 was rated as "Better" in 83% (10/12) of subjects in the lansoprazole 0.5 mg/kg/day dose group and in 75% (9/12) of subjects in the 1.0 mg/kg/day dose group. Overall GERD symptom relief was rated as "Not Changed" in 17% (2/12) of subjects in the lansoprazole 0.5 mg/kg/day dose group and in 25% (3/12) of subjects in the 1.0 mg/kg/day dose group.

Reviewer's comments: Based on symptom relief and the number of regurgitation/vomiting episodes, there is no exposure/response relationship.

Infants: There is little change in the number of patients with regurgitation/vomiting among either dose group. There is improvement in the other categories (feeding refusal/crying, spells of arching, irritability, and cough) that may be dose- and time-dependent. A separate clinical study with more subjects and a longer duration of treatment found no difference in GERD symptom response after four weeks of lansoprazole relative to placebo.

GERD Symptom[a]	Day -1	Dosing Day 1	Dosing Day 2	Dosing Day 3	Dosing Day 4	Dosing Day 5
	Lansoprazole 1.0 mg/kg/day[b]					
Regurgitation/Vomiting	92	92	83	75	75	83
Feeding Refusal/Crying	33	33	42	33	8	17
Spells of Arching	50	50	42	42	25	17
Irritability	50	50	58	50	17	33
Cough	42	25	17	25	25	33
	Lansoprazole 2.0 mg/kg/day[b]					
Regurgitation/Vomiting	75	92	83	83	83	67
Feeding Refusal/Crying	50	25	17	8	17	0
Spells of Arching	50	25	42	8	17	0
Irritability	50	25	25	25	8	17
Cough	75	42	42	33	25	0
	All Subjects[c]					
Regurgitation/Vomiting	83	92	83	79	79	75
Feeding Refusal/Crying	42	29	29	21	12	8
Spells of Arching	50	37	42	25	21	8
Irritability	50	37	42	37	12	25
Cough	58	33	29	29	25	17

Note: Data are percentages of subjects
Note: There were no reported episodes of apnea for any subject.
a Symptoms present in ≥40% of subjects at Baseline are included.
b Days -1 to Dosing Day 4 (n=12); Dosing Day 5 (n=6).
c Days -1 to Dosing Day 4 (n=24); Dosing Day 5 (n=12).

2.2.9 What is the exposure/adverse events relationship?

Neonates:

Table 10. Summary of Treatment-Related Adverse Events

MedDRA High-Level Term Preferred Term	Lansoprazole 0.5 mg/kg/day (n=12)		Lansoprazole 1.0 mg/kg/day (n=12)	
	Dosing Period[a]	Postdosing Period[b]	Dosing Period[a]	Postdosing Period[b]
Total subjects with at least 1 AE	2 (17%)	0	2 (17%)	0
Anaemias NEC Anaemia	1 (8%)	0	0	0
Peripheral Vascular Disorders NEC Flushing	1 (8%)	0	1 (8%)	0
Liver Function Analyses Transaminases Increased	0	0	1 (8%)	0

Note: Data values are n (%).
Note: AEs coded using MedDRA Version 8.1.
a Dosing Period AEs occurred after the first dose and within 3 days of the last dose of study drug.
b Postdosing Period AEs occurred >3 days and ≤30 days after the last dose of study drug.
NEC = not elsewhere classified

Occurrence of anaemias might be due to blood samplings for pharmacokinetic analysis. There is no dose/adverse event relationship. Since AUC and Cmax increased approximately dose proportionally, there is no exposure/adverse events relationship.

Infants: Infants in both dose groups experienced AEs at the same rate and all AEs were mild or moderate in severity. Of the 24 infants, 14 (58%) experienced and AE during the study with 10 (42%) experiencing an AE during the dosing period and 8 (33%)

experiencing an AE in the postdosing period. Only one AE (hepatic enzyme increase) was considered related to the treatment. One infant in the 2mg/kg/day group experienced a seious AE (viral pneumonia) during the postdosing period but this AE was not considered to be treatment related.

2.3 Intrinsic Factors

The ontogenic development of CYP2C19 activity affects lansoprazole pharmacokinetics. This was discussed in Section 2.2.5.

2.4 General Biopharmaceutics

2.4.1 How does the formulation used in this NDA submission compare to those approved previously?

The formulations of Prevacid® (lansoprazole) Delayed-Release Capsules, Prevacid® (lansoprazole) Delayed-Release Oral Suspension, Prevacid® Solu Tab (lansoprazole) Delayed-Release Orally Disintegrating Tablets are approved for the treatment of Symptomatic GERD and erosive esophagitis in adults as well as use in the pediatric patients 1-17 years of age.

For neonates and infant 0-11 months of age, lansoprazole pediatric suspension is formulated by (b) (4)

2.5 Analytical Section

2.5.1 What analytical methods were used to assess concentrations?

For neonate study, lansoprazole concentrations in plasma were determined using a validated liquid chromatography assay with tandem mass spectrometric (LC-MS/MS) detection at (b) (4)

2.6.2 Are the analytical assay methods adequately validated?

Neonate study

The standard curves contained 10 concentrations of lansoprazole ranging from 5.00 ng/mL to 1200.00 ng/mL, and had correlation coefficients of ≥0.9970. The LLOQ with a 0.1 mL plasma sample was 5 ng/mL. The back-calculated values for the calibration standards resulted in mean absolute deviations from theoretical concentrations of 0.5% to 3.0% and coefficients of variation of 0.5% to 3.7%. Plasma QC samples for lansoprazole were prepared at nominal concentrations of 15.0, 100, 900, and 2400 ng/mL, and had coefficients of variation and absolute deviations from nominal

concentrations of ≤6.1% and ≤7.1%, respectively. Diluted plasma QC samples (900 ng/mL 1:2, 2400 ng/mL 1:5 and 1:10) had coefficients of variation and absolute deviations from nominal concentrations of ≤6.1% and ≤7.1%, respectively. The analytical assay methods were adequately validated.

