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

PROTOCOL NO.: 3001B3-335

PROTOCOL TITLE: A Multicenter, Open Label Safety Study of 2 Doses of Pantoprazole Sodium Enteric-Coated Spheroid Suspension in Infants Aged Less Than 12 Months With Presumed GERD

Study Centers: A total of 15 centers took part in this study and enrolled subjects; 8 centers in the United States (US), 3 centers in Poland, 2 centers in Italy and 1 center each in Belgium and France.

Study Initiation Date and Final Completion Date: 14 March 2006 to 25 March 2008

Phase of Development: Phase 3

Study Objectives: The objective was to assess safety and tolerability of pantoprazole in infants <12 months with presumed gastroesophageal reflux disease (GERD).

METHODS

Study Design: This study was a multi-center, open-label, safety study in infants aged <12 months with presumed GERD. All subjects who had successfully completed previous study 1 (A Multicenter, Randomized, Open Label, Single and Multiple Dose Study of the Pharmacokinetics[PK] and Pharmacodynamics [PD] of 2 Dose Levels of Pantoprazole Sodium Enteric-Coated Spheroid Suspension in Infants Aged 1 Through 11 Months With Presumed GERD [NCT00259012]) and subjects at selected sites in previous study 2 (A Multicenter, Open-Label, PK, PD and Safety Study of Pantoprazole Delayed-Release Granules Administered as a Suspension in Neonates and Preterm Infants With a Clinical Diagnosis of GERD [NCT00362609]) were eligible to participate. All subjects who had successfully completed previous study 1 were allowed to continue on the same dose or received a higher dose based upon their clinical response or pH-metry results in that study (previous study 1). Subjects in previous study 2 received a 2.5 mg dose or a higher dose based upon their clinical response or pH-metry results in that study (previous study 2). These decisions were made by the Investigator caring for the subject.

All procedures from the final evaluation visit for previous study 1 or previous study 2 were used as the on-treatment Baseline for this study.

If a subject had his/her last dose of pantoprazole >17 days before the start of this study, enrollment had to be approved by the medical monitor. In addition, an unscheduled visit occurred at the time of enrollment, which included a physical exam (PE), vital sign (VS) measurements including temperature (rectal, axillary, or tympanic),pulse or heart rate, blood pressure , respirations, weight, length, and head circumference, as well as routine clinical laboratory tests. The unscheduled evaluations at the time of enrollment were used as the Baseline for these subjects.

Subjects participated for approximately 8 weeks, including a 6-week treatment period and a 2-week follow-up period. The pantoprazole doses were dispensed on study Day 1, however, the first dose was not to be taken until the next morning if the infant had already been given a dose (last visit of previous study 1 or previous study 2) on study Day 1.

The schedule of assessment is given in Table 1.

Table 1. Study Flowchart

Study Phase (Day)	1[a]	7±2	14±2	21±2	28±2	35±2	42±2[b]	57±2 (Follow-Up)	Early Termination
Study Interval	**Active Phase**								
Subject visit	X			X			X		X
Telephone contact		X	X		X	X		X	
Informed consent	X								
Medical history	X								
Demographics	X								
Physical examination	X			X			X		X
Vital signs[c]	X			X			X		X
Laboratory evaluation	X						X		X
Test article dispensing	X			X					
Test article administration	X----------X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	X[d]	X	X	X	X	X	X	X	X

a. Day 1 ("on treatment Baseline") data for laboratory, physical examination, vital signs and continuing AEs were taken from the final visit of previous study 1 or previous study 2. Medical history was taken from the medical history data collected for study previous study 1 or previous study 2 on the screening visit. If the subject enrolled >17 days after the last dose of pantoprazole, repeat clinical laboratory tests were performed along with physical examination and vital signs including weight, length, and head circumference. The laboratory tests might have been performed at a local laboratory. If study Day 1 was >17 days after the last dose of pantoprazole in previous study 1 or previous study 2, an unscheduled visit was performed. Medical monitor approvals were required in these cases.

b. Day 42 (±2) was the final study evaluation day.

c. Vital signs included blood pressure, pulse or heart rate, respiratory rate, rectal, axillary or tympanic temperature (°F or °C), weight (kg or g), length (cm), and head circumference (cm) on study Days 1 and 42, and weight only on study day 21 ± 2 only.

d. Adverse events that did not resolve during previous study 1 or previous study 2 were recorded as ongoing adverse events in this study.

