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

PROTOCOL NO.: 3001B3-333-WW (B1791058)

PROTOCOL TITLE: A Multicenter, Randomized, Open-Label, Single and Multiple-Dose Study of the Pharmacokinetics and Pharmacodynamics of 2 Dose Levels of Pantoprazole Sodium Enteric-Coated Spheroid Suspension in Infants Aged 1 through 11 Months With Presumed GERD

Study Centers: A total of 17 centers took part in the study and randomized subjects; 1 each in Australia, Belgium, France and Germany, 2 in Italy, 3 in Poland and 8 in the United States.

Study Initiation Date and Final Completion Date: 01 February 2006 to 29 January 2008

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

The primary objective was to characterize the pharmacokinetic (PK) profile of single and repeated doses and the pharmacodynamic (PD) profile at Baseline and at steady-state after multiple-doses of pantoprazole in infants aged 1 through 11 months with presumed gastroesophageal reflux disease (GERD).

Secondary Objective:

The secondary objective was to assess safety and tolerability of pantoprazole in infants aged through 11 months with presumed GERD. Growth parameters (length, weight, and head circumference) were also be assessed as part of the safety evaluation.

METHODS

Study Design: This was a Phase 3, multicenter, randomized, open-label, single-dose and multiple-dose PK, safety, and multiple-dose PD study in infants aged 1 month through 11 months with presumed GERD. Hospitalized subjects or outpatients participated in 1 of 2 strata: PK or PD. After screening, subjects whose weight was 2.5 kg to <7 kg were randomly assigned in a 1:1 fashion to receive either a 5-mg (high, 1.2 mg/kg) daily dose or a 2.5-mg (low, 0.6 mg/kg) daily dose of pantoprazole, and subjects whose weight was at least 7 kg but not >15 kg were randomly assigned in a 1:1 fashion to receive either a 10-mg (high, 1.2 mg/kg) daily dose or a 5-mg (low, 0.6 mg/kg) daily dose of pantoprazole.

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

Safety evaluations were performed on an ongoing basis by review of adverse events (AEs) and clinically important laboratory test results as described in the pediatric written request.

A flowchart of study procedures is presented in Table 1. Flowcharts for PK procedures on study Days -1 through 10 and for PK procedures on the final day of pantoprazole administration and at the final study evaluation are presented in Table 2 and Table 3, respectively. Flowcharts for PD procedures on study Days -1 through 10 and for PD procedures on the final day of pantoprazole administration and at the final study evaluation are presented in Table 4 and Table 5 respectively.

Table 1. Study Workflow

Study Phase	Prescreening	Screening[a]	Treatment Period					Follow-Up Contact
Study day	-7	-7 to -2	-1	1	2–7	7±2[b] (Final day of test article administration)	Final study evaluation	24 (±3)
Informed consent	X							
PD subjects on PPIs or H_2RAs (washout)[c]	X							
Subject visit		X	X	X		X	X	
Telephone contact								X
Medical history		X						
Physical examination[d]		X				X	X	
Vital signs[e]		X	X	X		X	X	
ECG (12-lead)		X					X	
Laboratory evaluation[f]		X[g]					X[h,i]	
Buccal cell collection[j]				X				
Randomization			X					
Test article administration				X----------X				
PK blood sample collection				X		X		
pH-metry		X			X	X		
Feeding[k]		X	X	X		X		
Concomitant medication		X----------X						
Adverse event recording		X----------X						

Table 1. Study Workflow

eCRF = electronic case report form; ECG = electrocardiogram; H_2RAs = histamine 2-receptor antagonist(s); ICF = informed consent form; PD = pharmacodynamics; PK = pharmacokinetic; PPIs = proton pump inhibitors.

a. Within 1 week before test article administration; may have been combined with the study Day -1 procedures. Subjects in the PD portion of the study may have had up to an additional 5 days to complete screening.
b. Subjects must have received a minimum of 5 consecutive daily doses of pantoprazole to complete the study and may have received up to a maximum of 10 doses. Therefore, the final day of test article administration could have occurred on any day of study Days 5 through 10.
c. The parents of PD subjects signed an ICF before starting the washout period.
d. Physical examination included weight (kg), length (cm) and head circumference (cm).
e. Blood pressure and pulse rate, respiratory rate, and rectal, axillary, or tympanic temperature (ºF or ºC).
f. Hematology, blood chemistry, urinalysis, and 3 to 4 hours fasting serum gastrin (optional).
g. To minimize the amount of blood collected and number of venipunctures, laboratory studies performed within 1 week before test article administration may have been used as screening safety laboratory values provided that the information specified in the protocol was obtained.
h. To minimize the number of venipunctures, blood sample for the final study evaluation may have been collected with the Hour 4 PK sample.
i. To minimize the amount of blood collected, routine laboratory studies planned within 48 hours after the Hour 4 PK sample collection may also have been used as the final study evaluation safety laboratory values provided that the information specified in the protocol was obtained.
j. Pharmacogenomic information was not recorded in the eCRF.
k. Feedings were given at least 30 minutes after each pantoprazole administration. For PD subjects, feeding may have been given every 3 to 4 hours.

Table 2. Study Flowchart for Pharmacokinetic Procedures: Study Days -1 Through 10

Study day	-1	1									7±2[a]
Study hour		-2	0	0.5	1	2	4	6	8	12	
Subject visit	X	X----------X									X
Vital signs[b]	X	X				X			X	X	X
Buccal cell collection[c]		X									
Randomization	X										
Test article administration			X								X
PK blood sample collection		X		X	X	X	X	X		X	X
Feeding				X[d]			X		X	X	X
Adverse event recording	X----------X										
Concomitant medication	X----------X										

CYP = cytochrome P450; eCRF = electronic case report form; PK = pharmacokinetic.

a. Subject must have received a minimum of 5 consecutive daily doses of pantoprazole to complete the study and may have received up to a maximum of 10 doses. Therefore, the final day of pantoprazole administration could have occurred on study Days 5 through 10 (see Table 3).
b. Blood pressure and pulse rate, respiratory rate, and rectal, axillary, or tympanic temperature (ºF or ºC).
c. Buccal cell collection for CYP2C19 and CYP3A4 genotyping; pharmacogenomic information was not be recorded on the eCRF.
d. Pantoprazole was administered in the morning at least a half hour before feeding (ie, 30-60 minutes).

