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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Protonix® / Pantoprazole sodium

PROTOCOL NO.: 3001B3-331-WW (B1791057)

PROTOCOL TITLE: 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 Centers: Twenty four (24) centers took part in the study and randomized subjects: 18 in the United States; 2 in Poland; 1 each in France, Canada, Belgium and Italy.

Study Initiation and Final Completion Dates: 23 July 2006 to 20 December 2007

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To determine whether or not consistent exposures can be achieved in neonates and preterm infants with presumed gastroesophageal reflux disease (GERD) receiving oral doses of pantoprazole.

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of oral pantoprazole after a single dose and at steady state when consistent exposures can be achieved in neonates and preterm infants with presumed GERD at doses expected to produce exposures similar to older children and adults given standard doses.

- To provide the pharmacodynamic (PD) assessment of pantoprazole at Baseline and at steady-state by measurement of intragastric and intraesophageal pH by pH-metry in neonates and preterm infants with presumed GERD.

- To characterize the change in clinical GERD and respiratory symptoms from Baseline, after single-dose and multiple-doses of pantoprazole in neonates and infants with presumed GERD.

- To describe the safety of pantoprazole in neonates and preterm infants with presumed GERD throughout the study.

METHODS

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 1 dose level (2.5 mg) in neonates and preterm infants with a clinical indication for acid suppression to treat a presumed diagnosis of GERD. Subjects were neonates and preterm infants admitted to a neonatal intensive care unit (NICU) or special care nursery at the time of enrollment.

Each subject participated in the study for a period of 3 to 5 weeks, which included a screening evaluation within 2 to 7 days of test article administration, treatment for 5 to 10 days, and a follow-up contact (telephone call or visit) with the parent approximately 15±3 days after discharge from the study.

Subjects were assigned to 1 of 3 assessment strata: the PK stratum, the PK/PD stratum, or the PD stratum. Subjects in the PK and PK/PD strata were randomly assigned to (1:1) to receive daily doses of 1.25 or 2.5 mg of pantoprazole. To reduce the number of PK specimens drawn, each subject was then assigned to 1 of 2 PK collection schedules for Day 1: group A or group B. All subjects in the PD stratum received 2.5-mg doses.

The study flowcharts for the subjects assigned to the PK, PD, and PK/PD populations are presented in Table 1, Table 2, and Table 3 respectively.

Table 1. Study Flowchart for PK Subjects

Study Phase	Screening [a]	Baseline		Active Study (Treatment) Period											Early Termination [b]	Poststudy [c]	Optional Days (7–10)
Study Day	**-7 to -2**	**-1**	**1**	**1**							**2–5**	**6**		**Final Study Evaluation**		**23±5**	
Study Hour			**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**18**		**0**	**3**	**6**			
Informed consent	X																
Record nonstudy/ treatment medications	X----------X																
Adverse event recording	X----------X																
Medical history and demography	X																
GERD and respiratory symptoms worksheet [d]	X	X						X			X		X		X		X
Recent treatment for GERD	X	X	X								X		X		X		X
Feeding type and regimen [e]	X	X	X								X	X			X		X
Physical examination [f]	X													X	X		
Measurement of weight	X	X		X							X	X			X		X
Vital signs [g]	X	X		X							X	X			X		X
Electrocardiogram [h]	X													X	X		
Laboratory evaluation, including urinalysis [i]	X													X	X		
Buccal cells for PG analysis [j]	X														X		X
Blood sample for single-dose PK [k]			X		X	X	X	X	X	X							
Pantoprazole administration [l]				X							X	X					X
Blood sample for multiple-dose PK [m]													X	X	X [m]		
Follow-up contact																X	

ECG = electrocardiogram; h = hour; GERD = gastroesophageal reflux disease; PG = pharmacogenomic; PK = pharmacokinetic.

a. Within 7 days before pantoprazole administration, but could have been combined with Day -1.
b. For the early termination visit evaluations, the procedures already captured for that day were not to be duplicated.
c. Poststudy safety evaluation (may have been a visit or a phone contact) was to occur approximately 15±3 days after the last dose of pantoprazole was administered or any time a subject withdrew from the study.
d. GERD symptoms for the prior 24 hours were recorded daily on the worksheet based on nursing and/or physician clinical observations.
e. Feeding type (breast milk, infant formula, or breast milk with human milk fortifier or infant formula with human milk fortifier) and regimen at Screening and 24 hours before pantoprazole administration until the final visit.
f. Included weight (g), length (cm), and head circumference (cm).
g. Rectal or axillary temperature, respiratory rate, supine blood pressure, and heart rate or as recorded in the subject's chart. Vital signs were assessed within 15 minutes of the scheduled time. Whenever vital signs were assessed, the assessment was performed prior to any blood collection procedures.
h. ECG was recorded during screening if >3 days had elapsed since previous ECG. This could have been combined with Day -1.