Number of Subjects (Planned and Analyzed): Approximately 92 subjects were planned for the study (56 from previous study 1 and 36 from previous study 2). A total of 58 subjects were enrolled (39 subjects in the US, 15 subjects in Poland, 2 subjects in Italy, 1 subject in Belgium and 1 subject in France)which included 49 subjects from previous study 1 and 9 subjects from previous study 2. Twelve (12) subjects were assigned to the low-dose group (0.6 mg/kg) and 46 subjects were in the high-dose (1.2 mg/kg) group. All of the subjects from previous study 2 were in the high-dose (1.2 mg/kg) group.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged less than 12 months, and who had successfully completed previous study 1 or previous study 2.

Exclusion Criteria: Subjects who required chronic use of warfarin, carbamepazine, or phenytoin were excluded from the study.

Study Treatment: Subjects continued on the same dose of pantoprazole as in previous study 1 or received a higher dose based on their clinical response or pH-metry results in that study. Subjects in previous study 2 received 2.5 mg or a higher dose based upon their clinical response or pH-metry results. These decisions were made by the Investigator caring for the subject.

Pantoprazole sodium enteric-coated spheroids were provided with an inactive powder blend. At the time of dose administration, 5 mL of water was added to form a grape-flavored oral suspension. The pantoprazole strengths provided were 2.5 mg, 5 mg, and 10 mg for administration to subjects in the low (2.5 mg for subjects <7 kg or 5 mg for subjects ≥7 to ≤15 kg) dose group and in the high (5 mg for subjects <7 kg or 10 mg for subjects ≥7 to ≤15 kg) dose group.

Pantoprazole was dispensed in the clinic on study Days 1 and 21 and administered once daily by the parent at home (or by the nurse if the subject was in the hospital) from study Day 2 through study Day 42. Pantoprazole was administered at approximately the same time that it was administered on study Day 1 of the previous study (1 or 2), and feeding occurred at least 30 minutes later.

Safety Endpoints:

- Adverse events (AEs), treatment emergent adverse events (TEAEs), and serious adverse events (SAEs).
- AEs and SAEs related to study drug continuing from previous studies (1 or 2).
- Physical examination: body weight (kg), length (cm), and head circumference (cm).
- VS measurements, including potentially clinically important (PCI) results.
- Laboratory evaluations, including PCI results.
- Premature terminations due to safety reasons.

- Non-study medications.

No efficacy evaluations were performed in this study.

Safety Evaluations: Throughout the study period, routine safety of pantoprazole was monitored based on reported signs and symptoms, and the results of scheduled PEs, VS, length, weight, and head circumference, and clinical laboratory tests.

Statistical Methods: The safety population was defined as all subjects who received at least 1 dose of pantoprazole in this extension study.

Descriptive summary statistics for all subjects and by treatment dose group were prepared for demographic (gender, age and age groups, <1 month, ≥1 month, but <6 months or >6 months), and other Baseline characteristics. Comparability of treatment dose groups was evaluated by an analysis of variance (ANOVA) with treatment dose group as a factor in the model for all variables except nominal attributes (eg, gender), which were compared by Fisher's exact test.

The data were reported by previous study, ie, study previous study 1 or previous study 2, and the 2 studies combined. The number of subjects with AEs, TEAEs, abnormal and/or PCI laboratory test results and VS were summarized for all subjects and by treatment dose group and compared, using Fisher's exact test. Mean changes from Baseline in safety (VS and laboratory test results) and growth (weight, length and head circumference) parameters were summarized accordingly on days evaluated. Changes from the original Baseline (predose measurement in the previous lead-in study) were calculated and presented by treatment dose group using analysis of covariance (ANCOVA).

The number of subjects who were prematurely withdrawn from the study due to any reason and by specific reason was summarized and analyzed for all subjects and by treatment dose group using Fisher's exact test.

Changes in growth parameters and their z-scores were summarized and compared within groups by a one-sample 2-sided paired t-test. The z-scores were calculated based on length-for age, weight-for-age, and head circumference-for-age charts from the US Centers for Disease Control and Prevention. Changes from Baseline were also compared between dose groups using an ANCOVA model with dose group as a factor and Baseline value as a covariate. Analyses were performed for the change from on-treatment Baseline as well as for the change from original Baseline (predose measurement in the lead-in studies: previous studies 1 and 2) by previous study and combined.