Table 3. Study Flowchart for Pharmacokinetic Procedures: Final Day of Pantoprazole Administration and Final Study Evaluation

Study day	Final day of pantoprazole administration[a]					Final study evaluation[b]	Follow-up contact
Study day	7±2						24(±3)
Study hour	-1	0	0.5	2	4		
Subject visit	X----------				----------X		
Telephone contact							X
Physical examination[c]						X	
Vital signs[d]	X			X		X	
Laboratory evaluation[e]						X[f,g]	
ECG(12-lead)						X	
Test article administration		X					
PK blood sample collection				X	X		
Feeding			X[h]		X		
Adverse event recording	X----------						----------X
Concomitant medications	X----------						----------X

ECG = electrocardiogram; PK = pharmacokinetics.

a. Subject must have received a minimum of 5 consecutive daily doses of pantoprazole to complete the study and may have taken up to a maximum of 10 consecutive daily doses. Therefore, the final day of pantoprazole administration could have occurred on study Days 5 through 10.
b. Within approximately 2 hours after the last PK sample collection on the final day of test article administration.
c. Physical examination included weight (kg), length (cm) and head circumference (cm).
d. Blood pressure and pulse rate, respiratory rate, and rectal, axillary, or tympanic temperature (ºF or ºC).
e. Hematology, blood chemistry, urinalysis, and 3 to 4 hours fasting serum gastrin (optional).
f. To minimize the number of venipunctures, blood sample for the final study evaluation may have been collected with the Hour 4 PK sample.
g. To minimize the amount of blood collected, routine laboratory studies planned within 48 hours after the Hour 4 PK sample collection may also have been used as the final study evaluation safety laboratory values provided the information specified in the protocol was obtained.
h. Feedings were given at least 30 minutes after each pantoprazole administration.

Table 4. Study Flowchart for Pharmacodynamic Procedures: Study Days -1 Through 10

Study day	-1	1								(Day 7±2)[a]
Study hour		-2	-1	0	0.5	2	3.5	4.5	7.5-9.5	10.5-12.5	
Subject visit	X	X……X									X
Vital signs[b]	X	X				X			X	X	X
Buccal cell collection[c]		X									
Randomization	X										
Test article administration[d]				X							X
pH-metry	X[e]										
PK blood sample collection			X[f]								X[f]
Feeding					X[g]			X[g]	X[g]	X[g]	
Adverse event recording	X----------X										
Concomitant medication	X----------X										

eCRF = electronic case report form; PK = pharmacokinetic; PD = pharmacodynamics.

a. Subject must have received a minimum of 5 consecutive daily doses of pantoprazole to complete the study and may have received up to a maximum of 10 doses total. Therefore, the final day of pantoprazole administration could have occurred on study Days 5 through 10.
b. Blood pressure and pulse rate, respiratory rate, and rectal, axillary, or tympanic temperature (ºF or ºC).
c. Pharmacogenomic information was not be recorded on the eCRF.
d. Pantoprazole was administered in the morning at least a half hour before feeding and after completing the first PD assessment.
e. Baseline pH assessment may have been done any time after signing of the informed consent form and was completed before the first dose of pantoprazole.
f. A blood sample for population PK was collected before the first dose of pantoprazole and 3±1 hours after the last dose of pantoprazole.
g. Feedings were given at least 30 minutes after each pantoprazole administration and approximately every 4 hours afterwards.

Table 5. Study Flowchart for Pharmacodynamic Procedures: Final Day of Pantoprazole Administration and Final Study Evaluation

Study Day	**Final Day of Test Article Administration**[a]								**Final Study Evaluation**[b]	**Follow-Up Contact**
Study day	Day 7±2									Day 24±3
Study hour	-1[c]	0	0.5	2.0	3.0	4.5	8.0	12.0 - 24.0		
Subject visit	X----------							----------X	X	
Telephone contact										X
Physical examination[d]									X	
Vital signs[e]	X			X			X	X	X	
Laboratory evaluation[f]									X[g,h]	
ECG (12-lead)									X	
Test article administration		X								
PK blood sample collection					X[i]					
pH-metry	X----------							---------- X		
Feeding			X[j]			X[j]	X[j]	X[j]		
Adverse event recording	X----------									----------X
Concomitant medications	X----------									----------X

ECG = electrocardiogram; PK = pharmacokinetics; PD = pharmacodynamics.

a. Subject must have received a minimum of 5 consecutive daily doses of pantoprazole before the trough (hour –1) sample was collected. The fifth (final) dose was administered after trough sample was collected. A completed subject received at least 5 consecutive daily doses and no >10 doses total. Therefore, the final day of pantoprazole administration could have occurred between study Days 5 and 10. If a dose was missed, the subject may have received up to 10 doses in order to have achieved 5 consecutive daily doses for PK or PD assessments.
b. Within approximately 2-4 hours after the last PD assessment.
c. 22-24 hours after previous dose.
d. Physical exam included weight (kg), length (cm) and head circumference (cm).
e. Blood pressure and pulse rate, respiratory rate, and rectal, axillary, or tympanic temperature (ºF or ºC).
f. Hematology, blood chemistry, urinalysis, and 3 to 4 hours fasting serum gastrin.
g. To minimize the number of venipuncture, blood sample for the final study evaluation may have been collected with the Hour 4 PK sample.
h. To minimize the amount of blood collected, routine laboratory studies planned within 48 hours after the Hour 4 PK sample collection may also have been used as the final study evaluation safety laboratory values provided that the information specified in the protocol was obtained.
i. Between 3±1 hour after final dose of pantoprazole.
j. Feedings were given at least 30 minutes after each test article administration and every 4 hours afterwards; between hours 4.5 and 9.5, feedings may have been given more frequently. There was at least 3 hours between the completion of a feeding and gastric secretion collection.

Number of Subjects (Planned and Analyzed): The study planned to enroll 56 subjects (32 in the PK and 24 in the PD). Eighty-one (81) subjects were enrolled in the study. Fourteen (14) subjects were screen failures. Sixty-seven (67) were randomly assigned to treatment and received at least 1 dose of pantoprazole. Thirty-three (33) subjects were randomly assigned in a 1:1 fashion to receive the low dose (0.6 mg/kg), and 34 subjects were randomly assigned to the high-dose (1.2 mg/kg) group. The safety population consisted of 39 male and 28 female infants aged 1 month through 11 months with presumed GERD.

Diagnosis and Main Criteria for Inclusion: Male or female subjects <44 weeks beyond neonatal period but >12 months with presumptive diagnosis of GERD, weight >2.5 kg but <15 kg.