Table 1. Study Flowchart for PK Subjects

i. Hematology and chemistry. Every effort was made to minimize the amount of blood collected. Therefore, clinical laboratory studies performed within 7 days before pantoprazole administration were to serve as Screening safety laboratory values provided the information specified in the protocol was obtained. Minimal safety laboratory tests and urinalysis were performed if not performed for clinical reasons. Laboratory studies performed within 72 hours after the last dose of pantoprazole could have been used as the final study evaluation safety laboratory values. When collecting blood samples, procedures were used to minimize or avoid wasting of blood. The laboratory was asked to retain blood specimens in the event that additional testing was needed.

j. Buccal cell samples and discarded blood cells (ie, PK blood samples) may have been collected at any time during Screening or at any time during the study, but must have been collected prior to the subject's final study visit. Discarded blood cells from PK samples performed at Baseline or during the study should have been collected to provide back-up DNA specimens in the event the buccal cells were not sufficient or could not be obtained.

k. Subjects were randomly assigned to PK collection times (Group A or Group B) and were to have 0.25 mL of blood collected, as shown in the table 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	

l. Subjects received pantoprazole once daily at approximately the same time of day as on study Day 1 (ie, approximately half-hour before the morning feeding).

m. Blood samples for multiple-dose PK analysis were collected, as specified, after pantoprazole administration on the final study day. If a subject was withdrawn on a non-PK day, PK samples were obtained, as specified, after the last dose of pantoprazole (see table below). The medical monitor or designee was notified. The final study evaluation was performed after the final multiple-dose PK sample was drawn.

Day 6: PK Collection Times	
3 h	6 h
X	X

Table 2. Study Flowchart for PD Subjects (2.5-mg Doses Only)

Study Phase	Screening[a]	Baseline		Active Study Period								Early Termination[b]	Poststudy[c]	Optional Days 7–10
Study Day	**-7 to -2**	**-1**	**1**	**1**		**2–5**	**6**				**Final Study Evaluation**		**23±5**	
Study Hour			**-2**	**0**	**24**		**0**	**3**	**6**	**24**				
Informed consent	X													
Record nonstudy treatment medication	X ----------X													
Adverse event recording	X ----------X													
Medical history and demography	X													
GERD and respiratory symptoms worksheet[d]	X	X		X		X	X				X	X		X
Recent treatment for GERD	X	X	X			X	X					X		X
Feeding type and regimen[e]	X	X	X			X	X					X		X
Physical examination[f]	X										X	X		
Measurement of weight	X	X		X		X	X					X		X
Vital signs[g]	X	X		X		X	X					X		X
Electocardiogram[h]	X										X	X		
Laboratory evaluation including urinalysis[i]	X										X	X		
Buccal cells for PG analysis[j]	X											X		X
Pantoprazole administration[k]				X		X	X							X
Blood sample for multiple-dose PK[l]			X					X	X			X		
pH-metry assessment[m]	X						X----------X							
Follow-up contact													X	

ECG = electrocardiogram; GERD = gastroesophageal reflux disease; PG = pharmacogenomic; PK = pharmacokinetic.

a. Within 7 days before pantoprazole administration, but could have been combined with Day -1.

b. For the early termination visit evaluations, the procedures already captured for that day were not duplicated.

c. Poststudy safety evaluation (may have been a visit or a phone contact) occurred approximately 15±3 days after the last dose of pantoprazole was administered or any time a subject withdrew from the study.

d. GERD symptoms for the prior 24 hours were recorded daily on the worksheet based on nursing and/or physician clinical observations.

e. Feeding type (breast milk, infant formula, or breast milk with human milk fortifier or infant formula with human milk fortifier) and regimen at Screening and 24 hours before pantoprazole administration until the final visit.

f. Included weight (g), length (cm), and head circumference (cm).

g. Rectal or axillary temperature, respiratory rate, supine blood pressure, and heart rate or as recorded in the subject's chart. Vital signs were assessed within 15 minutes of the scheduled time. Whenever vital signs were assessed, the assessment was performed before blood collection procedures.

h. ECG was recorded during Screening if >3 days had elapsed since previous ECG. This could have been combined with Day -1.

i. Hematology and chemistry. Every effort was made to minimize the amount of blood collected. Therefore, clinical laboratory studies performed within 7 days before pantoprazole administration were to serve as screening safety laboratory values provided the information specified in the protocol was obtained. Minimal safety

Table 2. Study Flowchart for PD Subjects (2.5-mg Doses Only)

laboratory tests and urinalysis were performed if not performed for clinical reasons. Laboratory studies performed within 72 hours after the last dose of pantoprazole could have been used as the final study evaluation safety laboratory values. When collecting blood samples, procedures were used to minimize or avoid wasting of blood. The laboratory was asked to retain blood specimens in the event that additional testing was needed.

j. Buccal cell samples and discarded blood cells (ie, PK blood samples) could have been collected at any time during Screening or at any time during the study, but must have been collected prior to the subject's final study visit. Discarded blood cells from PK samples performed at Baseline or during the study should have been collected to provide back-up DNA specimens in the event the buccal cells were not sufficient or could not be obtained.

k. Subjects received pantoprazole once daily at approximately the same time of day as on study Day 1 (ie, approximately ½ hour before the morning feeding).

l. Two (2) blood samples for multiple-dose PK analysis were collected, as specified, after pantoprazole administration on the final study day (see table below). If a subject was withdrawn on a non-PK day, PK samples were obtained, as specified, after the last dose of pantoprazole. The medical monitor or designee was notified. The final study evaluation was performed after the final multiple-dose PK sample was drawn.

Day 6: PK Collection Times	
3 h	6 h
X	X

m. pH-metry assessments were made at Screening (Baseline) and on study Day 6 (final dose of pantoprazole). The subjects could have been fed every 3 to 4 hours as appropriate, with feeding duration limited to 30 minutes. Data collected during the 30 minute feedings and for 30 minutes after feedings were excluded from data analysis.