Infant study: Like the neonate study, the range of the standard curve was 5 to 1200 ng/mL. Between-batch precision was ≤ 6.5% and accuracy ranged from -0.3 to 4.7%. For the diluted samples, precision was ≤ 7.3% and accuracy ranged from 1.4 to 4.6%. The back-calculated calibration curve accuracy ranged from -2.5 to 1.4% with an R-square of 0.9963 or better.

3 Detailed Labeling Recommendations

The sponsor did not add any statements to the approved label regarding treatment of GERD in neonates or infants.

OCP will recommend appropriate description about the PK/PD results in the approved lansoprazole level.

4 Appendix

Name of Company: TAP Pharmaceutical Products Inc **Name of Finished Product:** Lansoprazole Microgranules Oral Suspension for Pediatric Use **Name of Active Ingredient:** Lansoprazole; 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole	
Title of Study: A Phase 1, Single- and Repeated-Dose, Randomized, Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Lansoprazole in Neonates with Clinically Evident Gastroesophageal Reflux Disease	
Investigators: 4 (1 United States, 3 Poland)	
Study Centers: 4 (1 United States, 3 Poland)	
Publication (reference): Zhang W, Kukulka MJ, Witt G, Sutkowski-Markmann D, North J, Atkinson S. Substantial differences in lansoprazole pharmacokinetics between older and younger infants and neonates [Abstract]. *Gastroenterology*. 2006; 130(Suppl 2):A-4. Springer M, Zhang W, Atkinson S, North J, Raanan M, Witt G. Pharmacokinetic and pharmacodynamic profiles and symptom relief in infants with clinically evident GERD treated with lansoprazole. E-PAS2006:59:4811.49.	
Study Period: Date of First Dose: 13 May 2005 Date of Last Procedure: 11 August 2005	**Phase of Development:** 1
Objective(s): The objectives of this study were to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles and to assess the safety profile of single and repeated doses of once-daily administration of Lansoprazole Microgranules Oral Suspension for Pediatric Use (lansoprazole pediatric suspension) 0.5 mg/kg/day or 1.0 mg/kg/day in neonates with clinically evident gastroesophageal reflux disease (GERD).	
Methodology: This was a Phase 1, single- and repeated-dose, randomized, open-label, 2-country, multicenter study in 24 neonates with clinically evident GERD who were randomly assigned to 1 of 2 treatment groups (0.5 or 1.0 mg/kg/day) of lansoprazole pediatric suspension. All subjects received the first dose of study drug after a 30-minute fast midmorning on Dosing Day 1 at approximately 1000 hours. Dosing occurred each day for 5 days (Dosing Days 1 to 5) at approximately 24-hour intervals. Blood samples for pharmacokinetics were drawn from all subjects on Dosing Day 1 (at 0 h [predose] and at 1, 2, 3, 4, 6, 8, 12 h postdose) and Dosing Day 5 (at 0 h [predose] and at 2 and 6 h postdose). Lansoprazole concentrations in plasma were determined using a validated liquid chromatography assay coupled with tandem mass spectrometry (LC-MS/MS). A buccal sample for genotyping CYP2C19 was obtained from subjects with parent/legal guardian consent to determine CYP2C19 metabolizer status. Intragastric/intraesophageal pH monitoring was performed in 6 neonates at Baseline (Day -1) and on Dosing Days 1 and 5. The presence and the date and time of each episode of regurgitation/vomiting was recorded during the Pretreatment Period (on Days -3, -2, and -1) and on Dosing Days 1 to 5. Overall GERD symptom relief from Baseline was assessed by the investigator on Dosing Day 5. Safety was monitored through adverse event (AE) reports, concomitant medication usage, physical examinations, vital sign assessments, and laboratory evaluations.	
Number of Patients (planned and analyzed): 24 planned (12 each in lansoprazole 0.5 and 1.0 mg/kg/day dose groups); 24 analyzed for pharmacokinetics, GERD symptom assessment, and safety; 6 analyzed (as planned) for pharmacodynamics; and 22 analyzed for CYP2C19 genotype.	
Diagnosis and Main Criteria for Inclusion: Male or female neonates with clinically evident GERD with chronological age from birth to 28 days for term/postterm subjects or corrected age of <44 weeks for preterm subjects on Dosing Day 1.	

Test Product, Dose and Mode of Administration, Lot Numbers:

Test Product	Dose	Mode of Administration	Drug Product Lot Number	Drug Substance Lot Number
Lansoprazole pediatric suspension – 15 mg (investigational)	0.5 mg/kg/day	intraoral, orogastric, or nasogastric tube, or gastrostomy tube	040052	HG660
	1.0 mg/kg/day	intraoral, orogastric, or nasogastric tube, or gastrostomy tube	040052	HG660

Duration of Treatment: Twenty-four subjects received single daily doses of 0.5 or 1.0 mg/kg for 5 days. One of the 24 subjects vomited within 1 hour of dosing on Dosing Day 5 and study drug was visible in the emesis. In accordance with the protocol, this 1 subject received a dose of study drug on Dosing Day 6.