Study Treatment: Infants aged 1 month through 11 months were treated with pantoprazole sodium using either a low (0.6 mg/kg/d) or high dose (1.2 mg/kg/d) for at least 5 consecutive days. Study drug was administered as enteric-coated spheroid granules in an oral suspension provided in 3 strengths (2.5 mg, 5 mg, and 10 mg), used for both low and high dose administration (0.6 mg/kg). Subjects were dosed once daily with an oral syringe or small spoon approximately 30 minutes before the morning feeding.

Pharmacokinetic and Pharmacodynamic Endpoints:

Pharmacokinetic Endpoints:

PK parameters for one single-day dose included:

- Estimations of the peak concentration (C_{max})
- Time to C_{max} (T_{max})
- Areas under the concentration versus time curve from 0 to the time at which the last measurable concentration is obtained (AUC_{0-t})
- Areas under the concentration versus time curve from 0 to infinity ($AUC_{0-\infty}$)
- Terminal disposition half-life ($t_{½}$)
- Oral-dose clearance (CL/F)
- Weight normalized (CL/F)
- Terminal-phase volume of distribution (V_z/F)

PK parameters for multiple-day, once-daily doses included:

- Plasma concentration of pantoprazole at 2 and 4 hours following the last dose on Day 7±2 after at least 5 consecutive oral doses of pantoprazole for PK subjects

- Plasma concentration of pantoprazole collected between 2 and 4 hours following the last dose on Day 7±2 after at least 5 consecutive doses of pantoprazole for PD subjects

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
- pH of stomach at probe placement

No efficacy evaluations were performed in this study.

Safety Evaluations: Safety monitoring of pantoprazole was based on reported signs and symptoms and the results of scheduled physical examinations, vital signs measurements, length, weight, and head circumference, standard 12-lead electrocardiogram (ECG), and clinical laboratory tests. AEs were monitored and assessed by the Investigator.

Statistical Methods:

Analysis Set:

- Safety Population: Included all subjects who taken at least 1 dose of test article
- Valid-For-Efficacy Population: Evaluable subjects must not have any major protocol violations (eg, no prohibited medications, no inclusion/exclusion violations)

Pharmacokinetic Analyses: Descriptive statistics (eg. mean, standard deviation, coefficient of variation, standard error, median and range) were calculated for the PK parameters for each treatment group. Additionally limited statistical analysis might been performed by age group (<6 months and 6 months in corrected age and postnatal age), by cytochrome P450 (CYP) genotypes (CYP2C19 and CYP3A4 phenotypes), by dose per weight and dose per body surface area. Comparisons of pantoprazole concentration at 2 and 4 hours between Day 1 and Day 7 was made for each subject.

Treatment of below quantifiable limit (BQL) values: All BQL values occurring before C_{max} was replaced with 0. Data reported as BQL and occurring between 2 measurable concentrations was set as missing values. All PK calculations were performed with WinNonlin Professional version 4.01.

Descriptive statistics were used to summarize all pH-metry 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 intraesophageal pH <4 (reflux index), number of reflux episodes, number of reflux episodes >5 minutes, duration of longest reflux episode, AUC of the gastric H^+ concentration over time and pH of stomach at probe placement.

Two-sided 90% confidence intervals were constructed for Baseline, at steady-state, change from baseline, and difference of the changes between dose groups for each pH-metry endpoint. A comparison of the results at steady-state to Baseline was done for all pH-metry endpoints. The PD evaluable subject population was used.

Continuous safety parameters were analyzed using analysis of covariance with treatment as a factor and Baseline value as a covariate. Paired t-test was used for the comparisons to Baseline.

RESULTS:

Subject Disposition and Demography: A summary of subject disposition is provided in Table 6. Sixty-seven (67) subjects were included in the safety analysis population. Forty-two (42) subjects were included in the all-subject population for PK analyses after receiving one dose of study drug. Of these, thirty-five subjects had valid PK evaluation data after a single day dose, and 31 subjects had valid PK evaluation data after multiple days of single-daily dosing. Demographic characteristics were summarized in Table 7.

Table 6. Summary of Subject Disposition by Analysis Population and Treatment

Analysis Population	Pantoprazole 0.6 mg/kg	Pantoprazole 1.2 mg/kg	Total
Screened	-	-	81
Screen failures	-	-	14
Randomized subjects	33	34	67
Study completed	31 (93.9)	30 (88.2)	61 (91.0)
Discontinued[a]	2 (6.1)	4 (11.8)	6(9.0)
Adverse event	0	1 (2.9)	1 (1.5)
Failed to return	1 (3.0)	0	1 (1.5)
Investigator request	0	1 (2.9)	1 (1.5)
Lost to follow-up	0	1 (2.9)	1 (1.5)
Protocol violation	1 (3.0)	1 (2.9)	2 (3.0)
Safety population	33	34	67
All-subject PK single-dose population	21	21	42
All-subject PK multiple-dose population	19	18	37
Valid for PK evaluation single-dose population	17	18	35
Valid for PK evaluation multiple-dose population	15	16	31
Valid for PD evaluation population	11	10	21

PK = pharmacokinetic; PD = pharmacodynamics.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

Table 7. Demographic and Baseline Characteristics: Safety Population

Characteristic	Pantoprazole 0.6 mg/kg N=33	Pantoprazole 1.2 mg/kg N=34	Total N=67
Age (month)			
n	33	34	67
Mean	5.98	5.91	5.94
Standard deviation	2.98	3.42	3.19
Minimum	1.3	1.1	1.1
Maximum	13.9	12.6	13.9
Median	6	4.45	4.9
Gestational age (week)			
N	33	34	67
Mean	36.18	36.94	36.57
Standard deviation	4.38	3.3	3.86
Minimum	26	28	26
Maximum	41	41	41
Median	38	38	38
Corrected age (month)			
N	12	10	22
Mean	4.23	4.77	4.47
Standard deviation	3.54	3.94	3.65
Minimum	1.1	1.1	1.1
Maximum	11	11.2	11.2
Median	2.5	2.85	2.5
Missing	21	24	45
Age/corrected age (month)			
N	33	34	67
Mean	5.26	5.41	5.34
Standard deviation	2.97	3.48	3.22
Minimum	1.1	1.1	1.1
Maximum	11	12.1	12.1
Median	4.9	4.3	4.7
Sex			
Female	13 (39.39)	15 (44.12)	28 (41.79)
Male	20 (60.61)	19 (55.88)	39 (58.21)
Age group			
≥1 and <6 month	16 (48.48)	20 (58.82)	36 (53.73)
≥6 month	17 (51.52)	14 (41.18)	31 (46.27)

Corrected age is calculated for premature infants only. One subject was <12 months old on date of informed consent signature. For premature infants, corrected age instead of age (postnatal age) is used for summary statistics.
N = total number of subjects; n = number of subjects in specified area.