Table 3. Study Flowchart for PK/PD Subjects

Study Phase	Screening[a]	Baseline		Active Study (Treatment) Period														Final Study Evaluation	Early Termination[b]	Poststudy[c]	Optional Days (7–10)
Study Day	**-7 to -2**	**-1**	**1**	**1**								**2–5**	**6**							**23±5**	
Study Hour			**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**18**	**24**		**-1**	**0**	**3**	**6**	**24**				
Informed consent	X																				
Record nonstudy treatment medications	X----------X																				
Adverse event recording	X----------X																				
Medical history and demography	X																				
GERD and respiratory symptoms worksheet[d]	X	X		X								X	X					X	X		X
Recent treatment for GERD	X	X	X									X	X						X		X
Feeding type and regimen[e]	X	X	X									X		X					X		X
Physical examination[f]	X																	X	X		
Measurement of weight	X	X		X								X		X					X		X
Vital signs[g]	X	X		X								X		X				X	X		X
Electrocardiogram[h]	X																	X	X		
Laboratory evaluation including urinalysis[i]	X																	X	X		
Buccal cells for PG analysis[j]	X																		X		X
Blood sample for single-dose PK[k]			X		X	X	X	X	X	X											
Test article administration[l]				X								X		X							X
Blood sample for multiple-dose PK[m]															X	X			X[k]		
pH-metry[n]	X														X						
Follow-up contact																				X	

ECG = electrocardiogram; GERD = gastroesophageal reflux disease; PG = pharmacogenomic; PK = pharmacokinetic.

a. Within 7 days before pantoprazole administration, but could have been combined with Day -1.

b. For the early termination visit evaluations, the procedures already captured for that day were not duplicated.

c. Poststudy safety evaluation (may have been a visit or a phone contact) occurred approximately 15±3 days after the last dose of pantoprazole was administered or any time a subject withdrew from the study.

Table 3. Study Flowchart for PK/PD Subjects

d. GERD symptoms for the prior 24 hours were recorded daily on the worksheet based on nursing and/or physician clinical observations.

e. Feeding type (breast milk, infant formula, or breast milk with human milk fortifier or infant formula with human milk fortifier) and regimen at screening and 24 hours before pantoprazole administration until the final visit.

f. Included weight (g), length (cm), and head circumference (cm).

g. Rectal or axillary temperature, respiratory rate, supine blood pressure, and heart rate or as recorded in the subject's chart. Vital signs were assessed within 15 minutes of the scheduled time. Whenever vital signs were assessed, the assessment was performed prior to any blood collection procedures.

h. ECG was recorded during screening if >3 days had elapsed since previous ECG. This could have been combined with Day -1.

i. Hematology and chemistry. Every effort was been made to minimize the amount of blood collected. Therefore, clinical laboratory studies performed within 7 days before pantoprazole administration were to serve as screening safety laboratory values provided the information specified in the protocol was obtained. Minimal safety laboratory tests and urinalysis were performed if not performed for clinical reasons. Laboratory studies performed within 72 hours after the last dose of pantoprazole could have been used as the final study evaluation safety laboratory values. When collecting blood samples, procedures were used to minimize or avoid wasting of blood. The laboratory was asked to retain blood specimens in the event that additional testing was needed.

j. Buccal cell samples and discarded blood cells (ie, PK blood samples) could have been collected at any time during screening or at any time during the study, but must have been collected prior to the subject's final study visit. Discarded blood cells from PK samples performed at Baseline or during the study were collected to provide back-up DNA specimens in the event the buccal cells were not sufficient or could not be obtained.

k. Subjects were randomly assigned to PK collection times (group A or group B) and were to have 0.25 mL of blood collected, as shown in the table 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	

l. Subjects received pantoprazole once daily at approximately the same time of day as on study Day 1 (ie, approximately half hour before the morning feeding).

m. Blood samples for multiple-dose PK analyses were collected, as specified, after test article administration on the final study day. If a subject was withdrawn on a non-PK day, PK samples were obtained, as specified, after the last dose of test article. The medical monitor or designee was notified. The final study evaluation was performed after the final multiple-dose PK sample was drawn.

Day 6: PK Collection Times	
3 h	6 h
X	X

n. pH-metry assessments were made at Screening (Baseline) and on study Day 6 (final dose of pantoprazole). The subjects could have been fed every 3 to 4 hours as appropriate; each feeding lasting no >30 minutes. Data collected during the 30 minute feeding and 30 minutes post-feeding period were excluded from data analysis.

Number of Subjects (Planned and Analyzed): Approximately 56 subjects were required to ensure that an adequate number of evaluable subjects completed the study: approximately 36 PK or PK/PD subjects to ensure at least 24 evaluable subjects (12 at each dose level) and approximately 20 PD subjects to ensure at least 6 evaluable subjects. A total of 68 subjects were screened (52 in the United States, 11 in Poland, 2 in Canada, 1 each in Belgium, France and Italy) and 59 were randomized (19 subjects to pantoprazole 1.25 mg and 40 subjects to 2.5 mg).

Diagnosis and Main Criteria for Inclusion: Male and female hospitalized term and post term infants within the neonatal period (≤28 days postnatal age) or preterm infants with a gestational or corrected age of <44 weeks with a presumed diagnosis of GERD.

Exclusion Criteria: Subjects with cardiovascular instability, clinically significant laboratory abnormalities or previous use of warfarin, carbamazepine, phenytoin, or rifampin were excluded from the study.

Study Treatment: Pantoprazole delayed-release granules were provided in an inert powder blend in foil pouches in 1.25-mg 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 using an oral syringe, approximately 30 minutes before the first feeding. All subjects received once-daily dosing for at least 5 days of treatment (no more than 10), at approximately the same time as on study Day 1.

Pharmacokinetic, Pharmacodynamic, and Safety Endpoints:

Pharmacokinetic Endpoints: Single dose area under the concentration-time curves from time 0 to the time of the last measurable concentration (AUC_t). Population PK estimations of the peak concentration (C_{max}), time to C_{max} (T_{max}), terminal disposition half-life ($t_{½}$), area under the curve to infinity (AUC_{inf}), and oral-dose clearance (CL/F).