Reference Therapy, Dose and Mode of Administration, Lot Number: Not applicable.

Criteria for Evaluation

Efficacy:

The primary objective of this study was to assess pharmacokinetics (in all subjects) and pharmacodynamics (in a subset of 6 subjects). The GERD symptom of regurgitation/vomiting was also assessed as a secondary efficacy variable.

Pharmacodynamics:

The pharmacodynamics of lansoprazole were evaluated at Baseline (Day -1) and on Dosing Days 1 and 5. Criteria for evaluation included: 1) the mean of the 15-minute median intragastric pH values over the entire 24-hour period and for twelve 2-hour time intervals; 2) the percentages of time that intragastric pH was >3, >4, >5, and >6 over the entire 24-hour period; 3) percentage of time intraesophageal pH was <4 over the entire 24-hour period and for twelve 2-hour time intervals; and 4) integrated gastric acidity (area under the curve [AUC] of hydrogen ion concentration) over the entire 24-hour period.

GERD Symptoms:

Criteria were: 1) % of subjects with regurgitation/vomiting at Baseline and on Dosing Days 1 to 5, 2) the number of episodes per 24-hour period at Baseline and on Dosing Days 1 to 5, and 3) Investigator assessment of overall GERD symptom relief on Dosing Day 5 as compared to Baseline.

Pharmacokinetics:

Plasma concentrations of lansoprazole were determined at designated timepoints on Dosing Days 1 and 5. Pharmacokinetic parameters for lansoprazole on Dosing Day 1 were estimated using standard noncompartmental methods. These parameters included the observed peak plasma concentration (C_{max}), the time to reach the observed peak plasma concentration (t_{max}), the apparent terminal phase elimination rate constant (λ_z), the apparent terminal half-life ($t_{1/2z}$); and the AUC from time zero to the last measurable concentration (AUC_t) and to infinity (AUC_∞), the apparent clearance (CL/F), and apparent volume of distribution (V_z/F).

Safety:

Safety was monitored throughout the study through evaluations of AEs, concomitant medications usage, clinical laboratory assessments, physical examinations, and measurement of vital signs.

Statistical Methods:

Efficacy:

Pharmacodynamics:

Median intragastric pH values were calculated using all values obtained within each 15-minute interval for the

24-hour period at Baseline (Day -1) and on Dosing Days 1 and 5. The effect of treatment on intragastric pH was quantified using the mean of the 15-minute median intragastric pH values over the entire 24-hour period following dosing (or entire period following dosing in which pH was recorded) and for time intervals following dosing (hours 0 to 2, >2 to 4, >4 to 6, >6 to 8, >8 to 10, >10 to 12, >12 to 14, >14 to 16, >16 to 18, >18 to 20, >20 to 22, and >22 to 24). In addition, percentages of time that intragastric pH was >3, >4, >5, and >6 over the entire 24-hour period following dosing and the percentage of time intraesophageal pH was <4 over the entire 24-hour period following dosing (or over the entire postdose period that pH was recorded) were also determined. Descriptive statistics were generated for each of the twelve 2-hour postdose time intervals over the 24-hour period and for the percentages of time intragastric pH was >3, >4, >5, and >6 on Day -1 and on Dosing Days 1 and 5. Integrated acidity (AUC of hydrogen ion concentration) was evaluated using descriptive statistics.

GERD Symptom Assessment:
The percentages of subjects who experienced regurgitation/vomiting at Baseline (at least one episode during Days -3, -2, and -1) and on Dosing Days 2 to 5 were summarized overall and by dosing regimen using descriptive statistics. The number of episodes of regurgitation/vomiting per 24-hour period was determined for each subject at Baseline (average of episodes over Days -3, -2, and -1) and on Dosing Days 2 to 5. Mean changes in the number of episodes of regurgitation/vomiting from Baseline to Dosing Days 2 to 5 were summarized overall and by dosing regimen. Episodes of regurgitation/vomiting for Dosing Day 1 were not summarized because the number of episodes could not be collected for a full 24-hour period due to the dosing schedule. The first full 24-hour period of treatment was Dosing Day 2. Overall GERD symptom relief for each subject was rated by the investigator on Dosing Day 5 as Better, Not Changed, or Worse compared to Baseline. The numbers and percentages of subjects within each rating category were summarized overall and by dosing regimen.

Pharmacokinetics:
For each dosing regimen, lansoprazole concentrations in plasma at each scheduled timepoint on Dosing Days 1 and 5, and each PK parameter value on Dosing Day 1 were tabulated and descriptive statistics were computed. Descriptive statistics included n, mean, standard deviation, median, minimum and maximum values, and percentage of coefficient of variation (%CV). Additionally, the harmonic mean was determined for the terminal phase elimination half-life ($t_{1/2z}$). The relationships of AUC and C_{max} with body weight, age, and genotype were explored.