Pharmacokinetic and Pharmacodynamics Endpoint Results:

Pharmacokinetics Results: A total of 42 subjects (21 in the 0.6-mg/kg and 21 in the 1.2-mg/kg dose group) had a complete PK evaluation that was, PK samples were obtained at the times specified in the study protocol. One subject in the high-dose (1.2 mg/kg) group, was excluded from the all PK population because the subjects was withdrawn from the study early (study Day 2) and a postdose blood sample for PK analysis was not obtained. A summary of the mean PK parameter estimates of pantoprazole for each treatment group is presented in Table 8.

Table 8. Summary of Pharmacokinetic Parameter Estimates: All-Subject PK Population - Day 1

Mean ± SD (CV%) [Geometric Mean]	Pantoprazole 0.6 mg/kg N=21	Pantoprazole 1.2 mg/kg N=21
C_{max} (ng/ml)	503±506 (101%) [296]	1318±1307 (99%) [NC]
T_{max} (hr)[a]	1.03 (0.98, 11.83)	1.02 (0.5, 4.08)
T_{lag} (hr)[a]	0.50 (0.00, 1.03)	0.0 (0.00, 1.00)
AUC_t (ng•hr/ml)	842±912 (108%) [474]	3036±3242 (107%) [NC]

AUC_t = area under the concentration-time curve to last time measured; C_{max} = peak concentration; CV% = coefficient of variation; N = total number of subjects; NC = not calculated; PK = pharmacokinetic; SD = standard deviation; T_{lag} = lag time; T_{max} = time to peak concentration.
a. Values for T_{lag} and T_{max} are median (minimum, maximum).

Valid Pharmacokinetic-Evaluation Population (Day 1): A total of 35 subjects, (17 subjects in the 0.6-mg/kg dose group and 18 subjects in the 1.2-mg/kg dose group) had a complete, or nearly complete, PK profile and were considered valid for single-dose PK evaluation. Seven (7) subjects were excluded from the single-dose PK analysis. A summary of the mean PK parameter estimates of pantoprazole for the 2 dose groups ie, 0.6 mg/kg and 1.2 mg/kg is presented in Table 9 and Table 10 respectively.

Table 9. Summary of Pharmacokinetic Parameter Estimates After Single-Dose Administration of Pantoprazole 0.6 mg/kg: Valid for PK Evaluation Population

Parameters	Mean	SD	SE	Min	Median	Max	CV%	Geometric Mean
N	17	17	17	17	17	17	17	17
C_{max} (ng/ml)	567	534	129	14	380	1990	94	341
T_{max} (hr)	1.55	0.99	0.24	1.00	1.03	4.00	64	1.35
T_{lag} (hr)	0.53	0.28	0.07	0	0.50	1.03	52	NC
$t_{½}$ (hr)	1.78	1.30	0.31	0.45	1.63	5.61	73	1.44
AUC_t (ng•hr/ml)	949	969	235	48	669	3687	102	605
AUC (ng•hr/ml)	1046	1043	253	60	676	3809	100	671
CL/F	1.54	2.35	0.57	0.17	0.93	10.24	153	0.89
V_z/F (L/kg)	3.93	5.99	1.45	0.27	1.67	24.09	152	1.85

AUC = area under the concentration-time curve; AUC_t= area under the concentration-time curve to last time measured; CL/F = apparent oral clearance; C_{max} = peak concentration; CV% = coefficient of variation; Min = minimum; Max = maximum; NC = not calculated; SD = standard deviation; SE = standard error; T_{lag} = lag time; T_{max} = time to peak concentration; $t_{½}$ = terminal-phase disposition half-life; V_z/F = apparent volume of distribution during the terminal phase.

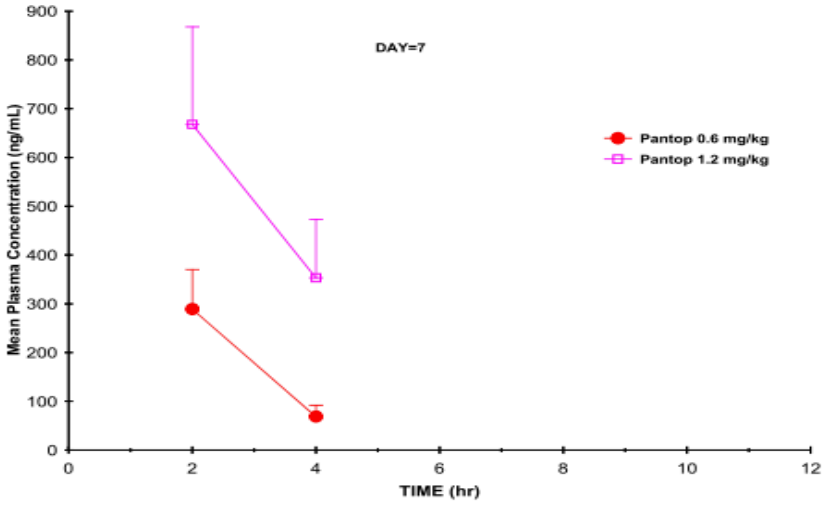
Table 10. Summary of Pharmacokinetic Parameter Estimates After Single-Dose Administration of Pantoprazole 1.2 mg/kg: Valid for PK Evaluation Population

Parameters	Mean	SD	SE	Min	Median	Max	CV%	Geometric Mean
N	18	18	18	18	18	18	18	18
C_{max} (ng/ml)	1527	1298	306	106	1405	4320	85	1009
T_{max} (hr)	1.63	1.19	0.28	0.50	1.02	4.08	73	1.33
T_{lag} (hr)	0.17	0.30	0.07	0	0	1.00	177	NC
$t_{½}$ (hr)	1.42	0.78	0.18	0.37	1.30	3.12	55	1.21
AUC_t (ng•hr/ml)	3513	3267	770	114	2760	11271	93	2107
AUC (ng•hr/ml)	3602	3269	771	122	2801	11359	91	2202
CL/F	0.87	1.36	0.32	0.12	0.40	5.92	156	0.48
V_z/F (L/kg)	1.52	2.28	0.54	0.23	0.68	9.72	150	0.83

AUC = area under the concentration-time curve; AUC_t = area under the concentration-time curve to last time measured; CL/F = apparent oral clearance; C_{max} = peak concentration; CV% = coefficient of variation; Min = minimum; Max = maximum; NC = not calculated; SD = standard deviation; SE = standard error; T_{lag} = lag time; T_{max} = time to peak concentration; $t_{½}$ = terminal-phase disposition half-life; V_z/F = apparent volume of distribution during the terminal phase.