RESULTS

Subject Disposition and Demography: Fifty-eight (58) subjects enrolled in this study (49 subjects from previous study 1 and 9 subjects from study previous study 2). Twelve (12) subjects were in the low-dose group (0.6 mg/kg) and 46 subjects were in the high-dose (1.2 mg/kg) group. All of the subjects from study previous study 2 were in the high-dose

(1.2 mg/kg) group in this study. Fifty-five (55, 94.8%) subjects completed the study. Subject disposition is presented in Table 2.

Table 2. Summary of Reasons for Conclusion of Subject Participation - Safety Population

	Pantoprazole Treatment		
Conclusion Status Reason[a], n (%)	**0.6 mg/kg N=12**	**1.2 mg/kg N=46**	**Total N=58**
Total	12 (100)	46 (100)	58 (100)
Study completed	12 (100)	43 (93.5)	55 (94.8)
Discontinued	0	3 (6.5)	3 (5.2)
Adverse event	0	2 (4.3)	2 (3.4)
Parent request	0	1 (2.2)	1 (1.7)

N = total number of subjects; n = number of subjects in the specified category.
a. Total discontinued is the sum of individual reasons since they are mutually exclusive by subject.

A summary of demographic and Baseline characteristics for all subjects is presented in Table 3. Of the 58 subjects enrolled in this study, 26 (44.8%) were female and 32 (55.2%) were male; all subjects were aged <12 months at the time of entry into the previous study, and all had a presumed diagnosis of GERD. Most of the subjects in the study were white (43, 74.1%) and most were non-Hispanic, non-Latino (55, 94.8%).

Table 3. Demographic and Baseline Characteristics - Safety Population

		Pantoprazole Treatment		
Characteristic	**p-Value**	**0.6 mg/kg N=12**	**1.2 mg/kg N=46**	**Total N=58**
Age (month)				
Mean	0.106[a]	7.34	5.55	5.92
Standard deviation		3.06	3.44	3.42
Sex	1.000[a]			
Female		5 (41.67)	21 (45.65)	26 (44.83)
Male		7 (58.33)	25 (54.35)	32 (55.17)
Race	0.594[a]			
Black or African American		3 (25.00)	9 (19.57)	12 (20.69)
Other		1 (8.33)	2 (4.35)	3 (5.17)
White		8 (66.67)	35 (76.09)	43 (74.14)
Baseline length (cm)				
Mean	0.016[b]	69.33	61.80	63.36
Standard deviation		5.47	10.12	9.80
Baseline weight (kg)				
Mean	0.016[b]	7.97	6.21	6.58
Standard deviation		1.40	2.33	2.28

N = number of subjects
a. One-way analysis of variance with treatment as factor.
b. Fisher's exact test p-value (2-Tail).

Efficacy Results: No efficacy evaluations were performed in this study.

Safety Results: TEAEs reported for >1 subject during the study, by treatment is summarized in Table 4.

Table 4. Number (%) of Subjects With Treatment-Emergent Adverse Events Reported for >1 Subject-Safety Population

Body System Adverse Event	Pantoprazole Treatment		
	0.6 mg/kg N=12	1.2 mg/kg N=46	Total N=58
Any adverse event	8 (66.7)	30 (65.2)	38 (65.5)
Body as a whole	3 (25.0)	7 (15.2)	10 (17.2)
Fever	1 (8.3)	4 (8.7)	5 (8.6)
Digestive system	4 (33.3)	13 (28.3)	17 (29.3)
Constipation	0	3 (6.5)	3 (5.2)
Gastroenteritis	0	2 (4.3)	2 (3.4)
Gastroesophageal reflux disease	2 (16.7)	1 (2.2)	3 (5.2)
Tooth disorder	1 (8.3)	4 (8.7)	5 (8.6)
Vomiting	1 (8.3)	3 (6.5)	4 (6.9)
Respiratory system	6 (50.0)	10 (21.7)	16 (27.6)
Cough increased	2 (16.7)	3 (6.5)	5 (8.6)
Pharyngitis	1 (8.3)	1 (2.2)	2 (3.4)
Rhinitis	4 (33.3)	4 (8.7)	8 (13.8)
Upper respiratory infection	2 (16.7)	3 (6.5)	5 (8.6)
Skin and appendages	3 (25.0)	8 (17.4)	11 (19.0)
Eczema	0	3 (6.5)	3 (5.2)
Rash	1 (8.3)	2 (4.3)	3 (5.2)
Special senses	2 (16.7)	7 (15.2)	9 (15.5)
Conjunctivitis	0	2 (4.3)	2 (3.4)
Otitis media	2 (16.7)	5 (10.9)	7 (12.1)