Pharmacodynamic Endpoints:

- Mean and median intraesophageal pH;
- Mean and median intragastric pH;
- Percentage of time intragastric pH >4;
- Percentage of time intragastric pH >3;
- Percentage of time esophageal pH <4 (reflux index);
- Number of reflux episodes;
- Number of reflux episodes >5 minutes;
- Duration of the longest reflux episodes;

- AUC of gastric hydrogen ion (H^+) concentration over time.

GERD and Respiratory Symptom Frequency Scores: Total daily GERD symptom score.

Safety Endpoints:

- Adverse events (AEs), TEAEs, and serious adverse events (SAEs);
- Comorbidities of prematurity (eg, sepsis, pneumonia/aspiration pneumonia, apnea, necrotizing enterocolitis , bronchopulmonary dysplasia, upper gastrointestinal (GI) bleeding, and Retinopathy of prematurity;
- Physical examination: body weight (kg), length (cm), and head circumference (cm);
- Vital signs measurements, including potentially clinically important (PCI) results;
- Laboratory evaluations, including PCI results;
- Standard 12-lead electrocardiogram (ECG), including heart rate, PR, QRS, QT, and RR intervals;
- Premature terminations due to safety reasons;
- Non-study medications.

No efficacy evaluations were performed for this study.

Safety Evaluations: Safety was assessed by reviewing all safety data, including overall mortality, AEs, SAEs, clinically significant changes in routine clinical laboratory test results; clinically significant changes in physical examination, vital sign measurements, and growth parameters.

Statistical Methods:

Analysis Populations:

Safety Population: The safety population was defined as all subjects who took at least 1 dose of pantoprazole.

Valid-For-Efficacy (VFE) Population: Evaluable subjects were defined as those without any major protocol violations (eg, no prohibited medications, no inclusion/exclusion violations.)

In addition, each VFE population was defined as follows:

- Subjects who completed the single-dose PK determinations were evaluable for the single-dose PK analysis. Subjects must have taken pantoprazole on the date the PK samples were taken.

- Subjects who had taken at least 5 consecutive doses of pantoprazole and provided the 1 or 2 multi-dose PK specimens were evaluable for the population PK analysis.

- PD subjects were those with Baseline and steady state pH-metry, a total recording time of at least 16 hours and at least 5 consecutive doses of pantoprazole prior to the steady state pH-metry.

Single and multiple-dose PK parameters were descriptively summarized by treatment group. Population PK analysis was done using nonlinear mixed-effects modeling approaches.

Descriptive statistics were provided for all pH-metry parameters, reported by study time points. Two (2)-sided 90% confidence intervals were constructed for each time point. Results at steady state were compared with Baseline values using 1 sample 2-sided paired t-tests.

Descriptive statistics and changes from Baseline for the derived daily GERD score were reported by study day and dose group using a 1 sample 2-sided paired t-test. The comparison between the 2 dose groups used an analysis of covariance (ANCOVA) model with dose group as a factor and baseline value as a covariate. Similar analyses were done for each GERD symptom frequency score and the respiratory symptom frequency score.

RESULTS

Subject Disposition and Demography: A total of 68 hospitalized subjects were screened for the study of which 9 subjects were screen failures. The remaining 59 subjects were allocated to an assessment stratum (PK, PK/PD, or PD), assigned to daily doses of 1.25 or 2.5-mg pantoprazole, and assigned to a PK sampling schedule group (A or B). A total of 57 (96.6%) of 59 subjects completed the study (Table 4).

Table 4. Summary of Subject Disposition by Assessment Stratum, Analysis Population and Dose Group

	Pantoprazole 1.25 mg	Pantoprazole 2.5 mg	Total
Screened 68			
Randomized subjects	19	40	59
PK (Group A)	9 (47.37)	10 (25.00)	19 (32.20)
PK (Group B)	9 (47.37)	9 (22.50)	18 (30.51)
PD	0	19 (47.50)	19 (32.20)
PK (Group A)/PD	1 (5.26)	1 (2.50)	2 (3.39)
PK (Group B)/PD	0	1 (2.50)	1 (1.69)
Completed	19 (100)	38 (95.0)	57 (96.6)
Discontinued[a]	0	2 (5.0)	2 (3.4)
Parent/legal guardian request	0	1 (2.5)	1 (1.7)
Protocol violation	0	1 (2.5)	1 (1.7)
Safety[b]	19 (100)	40 (100)	59
Evaluable for single-dose PK	19 (100)	21 (52.5)	40
Evaluable for multiple-dose PK	19 (100)	36 (90.0)	55
Evaluable for PD endpoints	0	16 (40.0)	16

To be evaluable for PK or PD, a subject must not have had any major protocol violations. If a subject was evaluable for both PK and PD, then he or she was counted in both populations.
N = number of subjects; PK = pharmacokinetics; PD = pharmacodynamics.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Table 4. Summary of Subject Disposition by Assessment Stratum, Analysis Population and Dose Group

b. Safety population=all subjects who had at least 1 dose of pantoprazole.

Demographic and Baseline information about subjects in the safety population is presented in Table 5.