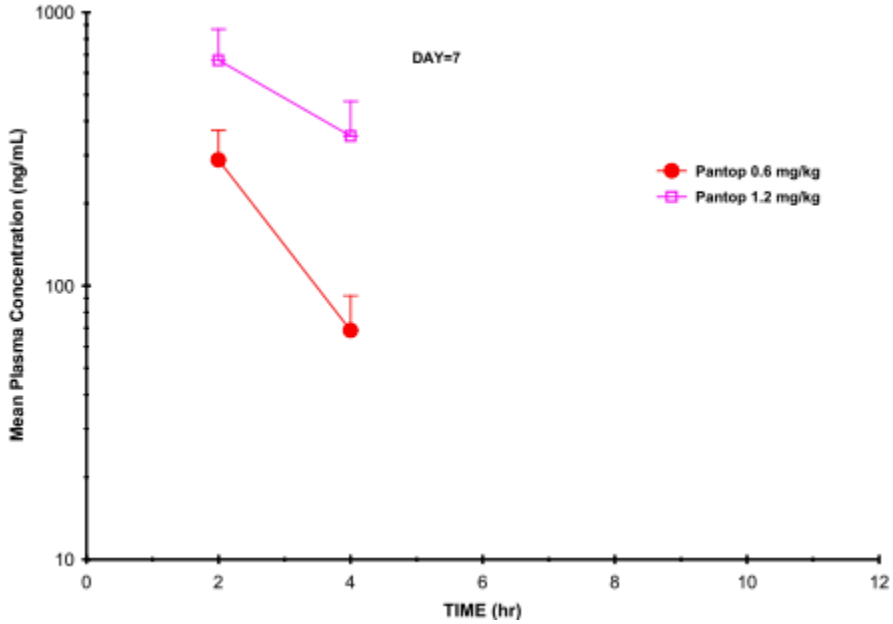
Mean plasma concentration-time data after multiple-dose administration for all subjects in the 0.6-mg/kg and 1.2-mg/kg dose groups are presented in Figure 1 and Figure 2, on a linear scale and log scale, respectively.

Figure 1 Mean Plasma Concentration-Time Profiles of Pantoprazole After Multiple-Dose Oral Administration of Pantoprazole Spheroid Suspension (Linear Scale) – All-Subject PK Population



PK = pharmacokinetic; Pantop = pantoprazole.

Figure 2 Mean Plasma Concentration-Time Profiles of Pantoprazole After Multiple-Dose Oral Administration of Pantoprazole Spheroid Suspension (Semi-log Scale All-Subject PK Population



PK = pharmacokinetic; Pantop = pantoprazole.

A total of 31 subjects (15 in the 0.6-mg/kgdose group and 16 in the 1.2 mg/kg dose group) had plasma concentrations at either 2 or 4 hours after the initial single-dose and after the last of the multiple-doses.

Pharmacodynamics Results:

For PD assessments, descriptive statistics and analysis of stomach pH at time of probe placement are presented in Table 11.

Descriptive statistics and analysis of mean and median intragastric pH for the entire monitoring period (ie, 0 to end) at the Baseline and the steady-state evaluations in the valid for PD evaluation population are presented in Table 12 and Table 13, respectively.

Table 11. Descriptive Statistics and Analysis of Initial Stomach pH Valid for PD Evaluation Population

	Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg-0.6 mg/kg)
Visit	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean (90% CI)**
Baseline							
N	10	-	-	10	-	-	-
Mean ± SD	2.4 ± 1.5	-	-	2.8 ± 1.9	-	-	-
Median	2.0	-	-	2.4	-	-	-
Min, Max	0.4, 5.5	-	-	0.3, 6.8	-	-	-
90% CI	1.5, 3.2	-	-	1.7, 4.0	-	-	-
Steady-state							
N	10	10	-	10	10		-
Mean ± SD	2.6 ± 1.3	0.2 ± 1.7	0.721	2.8 ± 2.5	-0.0 ± 2.7	0.973	-
Median	2.0	0	-	1.9	0.4	-	-
Min, Max	1.2, 4.5	-2.8, 2.4	-	0.3, 6.5	-4.7, 4.6	-	-
90% CI	1.9, 3.3	-0.8, 1.2	-	1.4, 4.2	-1.6, 1.5	-	-0.2 (-2.0, 1.5)

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

Table 12. Descriptive Statistics and Analysis of Mean Intragastric pH Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 – End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	4.2±1.4	-	-	3.0±1.4	-	-	-
	Median	4.3	-	-	3.4	-	-	-
	Min, Max	1.8, 6.6	-	-	0.9, 4.5	-	-	-
	90% CI	3.4, 5.0	-	-	2.2, 3.8	-	-	-
	Steady-state							
	N	11	11	-	10	10	-	-
	Mean ± SD	4.8±1.3	0.6±1.1	0.087	4.2±1.5	1.2±1.3	0.019	-
	Median	5.2	0.9	-	4.3	0.9	-	-
	Min, Max	2.9, 7.0	-2.1, 1.9	-	1.9, 6.4	-1.0, 3.7	-	-
	90% CI	4.1, 5.5	0.0, 1.2	-	3.3, 5.0	0.4, 1.9	-	0.6 (-0.3, 1.4)

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

a. p-Value is obtained from 1 sample 2-sided paired t-test between steady-state and baseline.