Safety:
Adverse events (AEs) were summarized separately by Dosing and Postdosing Periods using descriptive statistics. For each study period, the numbers and percentages of subjects reporting an AE were summarized overall and by dosing regimen, severity level, and relatedness to study drug. Mean changes in clinical laboratory values from Baseline to Dosing Day 5 were summarized overall and by dosing regimen. Mean changes in vital signs were also summarized overall and by dosing regimen. Subjects with laboratory results that met predefined criteria for potentially concerning values or those who had vital sign values outside the normal range were identified.

Results:
Efficacy Results:
Efficacy was not the primary objective in this Phase 1 study; however, GERD symptom relief was assessed as a secondary endpoint. Pharmacodynamic, GERD symptom relief, and PK results are presented.

Pharmacodynamic Results:
Pharmacodynamic results are based on data obtained, in accordance with the protocol, from 6 subjects (n=4 and n=2 for lansoprazole 0.5 and 1.0 mg/kg/day dose groups, respectively).

On Dosing Day 1, the percentages of time intragastric pH was >3 and >4 were similar (>90%) for both dose groups. The percentages of time that intragastric pH was >5 and >6 was 76% and 48%, respectively, in the lansoprazole 0.5 mg/kg/day dose group, and 88% and 51%, respectively, in the lansoprazole 1.0 mg/kg/day dose group.

On Dosing Day 5, the percentages of time the intragastric pH was >3 and >4 over the 24-hour postdose period was >90% for both dose groups. The percentages of time that intragastric pH was >5 and >6 was 92% and 56%, respectively, in the lansoprazole 0.5 mg/kg/day dose group, and 84% and 40%, respectively, in the lansoprazole 1.0 mg/kg/day dose group.

	Lansoprazole 0.5 mg/kg/day (n=4)				Lansoprazole 1.0 mg/kg/day (n=2)			
Study Day	**pH >3**	**pH >4**	**pH >5**	**pH >6**	**pH >3**	**pH >4**	**pH >5**	**pH >6**
Day -1	83.6	76.6	60.9	24.5	66.1	58.8	42.7	14.6
Dosing Day 1	98.7	90.1	76.5	47.8	98.4	95.3	88.5	51.0
Dosing Day 5	98.7	96.6	91.9	56.3	100.0	99.0	84.4	39.6

The percentages of time intraesophageal pH was <4 over a 24-hour postdose period were increased from Baseline to Dosing Day 1 for both dose groups. Percentages of time intraesophageal pH was <4 on Dosing Day 5 were similar to the respective Baselines for both dose groups.

For both dosing regimens, a decrease from Baseline was noted for integrated gastric acidity on Dosing Days 1 and 5. This observed decrease is consistent with the observed increase from Baseline in 24-hour mean intragastric pH on Dosing Days 1 and 5.

Regurgitation/Vomiting Results:
Overall, the percentages of subjects with regurgitation/vomiting were 92% (22/24) at Baseline and 71% (17/24) on Dosing Day 5. At Baseline, 91.7% (11/12) of subjects in each dose group had experienced episodes of regurgitation/vomiting. On Dosing Day 5, 75% (9/12) of subjects in the 0.5 mg/kg/day dose group and 66.7% (8/12) of subjects in the 1.0 mg/kg/day dose group experienced episodes of regurgitation/vomiting.

The mean numbers of episodes of regurgitation/vomiting per the 24-hour postdose period were reduced from 3.3 at Baseline to 1.8 on Dosing Day 5 for both dose groups combined. At Baseline, the mean number of regurgitation/vomiting episodes reported was 3.4 and 3.3 for the 0.5 and 1.0 mg/kg/day dose groups, respectively. On Dosing Day 5, the mean number of episodes was 2.1 and 1.5, respectively.

Overall GERD Symptom Relief Results:
Overall GERD symptom relief on Dosing Day 5 was rated as Better in 83% (10/12) of subjects in the lansoprazole 0.5 mg/kg/day dose group and in 75% (9/12) of subjects in the 1.0 mg/kg/day dose group. Overall GERD symptom relief was rated as Not Changed in 17% (2/12) of subjects in the lansoprazole 0.5 mg/kg/day dose group and in 25% (3/12) of subjects in the 1.0 mg/kg/day dose group. No subject symptoms were rated as Worse in either dose group.

Pharmacokinetics Results:
The PK profile of lansoprazole was determined in 24 neonates following oral administration of 0.5 or 1.0 mg/kg/day lansoprazole pediatric suspension. Mean PK parameter estimates for lansoprazole on Dosing Day 1 are presented below:

Lansoprazole Dose Group	**Statistic**	**Corrected Age (weeks)**	**Body Wt (g)**	**t_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{∞} (ng·h/mL)**	**$t_{1/2}$ (h)**	**CL/F (L/hr/kg)**
0.5 mg/kg/day	Mean	40	3339	3.08	830.83	5086.19	2.76[a]	0.16
(n=12)	SD	3	763	2.15	381.36	2613.74	NA	0.18
1.0 mg/kg/day	Mean	39	2690	2.60	1672.08	9371.93	1.97[a]	0.16
(n=12)	SD	5	926	1.51	808.94	4792.98	NA	0.15

a Harmonic mean.
NA = not applicable.