Table 5. Demographic and Baseline Subject Characteristics - Safety Population

Characteristic		Pantoprazole Treatment		
	Overall p-Value	1.25 mg N=19	2.5 mg N=40	Total N=59
Gestational Age (weeks)				
Mean	0.992[a]	30.24	30.25	30.25
Standard Deviation		4.72	4.66	4.64
Postnatal Age (week)				
Mean	0.456[a]	8.63	7.70	8.00
Standard Deviation		4.86	4.20	4.40
Corrected Age (weeks)[b]				
n		18	36	54
Mean	0.129[a]	38.71	37.47	37.88
Standard Deviation		3.19	2.58	2.83
Missing		1	4	5
Sex	0.766[c]			
Female		5 (26.32)	13 (32.50)	18 (30.51)
Male		14 (73.68)	27 (67.50)	41 (69.49)

N = total number of subjects; n = number of subjects with specified criteria.
a. One (1)-way analysis of variance with treatment as factor.
b. Corrected age is calculated as gestational age + postnatal age for premature infants only.
c. Fisher exact test p-value (2-tailed).

Pharmacokinetic and Pharmacodynamic Results:

Single-Dose Pharmacokinetic Results: A total of 40 subjects from the PK and PK/PD strata were valid for single-dose PK evaluation: 19 subjects from the 1.25-mg dose group and 21 subjects from the 2.5-mg dose group.

Within each dose group, the AUC_t values were summarized by the PK sampling collection schedules (ie, Group A and Group B) and the variance between the different sampling schedules was calculated. The variance was 1.07 and 0.74 for the 1.25-mg and 2.5-mg dose groups, respectively.

Multiple-Dose PK Results: The AUC and CL/F of pantoprazole was estimated for 33 subjects using a population PK approach (Table 6), as the rest of the subjects had no measurable concentrations over the period of observations.

Table 6. Summary of Pharmacokinetic Results After Multiple Dose Administration of Pantoprazole (PK and PK/PD Strata)

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

AUC = area under the concentration-time curve to last time measured; CL/F = clearance; CV% = coefficient of variation; n = number of subjects; SD = standard deviation.
a. Excludes 2 poor metabolizers.

The mean (±SD) $t_{½}$ estimated from the population PK modeling was 3.1 hours (±1.5) and 2.7 hours (±1.1) for the 1.25-mg and 2.5-mg dose groups, respectively. The $t_{½}$ was longer than the typical $t_{½}$ of 1 hour seen in older children and adult subjects, and consistent with measurable pantoprazole concentrations observed even at 18 hours postdose.

PD Results of pH-metry: The 24-hour pH-metry data from 16 subjects in the valid for PD evaluation population were used to analyze the pH-metry parameters.

Mean Intragastric pH: A statistical analysis of the mean intragastric pH levels of 16 subjects for the monitoring interval 0 to end is presented in Table 7. A statistically significant (p=0.005) increase was observed in the mean intragastric pH levels, which rose from a mean of 4.26 at Baseline to 5.19 at steady state.

Table 7. Descriptive Statistics and Analysis of Mean Intragastric pH Levels During 24-Hour Periods at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	4.26±0.85		
		Median	4.25		
		Min, Max	2.40, 5.50		
		90% CI	3.89, 4.63		
	Steady state	N	16	16	
		Mean ± SD	5.19±0.98	0.94±1.14	0.005
		Median	5.40	0.90	
		Min, Max	3.40, 6.30	-0.70, 3.30	
		90% CI	4.77, 5.62	0.44, 1.44	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.
a. p-Value was obtained from 1 sample 2-sided paired t-test.

Median Intragastric pH: Table 8 presents statistics for the median intragastric pH levels of 16 subjects for the monitoring interval 0 to end. A statistically significant (p=0.004) increase was observed in the median intragastric pH, which rose from a mean of 4.33 at Baseline to 5.44 at steady state.

Table 8. Descriptive Statistics and Analysis of Median Intragastric pH Levels During 24-Hour Periods at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	4.33±1.09		
		Median	4.30		
		Min, Max	1.90, 5.80		
		90% CI	3.85, 4.80		
	Steady state	N	16	16	
		Mean ± SD	5.44±1.13	1.12±1.32	0.004
		Median	5.80	0.80	
		Min, Max	2.80, 6.70	-0.90, 4.10	
		90% CI	4.95, 5.94	0.54, 1.70	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.
a. p-Value was obtained from 1 sample 2-sided paired t-test.

Percentage of Time that Intragastric pH was >4: The percentage of time that intragastric pH was >4 at Baseline and steady state is presented in Table 9 for the monitoring interval 0 to end. The mean percentage of time that intragastric pH was >4 increased significantly (p=0.006) from 59.8% of the time at Baseline to 79.3% of the time at steady state.

Table 9. Descriptive Statistics and Analysis of Percentage of Time That Intragastric pH Was >4 During 24-Hour Periods at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	59.78±20.67		
		Median	56.85		
		Min, Max	14.80, 93.60		
		90% CI	50.72, 68.83		
	Steady state	N	16	16	
		Mean ± SD	79.31±20.47	19.54±24.16	0.006
		Median	88.05	18.95	
		Min, Max	42.30, 100.00	-20.80, 76.00	
		90% CI	70.34, 88.28	8.95, 30.13	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.
a. p-Value was obtained from 1 sample 2-sided paired t-test.

Percentage of Time that Intragastric pH was >3: The percentage of time that intragastric pH was >3 at Baseline and steady state is presented in Table 10 for the monitoring interval 0 to end. The percentage of time that intragastric pH was >3 increased significantly (p=0.035), from 72.8% of the time at Baseline to 86.2% of the time at steady state.

Table 10. Descriptive Statistics and Analysis of Percentage of Time That Intragastric pH Was >3 During 24-Hour Periods at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	72.79±19.35		
		Median	73.10		
		Min, Max	30.60, 99.00		
		90% CI	64.31, 81.27		
	Steady state	N	16	16	
		Mean ± SD	86.24±17.48	13.46±23.17	0.035
		Median	93.50	11.00	
		Min, Max	48.00, 100.00	-31.20, 65.30	
		90% CI	78.58, 93.91	3.30, 23.61	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.

a. p-Value was obtained from 1 sample 2-sided paired t-test.