Table 13. Descriptive Statistics and Analysis of Median Intragastric pH Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg-0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 - End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	4.2±1.7	-	-	2.8±1.5	-	-	-
	Median	4.4	-	-	3.1	-	-	-
	Min, Max	1.3, 6.7	-	-	0.8, 4.8	-	-	-
	90% CI	3.3, 5.2	-	-	2.0, 3.7	-	-	-
	Steady-state							
	N	11	11	-	10	10	-	-
	Mean ± SD	4.7±1.7	0.5±1.4	0.255	4.2±19	1.4±1.7	0.031	-
	Median	5.4	0.8	-	4.6	1.1	-	-
	Min, Max	2.0, 7.0	-3.2, 2.0	-	1.2, 6.4	-1.6, 4.1	-	-
	90% CI	3.8, 5.7	-0.3, 1.3	-	3.2, 5.3	0.4, 2.4	-	0.9 (-0.3, 2.0)

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

Descriptive statistics and analyses of mean and median intraesophageal pH values for the entire monitoring period (ie, 0 to end) at the baseline and the steady-state evaluations in the valid for PD evaluation population are presented in Table 14 and Table 15 respectively.

Table 14. Descriptive Statistics and Analysis of Mean Intraesophageal pH: Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg-0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 – End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	5.7±0.7	-	-	5.2±0.4	-	-	-
	Median	5.7	-	-	5.2	-	-	-
	Min, Max	4.7, 7.1	-	-	4.6, 6.0	-	-	-
	90% CI	5.4, 6.1	-	-	5.0, 5.5	-	-	-
	Steady-state							
	N	11	11		10	10	-	-
	Mean ± SD	5.6±0.8	-0.2±0.6	0.347	4.9±0.3	-0.3±0.3	0.012	-
	Median	5.5	-0.2	-	4.9	-0.3	-	-
	Min, Max	4.5, 7.3	-1.5, 0.5	-	4.5, 5.7	-0.8, 0.2	-	-
	90% CI	5.1, 6.0	-0.5, 0.1	-	4.7, 5.1	-0.5, -0.1	-	-0.1 (-0.5, 0.2)

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

Table 15. Descriptive Statistics and Analysis of Median Intraesophageal pH Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 – End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	5.8±0.7	-	-	5.3±0.5	-	-	-
	Median	5.7	-	-	5.1	-	-	-
	Min, Max	4.6, 7.0	-	-	4.6, 6.3	-	-	-
	90% CI	5.4, 6.2	-	-	5.0, 5.6	-	-	-
	Steady-state							
	N	11	11	-	10	10	-	-
	Mean ± SD	5.6±0.8	-0.2±0.6	0.339	4.9±0.4	-0.4±0.3	0.003	-
	Median	5.5	-0.1	-	4.8	-0.4	-	-
	Min, Max	4.5, 7.3	-1.6, 0.6	-	4.5, 5.9	-1.0, 0.1	-	-
	90% CI	5.1, 6.1	-0.5, 0.2	-	4.7, 5.2	-0.6, -0.2	-	-0.2 (-0.6, 0.2)

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

Descriptive statistics and analysis at Baseline and at the steady-state evaluations of the percentage of time that intragastric pH was >4 are presented in Table 16.

Table 16. Descriptive Statistics and Analysis of % Time That Intragastric pH Was >4 Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 – End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	55.5 ± 28.6	-	-	32.2 ± 24.1	-	-	-
	Median	56.9	-	-	34.1	-	-	-
	Min, Max	5.6, 98.3	-	-	0.1, 63.5	-	-	-
	90% CI	39.9, 71.1	-	-	18.2, 46.2	-	-	-
	Steady-state							
	N	11	11	11	10	10	-	-
	Mean ± SD	68.5 ± 28.3	13.0 ± 23.7	0.099	56.6 ± 31.1	24.4 ± 26.0	0.016	-
	Median	81.4	22.3	-	61.5	28.0	-	-
	Min, Max	27.5, 99.5	-44.3, 43.3	-	2.8, 99.9	-21.5, 66.9	-	-
	90% CI	53.1, 84.0	0.1, 26.0	-	38.6, 74.6	9.4, 39.5	-	11.4 (-7.3, 30.1)

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

Descriptive statistics and analysis at the Baseline and at the steady-state evaluation for the percentage of time that intragastric pH was >3 for the valid for evaluation population are presented in Table 17.

Table 17. Descriptive Statistics and Analysis of % Time That Intragastric pH Was >3 Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 – End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	68.4±26.3	-	-	43.5±29.8	-	-	-
	Median	72.8	-	-	51.7	-	-	-
	Min, Max	19.2, 99.4	-	-	0.2, 81.4	-	-	-
	90% CI	54.1, 82.8	-	-	26.2, 60.8	-	-	-
	Steady-state							
	N	11	11	-	10	10	-	-
	Mean ± SD	76.9±24.5	8.4±18.2	0.155	66.3±30.5	22.7±27.4	0.028	-
	Median	85.6	12.9	-	77.8	18.6	-	-
	Min, Max	36.0, 99.9	-35.8, 33.0	-	9.2, 100.0	-23.2, 80.7	-	-
	90% CI	63.5, 90.2	-1.5, 18.4	-	48.6, 83.9	6.9, 38.6	-	14.3 (-3.1, 31.7)

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

Descriptive statistics and analyses at the Baseline and the steady-state evaluation for the percentage of time that intraesopheal pH was <4 for the valid for evaluation population are presented in Table 18.

Table 18. Descriptive Statistics and Analysis of % Time That Intraesophageal pH Was <4 Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 – End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	4.6±3.9	-	-	8.0±5.6	-	-	-
	Median	4.7	-	-	5.7	-	-	-
	Min, Max	0.4, 12.6	-	-	3.2, 20.5	-	-	-
	90% CI	2.5, 6.8	-	-	4.7, 11.2	-	-	-
	Steady-state							
	N	11	11		10	10	-	-
	Mean ± SD	4.6±5.6	0.0±4.0	0.982	9.4±5.8	1.4±6.9	0.534	-
	Median	2.1	0	-	7.7	0.1	-	-
	Min, Max	0.1, 14.3	-5.7, 9.3	-	2.3, 19.5	-7.0, 13.2	-	-
	90% CI	1.6, 7.7	-2.2, 2.2		6.0, 12.8	-2.6, 5.4	-	1.4 (-2.8, 5.6)

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

Descriptive statistics and analysis of the baseline and the steady-state evaluations of the esophageal reflux area (the esophageal area < pH 4) for the valid for PD evaluation population are presented in Table 19.