An approximate dose-proportional increase in mean C_{max} values (from 831 ng/mL to 1672 ng/mL) and AUC values (from 5086 ng·h/mL to 9372 ng·h/mL) was noted for these 2 regimens. Although the lansoprazole concentrations in plasma on Dosing Day 5 were slightly different from those on Dosing Day 1 at the same timepoint for either dose, no meaningful accumulation was observed in neonates following oral administration of 0.5 or 1.0 mg/kg/day lansoprazole pediatric suspension for 5 days and the mean apparent clearance was identical for the 2 dose groups. Although mean apparent clearance, dose-normalized C_{max}, and AUC values for the six CYP2C19 heterozygous extensive metabolizers were lower than those observed for the 16 homozygous extensive metabolizers, this difference may be due to interindividual variability.

Safety Results:
During the Dosing Period, 42% (5/12) of subjects in the 0.5 mg/kg/day lansoprazole pediatric suspension dose group and 50% (6/12) of subjects in the 1.0 mg/kg/day dose group experienced at least 1 AE; all AEs were of mild or moderate severity. During the Postdosing Period, 8% (1/12) of subjects in the lansoprazole 0.5 mg/kg/day dose group and 17% (2/12) of subjects in the 1.0 mg/kg/day dose group experienced at least 1 AE; all were of mild or moderate severity, except in 1 subject in the lansoprazole 1.0 mg/kg/day dose group who had a serious adverse event (SAE) of Neonatal Respiratory Distress Syndrome (Medical Dictionary for Regulatory Activities Preferred Term [MedDRA PT]). This SAE was considered by the Investigator to be severe and not related to study drug. Four subjects (2 subjects [17%, (2/12)] in each dose group) experienced a treatment-related AE during the Dosing Period [MedDRA PT: Flushing (n=2), Anaemia (n=1), and Transaminase Increased (n=1)]. All of the treatment-related AEs were of mild severity. No subject experienced a treatment-related AE during the Postdosing Period.

No subject was discontinued from the study due to an AE. No clinically important trends were observed in the evaluation of vital signs, laboratory values, or physical examination results. No new safety signals were identified in neonates.

Summary-Conclusions:
Following 5-day treatment with lansoprazole pediatric suspension (0.5 or 1.0 mg/kg/day), an increase in the percentages of time intragastric pH was >3, >4, >5, and >6 over a 24-hour postdose period was observed on Dosing Days 1 and 5 compared to Baseline in the neonates in this study.

Decreases from Baseline to Dosing Day 5 in the percentages of subjects with regurgitation/vomiting and in the mean numbers of regurgitation/vomiting episodes per 24-hour period were observed for both dose groups. Overall GERD symptom relief was rated by the Investigator as Better on Dosing Day 5 compared with Baseline in the majority of subjects.

Following the administration of single and multiple oral doses of 0.5 or 1.0 mg/kg/day lansoprazole pediatric suspension in neonates, mean t_{max} and half-life values were longer, and total exposure was higher compared to those previously observed for children, adolescents, and adults. Approximate dose proportionality was observed for mean C_{max} and AUC values in neonates, and the mean apparent clearance was identical for the 2 dose groups. No meaningful accumulation was observed following multiple daily doses of lansoprazole for 5 days. Although mean apparent clearance and dose-normalized C_{max} and AUC values for the six CYP2C19 heterozygous extensive metabolizers were lower than those observed for the 16 homozygous extensive metabolizers, the differences may be due to interindividual variability.

Lansoprazole 0.5 mg/kg/day and 1.0 mg/kg/day administered for 5 days was safe and well tolerated by the neonates in this study.

Individual Study Synopsis C03-042

Name of Company: TAP Pharmaceutical Products Inc **Name of Finished Product:** Lansoprazole Microgranules Oral Suspension for Pediatric Use **Name of Active Ingredient:** Lansoprazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole	
Title of Study: A Phase 1, Single- and Repeated-Dose, Randomized, Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Lansoprazole in Infants with Clinically Evident Gastroesophageal Reflux Disease	
Investigator(s): 5 (2 in United States and 3 in Poland)	
Study Center(s): 5 (2 in United States and 3 in Poland)	
Publications (reference): Zhang W, Kukulka MJ, Witt G, Sutkowski-Markmann D, North J, Atkinson S. Substantial differences in lansoprazole pharmacokinetics between older and younger infants and neonates [abstract]. *Gastroenterology*. 2006; 130 (Suppl 2):A-4. Springer M, Zhang W, Atkinson S, North J, Raanan M, Witt G. Pharmacokinetic and pharmacodynamic profiles and symptom relief in infants with clinically evident GERD treated with lansoprazole. E-PAS2006:59:4811.49.	
Study Period: Date of First Dose: 17 January 2005 Date of Last Procedure: 28 July 2005	**Phase of Development:** 1
Objective(s): The objectives of this study were to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles, and to assess the safety profiles of single and repeated doses of Lansoprazole Microgranules Oral Suspension for Pediatric Use (lansoprazole pediatric suspension) 1.0 or 2.0 mg/kg/day over a 5-day period in infants with clinically evident gastroesophageal reflux disease (GERD).	
Methodology: This was a Phase 1, single- and repeated-dose, parallel-group, randomized, open-label, 2-country, multicenter study in 24 infants (1 to 11 months of age) with clinically evident GERD, who were randomly assigned to 1 of 2 treatment groups (1.0 or 2.0 mg/kg/day) of lansoprazole pediatric suspension. All subjects received the first dose of study drug on Dosing Day 1 after a 30-minute fast. Dosing occurred each day for 5 days (Dosing Days 1 to 5) at approximately 24-hour intervals. Blood samples for PK analyses were drawn from all subjects on Dosing Day 1 (at 0 h [predose] and at 1, 2, 3, 4, 6, 8, 12 h postdose) and on Dosing Day 5 (at 0 h [predose] and at 2 and 6 h postdose). Plasma concentrations of lansoprazole were determined using a validated liquid chromatography assay coupled with tandem mass spectrometry (LC-MS/MS). A buccal sample for genotyping CYP2C19 was obtained from subjects with parent/legal guardian consent to determine CYP2C19 metabolizer status. Intragastric and intraesophageal pH monitoring was performed in 6 infants at Baseline (Day -1) and on Dosing Days 1 and 5. The percentage of subjects with GERD symptoms and the numbers of episodes of GERD symptoms were assessed at Baseline and on Dosing Days 1 to 5. Overall GERD symptom relief from Baseline was assessed by the Investigator on Dosing Day 5. Safety was monitored through adverse event (AE) reports, concomitant medication usage, physical examinations, vital sign assessments, and laboratory evaluations.	
Number of Patients (planned and analyzed): 24 planned (12 each in lansoprazole 1.0 and 2.0 mg/kg/day dose groups); 24 analyzed for pharmacokinetics, GERD symptom assessment, and safety; 6 analyzed (as planned) for pharmacodynamics; and 20 analyzed for CYP2C19 genotype.	
Diagnosis and Main Criteria for Inclusion: Male or female subjects with clinically evident GERD who were term (38-42 weeks gestation) or postterm (>42 weeks gestation) infants beyond the neonatal period (>28 days) but <12 months of age, OR a preterm infant with a corrected age of ≥44 weeks but <94 weeks on Dosing Day 1.	