AE/SAE results are not separated out.
AE = adverse event; N = number of subjects; SAE = serious adverse event.

Three (3) subjects, all in the 1.2 mg/kg treatment group, had TEAEs that were considered by the reporting Investigator to be possibly or probably related to pantoprazole, including 1 subject with vomiting, 1 subject with rash, and 1 subject with eczema. The vomiting was considered to be moderate in severity, the rash and eczema were considered mild, and all of the events resolved. Treatment-related TEAEs are presented in Table 5.

Table 5. Number (%) of Subjects With Treatment-Related Treatment-Emergent Adverse Events-Safety Population

Body System Adverse Event	Pantoprazole Treatment		
	0.6 mg/kg N=12	1.2 mg/kg N=46	Total N=58
Any adverse event	0	3 (6.5)	3 (5.2)
Digestive system	0	1 (2.2)	1 (1.7)
Vomiting	0	1 (2.2)	1 (1.7)
Skin and appendages	0	2 (4.3)	2 (3.4)
Eczema	0	1 (2.2)	1 (1.7)
Rash	0	1 (2.2)	1 (1.7)

AE/SAE results are not separated out.
AE = adverse event; N = number of subjects; SAE = serious adverse event.

A summary of subjects who reported SAEs during the study is presented in Table 6. SAEs were reported for 3 (5.2%) subjects, 1 subject in the low-dose (0.6 mg/kg) group and

2 subjects in the high-dose (1.2 mg/kg) group. None of the SAEs was considered by the reporting Investigator to be related to treatment with pantoprazole.

Table 6. Number (%) of Subjects Reporting Serious Adverse Events - Safety Population

Body System[a] Adverse Event	Pantoprazole Treatment		
	0.6 mg/kg N=12	1.2 mg/kg N=46	Total N=58
Any adverse event	1 (8.3)	2 (4.3)	3 (5.2)
Digestive System	1 (8.3)	0	1 (1.7)
Gastroenteritis	1 (8.3)	0	1 (1.7)
Respiratory System	0	2 (4.3)	2 (3.4)
Respiratory disorder	0	1 (2.2)	1 (1.7)
Respiratory failure	0	1 (2.2)	1 (1.7)
Special Senses	1 (8.3)	0	1 (1.7)
Otitis media	1 (8.3)	0	1 (1.7)

N = number of subjects.

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

Discontinuations: The number (%) of subjects in the safety population for whom AEs were reported that caused withdrawal from the study is presented in Table 7. Two (2) subjects were withdrawn from the study because of TEAEs.

Table 7. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Study - Safety Population

Body System[a] Adverse event	Pantoprazole Treatment		
	0.6 mg/kg N=12	1.2 mg/kg N=46	Total N=58
Any adverse event	0	2 (4.3)	2 (3.4)
Digestive System	0	1 (2.2)	1 (1.7)
Vomiting	0	1 (2.2)	1 (1.7)
Respiratory System	0	1 (2.2)	1 (1.7)
Respiratory failure	0	1 (2.2)	1 (1.7)

N = number of subjects.

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

Deaths: There were no deaths reported during the study.

Clinical Laboratory Evaluations: A total of 14 (24.6%) subjects, 2 (16.7%) subjects in the low-dose (0.6-mg/kg) group and 12 (26.7%) subjects in the high-dose (1.2-mg) group, had PCI laboratory test results at the final evaluation. None of these laboratory findings were deemed to be clinically significant.

CONCLUSIONS: Pantoprazole was safe and generally well tolerated in infants aged <12 months with presumed GERD who received oral doses of 0.6 mg/kg or 1.2 mg/kg daily for 6 weeks.