Table 19. Descriptive Statistics and Analysis of Esophageal Reflux Area (pH•min) - Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 – End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	33.4±25.2	-	-	57.5±39.3	-	-	-
	Median	40.7	-	-	51.4	-	-	-
	Min, Max	3.3, 65.2	-	-	17.7, 141.3	-	-	-
	90% CI	19.6, 47.2	-	-	34.7, 80.3	-	-	-
	Steady-state							
	N	11	11	-	10	10	-	-
	Mean ± SD	24.5±36.7	-8.9±35.6	0.423	31.3±13.3	-26.2±39.5	0.066	-
	Median	14.7	-8.1	-	35.0	-24.2	-	-
	Min, Max	0.8, 129.5	-41.4, 83.5	-	9.9, 48.7	-99.7, 31.0	-	-
	90% CI	4.4, 44.6	-28.4, 10.5	-	23.6, 39.0	-49.1, -3.3	-	-17.2 (-45.5, 11.1)

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

Descriptive statistics and analysis of the normalized area of gastric H^+ activity over time (H•mmol/L) for the valid for evaluation PD population is presented in Table 20.

Table 20. Descriptive Statistics and Analysis of Normalized Area of Gastric Hydrogen Ion Activity Over Time (H•mmol/L) Valid for Evaluation PD Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 - End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	259.7±442.7	-	-	921.0±1290.1	-	-	-
	Median	81.6	-	-	312.3	-	-	-
	Min, Max	3.3, 1289.3	-	-	22.8, 3673.0	-	-	-
	90% CI	17.8, 501.7	-	-	173.1, 1668.9	-	-	-
	Steady-state							
	N	11	11	-	10	10	-	-
	Mean ± SD	102.3±118.6	-157.5±349.9	0.166 (0.278)	303.6±524.9	617.4±1132.8	0.119 (0.049)	-
	Median	47.5	-34.1	-	71.4	-222.3	-	-
	Min, Max	0.2, 334.3	-1006.0, 154.8	-	0.0, 1648.8	-3652.3, 71.4	-	-
	90% CI	37.5, 167.1	-348.6, 33.7	-	0.0[b], 607.9	-1274.1, 39.2	-	-460.0 (-1079.4, 159.5)

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

a. p-Value is obtained from 1 sample 2-sided paired t-test between steady-state and baseline. Because 1 subject had an extremely large value (3673 H•mol/L), p-values from Wilcoxon Signed-Rank Test were also provided in parentheses.

b. The negative lower limit of 90% CI for actual was set to 0.

Descriptive statistics and analysis of the normalized area of esophageal H^+ activity over time (H•mmol/L) for the valid for evaluation PD population is presented in Table 21.

Table 21. Descriptive Statistics and Analysis of Normalized Area of Esophageal Hydrogen Ion Activity Over Time (H•mmol/L) Valid for Evaluation PD Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 - End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	2.1±1.6	-	-	3.5±2.3	-	-	-
	Median	1.6	-	-	3.5	-	-	-
	Min, Max	0.4, 5.6	-	-	0.6, 7.4	-	-	-
	90% CI	1.2, 3.0	-	-	2.2, 4.8	-	-	-
	Steady-state							
	N	11	11		10	10	-	-
	Mean ± SD	1.5±2.4	-0.6±2.3	0.387	1.5±0.6	-2.0±2.3	0.021	-
	Median	0.9	-1.0	-	1.4	-1.5	-	-
	Min, Max	0.2, 8.5	-4.4, 5.0	-	0.6, 2.7	-6.1, 0.8	-	-
	90% CI	0.2, 2.8	-1.9, 0.6	-	1.1, 1.8	-3.4, -0.7	-	-1.4 (-3.1, 0.3)

CI = confidence interval; Min = minimum; Max = maximum; N = number of subjects; PD = pharmacodynamics; SD = standard deviation.
a. p-Value is obtained from one sample two-sided paired t-test between steady-state and baseline.

Descriptive statistics and analysis of reflux episodes is presented in Table 22. In this study, the pH threshold for a reflux episode was 4, ie, a reflux episode began whenever the esophageal pH dropped below 4 and the episode ended when the esophageal pH increased to a value ≥4.

Table 22. Descriptive Statistics and Analysis of Number of Reflux Episodes During 24 Hours at Baseline and Steady-State-Valid for PD Evaluation Population

		Pantoprazole 0.6 mg/kg			Pantoprazole 1.2 mg/kg			Difference of Changes Between Groups (1.2 mg/kg - 0.6 mg/kg)
Time Interval	**Visit**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Actual**	**Change From Baseline**	**p-Value[a]**	**Mean(90% CI)**
0 - End	Baseline							
	N	11	-	-	10	-	-	-
	Mean ± SD	87.4±59.9	-	-	143.2±48.3	-	-	-
	Median	93.0	-	-	151.0	-	-	-
	Min, Max	5.0, 214.0	-	-	54.0, 195.0	-	-	-
	90% CI	54.6, 120.1	-	-	115.2, 171.2	-	-	-
	Steady-state		-	-				
	N	11	11		10	10	-	-
	Mean ± SD	109.1±121.0	21.7±83.9	0.410	212.6±112.6	69.4 ±137.1	0.144	-
	Median	66.0	1.0	-	251.5	61.0	-	-
	Min, Max	6.0, 406.0	-79.0, 192.0	-	37.0, 362.0	-132.0, 233.0	-	-
	90% CI	43.0, 175.2	-24.1, 67.6	-	147.4, 277.8	-10.1, 148.9	-	47.7 (-37.1, 132.5)

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

The mean number of reflux episodes lasting >5 minutes increased from Baseline to steady-state by 0.4±1.6 from 1.0 to 1.4 in the low dose (0.6 mg/kg) group (p=0.476), and by 1.2±3.3 from 2.2 to 3.4 in the high-dose (1.2 mg/kg) group (p=0.283). These changes were not statistically significant for either dose group.

The mean duration of the longest reflux episodes decreased from Baseline to steady-state by 2.8±7.3 minutes from 7.8 minutes to 5.0 minutes for the low-dose (0.6 mg/kg) group (p=0.231), and increased by 1.3±15.3 minutes, from 12.7 minutes to 14.0 minutes for the high-dose (1.2 mg/kg) group (p=0.794). These changes were not statistically significant for either dose group.

No efficacy evaluations were performed in the study.

Safety Results: Table 23 summarizes the treatment-emergent AEs (TEAEs) reported during the study by category.