Test Product, Dose and Mode of Administration, Batch Number:

Test Product	Dose	Mode of Administration	Drug Product Lot Number	Drug Substance Lot Number
Lansoprazole pediatric suspension – 30 mg (investigational)	1.0 mg/kg/day	intra-oral, oro- or naso-gastric tube, or gastronomy tube	040053	HG660
	2.0 mg/kg/day	intra-oral, oro- or naso-gastric tube, or gastronomy tube	040053	HG660

Duration of Treatment: All subjects received single daily doses of 1.0 or 2.0 mg/kg/day for 5 consecutive days.

Reference Therapy, Dose and Mode of Administration, Batch number: Not applicable.

Criteria for Evaluation

Efficacy:

A primary objective of this study was to assess pharmacokinetics (in all subjects) and pharmacodynamics (in a subset of 6 subjects). GERD symptoms were assessed as secondary efficacy variables.

Pharmacodynamics:

The pharmacodynamics of lansoprazole were evaluated at Baseline (Day -1) and on Dosing Days 1 and 5. Criteria for evaluation included: (1) the mean of the 15-minute median intragastric pH values over the entire 24-hour period and for twelve 2-hour time intervals; (2) the percentages of time that intragastric pH was >3, >4, >5, and >6 over the entire 24-hour period; (3) percentage of time intraesophageal pH was <4 over the entire 24-hour period and for twelve 2-hour time intervals; and (4) integrated gastric acidity (area under the curve [AUC] of hydrogen ion concentration) over the entire 24-hour period.

GERD Symptoms:

Clinical efficacy was assessed by GERD symptom relief. The presence of the GERD symptoms of regurgitation/vomiting, apnea, irritability, feeding refusal/crying during feedings, wheezing or stridor, hoarseness, cough, and spells of arching were obtained at Baseline and on each day of dosing (Dosing Days 1 to 5). The number of episodes of each of the a priori-selected symptoms regurgitation/vomiting, apnea, feeding refusal/crying during feedings, and spells of arching per 24-hour period was recorded for each subject at Baseline and on Dosing Days 1 to 5. On the final day of dosing, overall GERD symptom relief was evaluated by the Investigator as Better, Not Changed, or Worse as compared to Baseline.

Pharmacokinetics:

Plasma concentrations of lansoprazole were determined at designated timepoints on Dosing Days 1 and 5. Pharmacokinetic parameters for lansoprazole on Dosing Day 1 were estimated using standard noncompartmental methods. These parameters included the observed peak plasma concentration (C_{max}), the time to reach the observed peak plasma concentration (t_{max}), the apparent terminal phase elimination rate constant (λ_z), the apparent terminal half-life ($t_{1/2z}$); and the area under the plasma concentration time curve (AUC) from time zero to the last measurable concentration (AUC_t) and to infinity (AUC_∞), the apparent clearance (CL/F), and apparent volume of distribution (V_z/F).

Safety:

Safety was monitored throughout the study through evaluations of AEs, concomitant medications usage, clinical laboratory assessments, physical examinations, and measurement of vital signs.

Statistical Methods

Efficacy:

Pharmacodynamics:

Median intragastric pH values were calculated using all values obtained within each 15-minute interval for the 24-hour period at Baseline (Day -1) and on Dosing Days 1 and 5. The effect of treatment on intragastric pH was quantified using the mean of the 15-minute median intragastric pH values over the entire 24-hour period following dosing (or entire period following dosing in which pH was recorded) and for time intervals following dosing (hours 0 to 2, >2 to 4, >4 to 6, >6 to 8, >8 to 10, >10 to 12, >12 to 14, >14 to 16, >16 to 18, >18 to 20, >20 to 22, and >22 to 24). In addition, the percentages of time that the intragastric pH was >3, >4, >5, and >6 over the entire 24-hour period following dosing and the percentages of time that the intraesophageal pH was <4 over the entire 24-hour period following dosing (or over the entire period postdose that pH was recorded) were also determined. Descriptive statistics were generated for each of the twelve 2-hour postdose time intervals over the 24-hour period and for the percentages of time intragastric pH was >3, >4, >5, and >6 on Day -1 and on Dosing Days 1 and 5. Integrated acidity (AUC of hydrogen ion concentration) was evaluated using descriptive statistics.