Mean Intraesophageal pH: A statistical analysis of the mean intraesophageal pH levels of 16 subjects for the monitoring interval 0 to end is presented in Table 11. A decrease was observed in the mean intraesophageal pH, which declined from a mean of 5.06 at Baseline to 4.91 at steady state. However, the mean pH at both time points was >4, and the decrease in mean pH from Baseline was not statistically significant (p=0.06).

Table 11. Descriptive Statistics and Analysis of Mean Intraesophageal pH Levels During 24-Hour Periods at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	5.06±0.28		
		Median	4.95		
		Min, Max	4.70, 5.60		
		90% CI	4.94, 5.19		
	Steady state	N	16	16	
		Mean ± SD	4.91±0.31	-0.16±0.31	0.060
		Median	4.85	-0.10	
		Min, Max	4.20, 5.50	-0.70, 0.20	
		90% CI	4.77, 5.04	-0.29, -0.02	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.

a. p-Value was obtained from 1 sample 2-sided paired t-test.

Median Intraesophageal pH: An analysis of the median intraesophageal pH levels for the monitoring interval 0 to end is presented for 16 subjects in Table 12. A statistically significant (p=0.004) decrease was observed in the median intragastric pH measures, which declined from a mean of 5.14 at Baseline to 4.89 at steady state. However, the pH values at both time points were >4, making this change of no clinical significance.

Table 12. Descriptive Statistics and Analysis of Median Intraesophageal pH Levels During 24-Hour Periods at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	5.14±0.31		
		Median	5.20		
		Min, Max	4.60, 5.60		
		90% CI	5.00, 5.28		
	Steady state	N	16	16	
		Mean ± SD	4.89±0.34	-0.24±0.29	0.004
		Median	4.85	-0.20	
		Min, Max	4.10, 5.40	-0.80, 0.10	
		90% CI	4.74, 5.04	-0.37, -0.12	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.
a. p-Value was obtained from 1 sample 2-sided paired t-test.

Percentage of Time that Intraesophageal pH was <4 (Reflux Index): The mean reflux index (percentage of time that intraesophageal pH was <4) is presented in Table 13 for the monitoring interval 0 to end. The mean reflux index decreased slightly from 8.65% at Baseline to 7.34% at steady state. The change was not statistically significant (p=0.676).

Table 13. Descriptive Statistics and Analysis of Percentage of Time That Intraesophageal pH Was <4 (Reflux Index) at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	8.65±8.93		
		Median	5.80		
		Min, Max	0.10, 35.30		
		90% CI	4.74, 12.56		
	Steady state	N	16	16	
		Mean ± SD	7.34±8.63	-1.31±12.34	0.676
		Median	5.70	-0.05	
		Min, Max	0.10, 36.50	-28.40, 30.10	
		90% CI	3.56, 11.12	-6.72, 4.09	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.
a. p-Value was obtained from 1 sample 2-sided paired t-test.

Number of Reflux Episodes: A summary of the total number of reflux episodes for the monitoring interval 0 to end is presented in Table 14. The mean number of reflux episodes increased by almost 50% from 124.00 at Baseline to 184.38 at steady state. The variability at steady state was very high, as indicated by the large standard deviation (189.85) and wide range of episodes (7 to 798). A similarly wide range (-164 to 641) was seen in the changes in the number of reflux episodes from Baseline to steady state. As a consequence, although the mean change in the number of episodes was large, it was not statistically significant (p=0.206).

Table 14. Descriptive Statistics and Analysis of Number of Reflux Episodes During 24-Hour Periods at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change from Baseline	p-Value[a]
0–End	Baseline	N	16		
		Mean ± SD	124.00±77.47		
		Median	133.00		
		Min, Max	7.00, 256.00		
		90% CI	90.05, 157.95		
	Steady state	N	16	16	
		Mean ± SD	184.38±189.85	60.38±182.54	0.206
		Median	130.00	23.00	
		Min, Max	7.00, 798.00	-164.00, 641.00	
		90% CI	101.17, 267.58	-19.63, 140.38	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.

a. p-Value was obtained from 1 sample 2-sided paired t-test.

Number of Reflux Episodes >5 minutes: The number of reflux episodes lasting >5 minutes is summarized in Table 15. The mean number of reflux episodes lasting >5 minutes decreased from 3.44 at Baseline to 2.25 at steady state. The change was not statistically significant (p=0.495).

Table 15. Descriptive Statistics and Analysis of Number of Reflux Episodes >5 Minutes at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change From Baseline	p-Value[a]
0-End	Baseline	N	16		
		Mean ± SD	3.44±5.56		
		Median	2.00		
		Min, Max	0.00, 23.00		
		90% CI	1.00, 5.87		
	Steady state	N	16	16	
		Mean ± SD	2.25±3.36	-1.19±6.78	0.495
		Median	2.00	0.00	
		Min, Max	0.00, 14.00	-23.00, 11.00	
		90% CI	0.78, 3.72	-4.16, 1.79	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.

a. p-Value was obtained from 1 sample 2-sided paired t-test.

Duration of the Longest Reflux Episodes: A summary of the duration of the longest reflux episode is provided in Table 16 for the valid for PD evaluation population. The mean duration decreased from 13.69 minutes at Screening to 9.19 minutes at steady state. The decrease was not statistically significant (p=0.283).