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events - Safety Population (All Causality)

Body System Adverse Event[a]	Pantoprazole 0.6 mg/kg (N=33)	Pantoprazole 1.2 mg/kg (N=34)	Total (N=67)
Any adverse event	13 (39.4)	17 (50.0)	30 (44.8)
Body as a whole	6 (18.2)	6 (17.6)	12 (17.9)
Abdominal pain	1 (3.0)	1 (2.9)	2 (3.0)
Fever	3 (9.1)	4 (11.8)	7 (10.4)
Infection	1 (3.0)	2 (5.9)	3 (4.5)
Injection site pain	0	1 (2.9)	1 (1.5)
Sepsis	1 (3.0)	0	1 (1.5)
Cardiovascular system	1 (3.0)	0	1 (1.5)
Atrial septal defect	1 (3.0)	0	1 (1.5)
Digestive system	5 (15.2)	9 (26.5)	14 (20.9)
Diarrhea	2 (6.1)	4 (11.8)	6 (9.0)
Eructation	1 (3.0)	0	1 (1.5)
Flatulence	0	2 (5.9)	2 (3.0)
Gastroenteritis	1 (3.0)	2 (5.9)	3 (4.5)
Tooth disorder	0	2 (5.9)	2 (3.0)
Vomiting	2 (6.1)	0	2 (3.0)
Metabolic and nutritional	2 (6.1)	1 (2.9)	3 (4.5)
Creatine phosphokinase increased	1 (3.0)	0	1 (1.5)
Dehydration	1 (3.0)	0	1 (1.5)
Weight loss	0	1 (2.9)	1 (1.5)
Respiratory system	1 (3.0)	5 (14.7)	6 (9.0)
Apnea	0	1 (2.9)	1 (1.5)
Cough increased	0	1 (2.9)	1 (1.5)
Laryngitis	0	1 (2.9)	1 (1.5)
Rhinitis	1 (3.0)	3 (8.8)	4 (6.0)
Skin and appendages	4 (12.1)	5 (14.7)	9 (13.4)
Contact dermatitis	2 (6.1)	3 (8.8)	5 (7.5)
Dermatitis atopic	1 (3.0)	0	1 (1.5)
Eczema	0	1 (2.9)	1 (1.5)
Maculopapular rash	1 (3.0)	0	1 (1.5)
Rash	1 (3.0)	1 (2.9)	2 (3.0)

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events - Safety Population (All Causality)

Body System Adverse Event[a]	Pantoprazole 0.6 mg/kg (N=33)	Pantoprazole 1.2 mg/kg (N=34)	Total (N=67)
Special senses	0	3 (8.8)	3 (4.5)
Otitis media	0	3 (8.8)	3 (4.5)
Urogenital system	0	1 (2.9)	1 (1.5)
Urine abnormality	0	1 (2.9)	1 (1.5)

AEs/SAEs results are not separated out.
AEs = adverse events; N = total number of subjects; SAEs = serious adverse events.
a. Body system totals are not necessarily the sum of the individual adverse events since a patient may report 2 or more different adverse events in the same body system.

There were no statistically significant differences in the incidence of TEAEs between the 2 dose groups. Four (4) subjects had TEAEs that were considered by the reporting Investigator to be possibly or probably related to their treatment with pantoprazole, including 2 subjects with diarrhea (1 in each dose group), 1 subject with eructation (0.6-mg/kg dose group), and 1 subject with flatulence (1.2-mg/kg dose group). These TEAEs were all considered to be mild in severity; the 2 cases of diarrhea resolved in 2 days or less.
A summary of subjects who reported serious AEs (SAEs) during the study is presented Table 24.

Table 24. Number(%) of Subjects Serious Adverse Events

Body System[a] Adverse Event	Pantoprazole 0.6 mg/kg (N=33)	Pantoprazole 1.2 mg/kg (N=34)	Total (N=67)
Any adverse event	3 (9.1)	2 (5.9)	5 (7.5)
Digestive system	2 (6.1)	1 (2.9)	3 (4.5)
Gastroenteritis	1 (3.0)	1 (2.9)	2 (3.0)
Vomiting	1 (3.0)	0	1 (1.5)
Metabolic and nutritional	1 (3.0)	0	1 (1.5)
Dehydration	1 (3.0)	0	1 (1.5)
Respiratory system	1 (3.0)	1 (2.9)	2 (3.0)
Apnea	0	1 (2.9)	1 (1.5)
Stridor	1 (3.0)	0	1 (1.5)

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.
N = total number of subjects.

None of the SAEs were considered by the reporting Investigators to be related to treatment with pantoprazole.

No deaths were reported during the study.

One subject was withdrawn after being admitted to hospital because of a rotavirus gastroenteritis which was considered by the Investigator not to be related to treatment with pantoprazole.

A total of 17 (27.0%) of subjects, including 9 (27.3%) in the 0.6-mg/kg dose group and 8 (26.7%) in the 1.2-mg/kg dose group, were identified as having potentially clinically important (PCI) values in laboratory tests at the postbaseline evaluation.

Subjects had vital sign measurements at multiple time points during their first and second PK assessments. A few subjects had PCI readings for individual parameters (respiratory rate, systolic blood pressure, and diastolic blood pressure) at isolated time points. No subjects had sustained abnormal readings involving multiple parameters which might indicate a treatment effect of clinical concern.

Despite the short duration of this study, analyses of growth parameters showed statistically significant increases from baseline to final visit for weight, length, and head circumference. There were no significant changes from Baseline in the z-score for any parameter, indicating that the increases in length, weight, and head circumference were consistent with those expected for subjects of this age.

No statistically significant differences between the 2 dose groups was observed for the change from Baseline in growth parameters and their z-scores.

Three (3, 4.5%) subjects had abnormalities in ECG findings that met the PCI criteria during the study, 2 (6.1%) subjects in the 0.6-mg/kg dose group and 1 (2.9%) subject in the 1.2-mg/kg dose group.

CONCLUSIONS:

Pantoprazole was generally well tolerated in these infants, aged 1 month through 11 months who received daily doses of 0.6 mg/kg and 1.2 mg/kg of pantoprazole granules as an oral suspension for at least 5 consecutive days. The plasma concentrations obtained with the 1.2-mg/kg dose in infants aged 1 month through 11 months were similar to those obtained with a 40-mg dose in adults. The 1.2-mg/kg dose provided statistically significant increases in the gastric pH. The 1.2-mg/kg dose also provided statistically significant decreases in the AUC and the normalized AUC of the esophageal H^+ activity. The results of this study support the choice of the 1.2-mg/kg daily dose used in another study (A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Treatment-Withdrawal Study of the Efficacy and Safety of Pantoprazole Sodium Enteric-Coated Granules in Infants [1 Through 11 Months] With Symptomatic GERD [NCT00365300]), which was conducted in infants aged 1 month through 11 months.