GERD Symptom Assessment:

The number and percentage of subjects who experienced each GERD symptom (regurgitation/vomiting, apnea, feeding refusal/crying during feeding, arching, irritability, wheezing/stridor, hoarseness, and cough) were summarized at Baseline (Day -1) and on Dosing Days 1 to 5, overall, by dosing regimen, and by concomitant prokinetic drug use. The percent change from Baseline in the percentage of subjects with each GERD symptom was determined on Dosing Days 1 to 5 for each dosing regimen. The numbers of episodes per 24-hour period of a subset of a priori-selected symptoms (regurgitation/vomiting, apnea, feeding refusal/crying during feedings, and spells of arching) were determined for each subject at Baseline and on Dosing Days 1 to 5. Mean changes in the number of episodes for each symptom from Baseline to each of the 5 dosing days (Dosing Days 1 to 5) was summarized overall, by dosing regimen, and by concomitant prokinetic drug use. The numbers and percentages of subjects within each category of overall GERD symptom relief (Better, Not Changed, or Worse from Baseline) were summarized overall, by dosing regimen, and by concomitant prokinetic drug use.

Pharmacokinetics:

For each dosing regimen, lansoprazole concentration in plasma at each scheduled timepoint on Dosing Days 1 and 5, and each PK parameter value on Dosing Day 1 were tabulated and descriptive statistics were computed. Descriptive statistics included n, mean, standard deviation, median, minimum and maximum values, and %CV. Additionally, the harmonic mean was determined for the terminal phase elimination half-life ($t_{1/2z}$). The relationships of AUC and C_{max} with body weight and with age were explored.

Safety:

Adverse events (AEs) were summarized separately by Dosing and Postdosing Periods using descriptive statistics. For each study period, the numbers and percentages of subjects reporting an adverse event were summarized overall and by dosing regimen, severity level, and relatedness to study drug. Mean changes in clinical laboratory values from Baseline to Dosing Day 5 were summarized overall and by dosing regimen. Mean changes in vital signs were also summarized overall and by dosing regimen. Subjects with laboratory results that met predefined criteria for potentially concerning values or had vital sign values outside the normal range were identified.

Results

Efficacy Results:

Efficacy was not the primary objective in this Phase 1 study; however, GERD symptom relief was assessed as a secondary endpoint. Pharmacodynamic, GERD symptom relief, and PK results are presented.

Pharmacodynamic Results:

Pharmacodynamic results are based on data obtained, in accordance with the protocol, from 6 subjects (n=3 and n=3 for lansoprazole 1.0 and 2.0 mg/kg/day dose groups, respectively).

For both dose groups, an increase from Baseline was noted in the percentage of time that the intragastric pH was >3, >4, >5, and >6 over the 24-hour period following dosing on Dosing Days 1 and 5.

On Dosing Day 5, intragastric pH for both dose groups were >3, >4, >5, and >6 for approximately 90%, 85%, 76%, and 53% of the time, respectively, over the 24-hour period following dosing.

	Lansoprazole 1.0 mg/kg/day (n=3)				**Lansoprazole 2.0 mg/kg/day** (n=3)			
Study Day	**pH >3**	**pH >4**	**pH >5**	**pH >6**	**pH >3**	**pH >4**	**pH >5**	**pH >6**
Day -1	62.5	50.0	27.4	12.2	67.0	52.4	34.0	24.0
Dosing Day 1	81.1	71.5	60.2	34.0	64.2	60.0	55.1	41.7
Dosing Day 5	89.8	84.9	76.5	53.8	88.8	83.9	75.9	53.2

GERD Symptom Relief Results:

Because nonhospitalized subjects did not have individual GERD symptoms evaluated for the 24-hour period following the fifth dose of study drug (Dosing Day 5), the overall comparisons from Baseline to Dosing Day 4 (when data was available for all 24 subjects) are presented in this report along with comparisons from Baseline to Dosing Day 5. For subjects overall, a decrease in the percentage of subjects with GERD symptoms from Baseline to Dosing Day 4 was observed for feeding refusal/crying (42% vs 12%, respectively), spells of arching (50% vs 21%, respectively), irritability (50% vs 12%, respectively), and cough (58% vs 25%, respectively), and on Dosing Day 5 a decrease from Baseline in the percentage of subjects with GERD symptoms was also observed for these symptoms. There was little change in the percentage of subjects with regurgitation/vomiting from Baseline (83%, [20/24]) to Dosing Day 4 (79.2%, [19/24]) or Dosing Day 5 (75%, [9/12]). The most prevalent symptom overall was regurgitation/vomiting, occurring in 83.3% of subjects at Baseline and in 79.2% and 75.0% of subjects at Dosing Days 4 and 5, respectively. There was a reduction in the mean numbers of symptom episodes for regurgitation/vomiting, feeding refusal/crying during feedings, and spells of arching. No subject experienced apnea.