Table 16. Descriptive Statistics and Analysis of Duration of the Longest Reflux Episode (min) at Baseline and Steady State - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change From Baseline	p-Value[a]
0-End	Baseline	N	16		
		Mean ± SD	13.69±14.04		
		Median	10.00		
		Min, Max	0.00, 53.00		
		90% CI	7.54, 19.84		
	Steady state	N	16	16	
		Mean ± SD	9.19±6.93	-4.50±16.16	0.283
		Median	8.00	-1.50	
		Min, Max	0.00, 25.00	-51.00, 16.00	
		90% CI	6.15, 12.22	-11.58, 2.58	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.

a. p-Value was obtained from 1 sample 2-sided paired t-test.

Normalized AUC of Gastric H^+ Activity (Normalized Area of Gastric H^+ Activity over time): Descriptive statistics and analysis of the normalized area of gastric H^+ activity over time (H•mmol/L) for the valid for PD evaluation population is presented in Table 17.

Table 17. Descriptive Statistics and Analysis of Normalized Area of Gastric Hydrogen Ion Activity Over Time (H•mmol/L) - Valid for PD Evaluation Population

Time Interval	Visit	Statistics	Pantoprazole 2.5 mg		
			Actual	Change From Baseline	p-Value[a]
0–End	Baseline				
		N	16		
		Mean ± SD	154.57±191.76		
		Median	99.36		
		Min, Max	2.35, 696.12		
		90% CI	70.53, 238.61		
	Steady state				
		N	16	16	
		Mean ± SD	63.63±96.42	-90.94±210.20	0.104 (0.058)
		Median	16.99	-63.30	
		Min, Max	0.03, 257.22	-685.13, 191.86	
		90% CI	21.37, 105.89	-183.06, 1.18	

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.

a. p-Value was obtained from 1 sample 2-sided paired t-test between steady state and Baseline. Due to 1 subject with an extreme large value (=696.1 H•mmol/L) at Baseline, p-value from Wilcoxon Signed-Rank test was also provided in parenthesis.

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 in Table 18.

Table 18. Descriptive Statistics for Total Daily GERD Symptom Score at Baseline and Last Day on Therapy - Safety Population

Visit	Statistics	Pantoprazole 1.25 mg			Pantoprazole 2.5 mg			
		Actual	Change From Baseline	p-Value[a]	Actual	Change From Baseline	p-Value[a]	p-Value[b]
Baseline	N	17			35			
	Mean ± SD	3.26±2.55			2.94±2.10			
	Median	2.00			3.00			
	Min, Max	0.00, 10.00			0.00, 7.00			
Last on therapy	N	17	17		35	35		
	Mean ± SD	2.19±2.00	-1.07±2.59	0.107	2.17±1.54	-0.77±2.29	0.054	0.915
	Median	2.00	-1.00		2.00	-1.00		
	Min, Max	0.00, 8.00	-6.00, 5.50		0.00, 5.00	-5.00, 4.00		

Subjects without baseline data were excluded. The total daily GERD symptom score was the sum of items 1a, 2b, 3a, 4a, and the maximum frequency of (5a and 5b), where 1a was vomiting /regurgitation; 2b was irritability/fussiness; 3a was choking/gagging; 4a was arching back/head retraction; and 5a/5b was refusal to feed. The items were scored: 0= none, 1=1 to 3 times, 2=4 to 6 times, 3=more than 6 times.
ANCOVA = analysis of covariance; GERD = gastroesophageal reflux disease; Min = minimum; Max = maximum; N = number of subjects; SD = standard deviation.
a. p-Value was obtained from 1 sample 2-sided paired t-test for the within-group comparison.
b. p-Value was obtained from ANCOVA model with dose group as a factor and baseline value as a covariate for the between-group comparison.

Safety Results:

Treatment-Emergent Adverse Events: The number and percentage of TEAEs is presented by body system in Table 19. Overall, the most common TEAEs were anemia (5 subjects; 8.5%), hypoxia (4 subjects; 6.8%), constipation (3 subjects; 5.1%), and rhinitis (3 subjects; 5.1%). In the 1.25-mg dose group, the most common TEAE was contact dermatitis (diaper rash), which was reported in 2 (10.5%) subjects. In the 2.5-mg dose group, the most common TEAE was anemia, which occurred in 5 (12.5%) subjects. All of the TEAEs were mild to moderate in severity. Between-group differences were not statistically significant.

Table 19. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events-Safety Population

Body System[a] Adverse Event	p-Value[a]	Pantoprazole Treatment		
		1.25 mg N=19	2.5 mg N=40	Total[b] N=59
Any adverse event	0.254	5 (26.3)	18 (45.0)	23 (39.0)
Body as a whole	1.000	0	2 (5.0)	2 (3.4)
Fever	1.000	0	1 (2.5)	1 (1.7)
Hernia	1.000	0	1 (2.5)	1 (1.7)
Cardiovascular system	0.653	2 (10.5)	3 (7.5)	5 (8.5)
Bradycardia	0.544	1 (5.3)	1 (2.5)	2 (3.4)
Cardiovascular physical finding	0.322	1 (5.3)	0	1 (1.7)
Tachycardia	1.000	0	2 (5.0)	2 (3.4)
Ventricular extrasystoles	0.322	1 (5.3)	0	1 (1.7)
Digestive system	1.000	1 (5.3)	4 (10.0)	5 (8.5)
Constipation	1.000	1 (5.3)	2 (5.0)	3 (5.1)
Flatulence	1.000	0	1 (2.5)	1 (1.7)
Liver function tests abnormal	1.000	0	1 (2.5)	1 (1.7)
Hemic and lymphatic system	0.163	0	6 (15.0)	6 (10.2)
Anemia	0.165	0	5 (12.5)	5 (8.5)
Iron deficiency anemia	1.000	0	1 (2.5)	1 (1.7)
Metabolic and nutritional	1.000	0	1 (2.5)	1 (1.7)
Peripheral edema	1.000	0	1 (2.5)	1 (1.7)
Musculoskeletal system	0.100	2 (10.5)	0	2 (3.4)
Musculoskeletal anomaly	0.322	1 (5.3)	0	1 (1.7)
Osteopenia	0.322	1 (5.3)	0	1 (1.7)
Respiratory system	1.000	2 (10.5)	4 (10.0)	6 (10.2)
Apnea	0.322	1 (5.3)	0	1 (1.7)
Hypoxia	1.000	1 (5.3)	3 (7.5)	4 (6.8)
Lung disorder	1.000	0	1 (2.5)	1 (1.7)
Pulmonary physical finding	0.322	1 (5.3)	0	1 (1.7)
Rhinitis	1.000	1 (5.3)	2 (5.0)	3 (5.1)
Skin and appendages	0.240	2 (10.5)	1 (2.5)	3 (5.1)
Application site reaction	1.000	0	1 (2.5)	1 (1.7)
Contact dermatitis	0.100	2 (10.5)	0	2 (3.4)
Special Senses	0.240	2 (10.5)	1 (2.5)	3 (5.1)
Conjunctivitis	0.322	1 (5.3)	0	1 (1.7)
Retinal disorder	0.544	1 (5.3)	1 (2.5)	2 (3.4)
Urogenital System	0.544	1 (5.3)	1 (2.5)	2 (3.4)
Urinary tract infection	1.000	0	1 (2.5)	1 (1.7)
Urine abnormality	0.322	1 (5.3)	0	1 (1.7)

n = number of subjects.
a. Fisher exact test p-value (2-tailed).
b. Body system totals are not necessarily the sum of the individual adverse events (AEs) because a subject may have 2 or more different AEs in the same body system.

Treatment-Related Adverse Events: A summary of treatment-related TEAEs is presented in Table 20. Only 2 (3.4%) TEAEs were considered related to the test article. Both TEAEs were mild in severity, and both resolved.

Table 20. Number (%) of Subjects Reporting Treatment-Related Treatment Emergent - Safety Population

Body System Adverse Event	Pantoprazole Treatment		
	1.25 mg N=19	2.5 mg N=40	Total N=59[a]
Any adverse event	1 (5.3)	1 (2.5)	2 (3.4)
Digestive system	0	1 (2.5)	1 (1.7)
Liver function tests abnormal	0	1 (2.5)	1 (1.7)
Skin and appendages	1 (5.3)	0	1 (1.7)
Contact dermatitis	1 (5.3)	0	1 (1.7)

N = number of subjects.

a. Body system totals are not necessarily the sum of the individual AEs because a subject may have 2 or more different AEs in the same body system.

Serious Adverse Events: SAEs are presented in Table 21. SAEs were reported in 2 (3.4%) of 59 subjects. Both of the SAEs occurred after the treatment period of the study, and neither was considered related to pantoprazole.

Table 21. Number (%) of Subjects Reporting Serious Adverse Events – Safety Population

Body System[a] Adverse Event	Overall p-Value[b]	Pantoprazole Treatment		
		1.25 mg N=19	2.5 mg N=40	Total N=59
Any adverse event	1.000	0	2 (5.0)	2 (3.4)
Digestive system	1.000	0	1 (2.5)	1 (1.7)
Gastrointestinal hemorrhage	1.000	0	1 (2.5)	1 (1.7)
Urogenital system	1.000	0	1 (2.5)	1 (1.7)
Urinary tract infection	1.000	0	1 (2.5)	1 (1.7)

N = number of subjects

a. Body system totals are not necessarily the sum of the individual adverse events since a subject may report 2 or more different adverse events in the same body system.

b. Fisher exact test p-value (2-tailed).

Discontinuations due to Adverse Events: No subjects withdrew from the study because of AEs.

Deaths: No subjects died during the study.

Laboratory Evaluations: PCI laboratory test result abnormalities were common at Baseline and decreased over the period of the study. There were no clear dose-related abnormalities identified.

Growth Parameters: The subjects grew normally in weight, length, and head circumference during the study.

CONCLUSIONS:

- Pantoprazole sodium granules for oral suspension were safe and well tolerated in preterm infants and neonates. Mean exposures observed with the 2.5-mg dose were slightly higher compared with that of adults who received 40-mg doses. While a longer $t_{½}$ was observed in these subjects, there was no evidence of accumulation with repeated doses.

- The 2.5-mg dose also significantly raised the mean and median intragastric pH and the percentage of time intragastric pH was >4 and >3. This dose also provided a statistically significant decrease in the AUC and normalized AUC of the esophageal H^+ activity. This study did not demonstrate significant improvement in the reflux index with pantoprazole treatment, but this was largely due to the inclusion of subjects with only presumed GERD. GERD symptoms in preterm infants and neonates were surprisingly similar to those observed in older infants, and the symptoms responded similarly to treatment. Although this study was too short to adequately assess the symptoms, a trend toward improvement was demonstrated. Respiratory symptoms were infrequent at Baseline, making any meaningful conclusion beyond the scope of this study.

- Based on the results of this study, 2.5-mg of pantoprazole sodium delayed-release for oral suspension is the recommended dose for preterm infants and neonates in need of acid suppression to treat symptomatic GERD. Preterm infants and neonates with a presumptive diagnosis of GERD based solely on clinical symptoms are likely to have physiologic GERD and may or may not benefit from treatment with a proton pump inhibitor.