On Dosing Day 5, overall GERD symptom relief was assessed as Better in 83% (10/12) and 92% (11/12) of subjects in the lansoprazole 1.0 and 2.0 mg/kg/day groups, respectively.

Pharmacokinetic Results:

The PK profile of lansoprazole was determined in 24 infants with chronological ages 6 to 54 weeks (corrected ages of 46 to 84 weeks) following oral administration of 1.0 or 2.0 mg/kg/day lansoprazole pediatric suspension. Mean PK parameter estimates for lansoprazole on Dosing Day 1 are presented below:

Lansoprazole Dose Group		**Chronological Age (weeks)**	**Body Wt (g)**	**t_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{∞} (ng·h/mL)**	**$t_{1/2}$ (h)**	**CL/F (L/hr/kg)**
1.0 mg/kg/day	Mean	24	6232	1.83	959.08	2202.83	0.83[a]	0.71
(n=12)	SD	13	1629	1.19	472.10	2301.02	NA	0.40
2.0 mg/kg/day	Mean	24	6526	1.76	2086.83	5794.35	0.79[a]	0.61
(n=12)	SD	14	1453	1.06	1558.39	5618.94	NA	0.38

a harmonic mean.
NA=not applicable.

Results (Cont)
An approximate dose-proportional increase in mean C_{max} values (from 959 ng/mL to 2087 ng/mL, respectively) was noted for the 2 dose groups. However, a greater than dose-proportional increase (from 2203 ng·h/mL to 5794 ng·h/mL, respectively) was noted for mean AUC values. For each of the doses, the concentrations of lansoprazole in plasma on Day 5 were generally similar to those on Dosing Day 1 at the same timepoints. No accumulation of lansoprazole in plasma was observed in infants following 5 days of oral administration of lansoprazole pediatric suspension 1.0 or 2.0 mg/kg/day, and the apparent clearance was comparable for the 2 dose groups.

There was an apparent age effect on the pharmacokinetics of lansoprazole, with 3 subjects (chronological age of 6 weeks; 1 subject in the 1.0 mg/kg/day dose group and 2 in the 2.0 mg/kg/day dose group) having a substantially lower apparent clearance and higher dose-normalized C_{max} and AUC values compared to the other 21 subjects who had a chronological age of >10 weeks.

Safety Results:
During the Dosing Period, 42% (5/12) of subjects in the lansoprazole 1.0 mg/kg/day group and 42% (5/12) of subjects in the lansoprazole 2.0 mg/kg/day group experienced at least 1 AE; all were of mild or moderate severity. During the Postdosing Period, 25% (3/12) of subjects in lansoprazole 1.0 mg/kg/day group and 42% (5/12) of subjects in 2.0 mg/kg/day group experienced at least 1 AE; all AEs were of mild or moderate severity, except in 1 subject in the lansoprazole 2.0 mg/kg/day group with a serious AE (SAE) of Pneumonia Viral (MedDRA PT). This SAE was severe and considered not related to study drug. One treatment-related AE (MedDRA PT: Hepatic Enzyme Increased) was reported on Dosing Day 5 in 1 subject in the lansoprazole 2.0 mg/kg/day group, was mild in severity, considered probably related to study drug, and resolved with treatment during the Postdosing Period.

No subject prematurely discontinued from this study and no clinically important trends were observed in the evaluation of vital signs, laboratory values, or physical examination results. No new safety signals were identified in infants.

Summary-Conclusions:
Following 5-day treatment with lansoprazole (1.0 mg and 2.0 mg/kg/day), an increase in the percentages of time intragastric pH was >3, >4, >5, and >6 over a 24-hour postdose period was observed on Dosing Days 1 and 5 compared to Baseline in infants 1 to 11 months of age.

Decreases in the percentages of subjects with individual GERD symptoms were observed in both dose groups (lansoprazole 1.0 and 2.0 mg/kg/day) from Baseline to Dosing Day 4; these decreases from Baseline were also observed on Dosing Day 5. Decreases from Baseline in the mean numbers of symptom episodes were observed for both dose groups. Overall GERD symptom relief was rated by the Investigator as Better on Dosing Day 5 as compared with Baseline in a majority of subjects.

The PK profile of lansoprazole in infants with a chronological age of >10 weeks who were administered single and multiple oral doses of lansoprazole pediatric suspension was generally similar to those observed in children and adults. Based on the PK data in this study, an approximate dose of 1.3 mg/kg/day of lansoprazole in infants with a chronological age of >10 weeks should achieve similar mean total exposure (AUC) as a 30-mg dose of lansoprazole delayed-release capsule in adults. Compared to infants with a chronological age of >10 weeks, infants with a chronological age of ≤10 weeks had a substantially lower apparent clearance and higher dose-normalized C_{max} and AUC values, suggesting a lower dose is needed in infants with a chronological age of ≤10 weeks. Based on the PK

Summary-Conclusions (Cont)
information from three 6-week-old subjects in this study, an approximate dose of 0.24 mg/kg/day of lansoprazole should provide similar exposure in infants ≤10 weeks of age as 30-mg lansoprazole delayed-release capsule in adults.

Lansoprazole (1.0 and 2.0 mg/kg/day) administered orally for 5 days was safe and well tolerated in infants ages 1 to 11 months in this study.

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/s/

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