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

**PROTOCOL NO.:** 3001B3-329-WW (B1791056)

**PROTOCOL TITLE:** 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

**Study Centers:** Thirty one (31) centers took part in the study and enrolled subjects with 18 in the United States (US), 5 in South Africa, 3 in Canada, 2 in Poland, and 1 each in Belgium, Latvia, and Spain.

**Study Initiation Date and Final Completion Date:** 28 September 2006 to 26 November 2007.

**Phase of Development:** Phase 3

**Study Objectives:**

Primary Objective: The primary objective of this study was to assess the efficacy of treatment with pantoprazole granules administrated as an oral suspension in pediatric subjects 1 through 11 months of age. The difference in treatment-withdrawal rates was compared between 2 groups of subjects: those who continued treatment with pantoprazole and those who received placebo.

Secondary Objective: Other objectives were to assess safety, tolerability, gastroesophageal reflux disease (GERD) symptoms, growth parameters, compliance, respiratory symptoms, and antacid use in subjects 1 through 11 months with symptomatic GERD.

**METHODS**

**Study Design:** This was a multicenter, outpatient, randomized, double-blind, placebo-controlled, treatment-withdrawal study of oral pantoprazole in infants aged 1 through 11 months who had symptomatic GERD. Subjects received 1.2 mg/kg pantoprazole suspension in 5 or 10 mg doses, depending on the subject's body weight. Efficacy was compared with that of placebo in subjects who had received 4 weeks of open-label treatment with the pantoprazole granules for suspension formulation.

All subjects received standardized, nonpharmacologic, conservative treatment for GERD (hypoallergenic formula thickened with rice cereal and instruction on feeding and

positioning) during a 2-week screening phase and throughout the study. Subjects whose symptoms resolved with the conservative treatment during the screening phase were withdrawn. The remaining subjects entered a 4-week treatment run-in phase and received open-label oral pantoprazole granules for suspension daily for 4 weeks. Throughout the study GERD symptoms, respiratory symptoms, and the use of rescue medication antacid were recorded using an electronic diary (eDiary).

Subjects who were at least 80% compliant with study medication administration and eDiary completion entered a 4-week, double-blind, placebo-controlled, treatment-withdrawal phase. Subjects were stratified by body weight and randomly assigned to receive either pantoprazole or matching placebo daily for 4 weeks. Study visit procedure is presented in Table 1.

## Table 1. Study Flow Chart

| **Study Period** | **Screening Period**[a] | **Treatment Period to Final Visit**[b] | | | | | | | | | **Post-Treatment** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **Open-Label Run-in Phase** | | | | | **Double-Blind Withdrawal Phase** | | | | |
| **Study Week** | **-2** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **10** |
| **Study Day** | **-14±3** | **1** | | **14±3** | | **28±3** | | **42±3** | | **56±3** | |
| **Study Visit (V)**[c] | **V1** | **V2** | | **V3** | | **V4** | | **V5** | | **V6** | |
| **Telephone Contact (T)**[c] | | | **T1** | | **T2** | | **T3** | | **T4** | | **T5** |
| Informed consent | X | | | | | | | | | | |
| Demography and medical history | X | | | | | | | | | | |
| Inclusion and exclusion criteria | X | X | | | | | | | | | |
| Documentation of GERD testing[d] | X----------X | | | | | | | | | | |
| Prior and current medications | X | | | | | | | | | | |
| Complete physical exam[e] | X | X | | | | X | | | | X | |
| Brief physical exam | | | | X | | | | X | | | |
| Vital signs[f] | X | X | | X | | X | | X | | X | |
| Symptom questionnaire (GSQ-I)[g] | X | X | | | | | | | | | |
| Conservative GERD treatment instructions | X | X | X | X | X | X | X | X | X | X | |
| Provide eDiary and instructions | X | X | X | X | X | X | X | X | X | | |
| Routine laboratory evaluation[h] | X | | | | | X | | | | X | |
| Optional serum gastrin level[i] | X----------X | | | | | X | | | | X | |
| 12-lead ECG[h] | X----------X | | | | | | | | | X | |
| Record adverse events | X | X | X | X | X | X | X | X | X | X | X |
| Record concomitant medications | | X | X | X | X | X | X | X | X | X | X |
| Dispense study antacid, infant formula, cereal | X | X | | X | | X | | X | | | |
| Dispense test article[j] | | X | | X | | X | | X | | | |
| Daily test article administration | | X----------X | | | | | | | | | |
| Collect test article; verify compliance[k] | | | | X | | X | | X | | X | |
| Document antacid use; collect unused antacid[l] | | X | | X | | X | | X | | X | |
| Review eDiary[m] | | X | | X | | X | | X | | X | |
| Collect eDiary and all accessories | | | | | | | | | | X | |

## Table 1. Study Flow Chart

ECG = electrocardiogram; eDiary = electronic diary; GERD = gastroesophageal reflux disease; GSQ-I = GERD Symptom Questionnaire in Infants.

a. All screening procedures were conducted within 2 weeks before test article administration at Week 0. If necessary, an infant who was being treated with a proton pump inhibitor (PPI) or histamine$_2$ receptor antagonist ($H_2RA$) could have an initial GSQ-I ≤16; such an infant could have an additional 2 week's screening for washout of prior acid suppressants. Results of screening test (except serum gastrin) had to have been available before random assignment.

b. A final visit was conducted after the last study-related procedure was performed or any time a subject withdrew or was withdrawn by the Investigator.

c. All visits during the screening period, treatment period (with the exception of the Baseline visit) and telephone contacts took place within ±3 days of the study week, as scheduled. The visit schedule was planned so that the subjects completed 28 days +3 days per treatment phase. The date of first dose of test article at Baseline visit (start of open-label phase) and at the random assignment visit (start of double-blind phase) was the reference point.

d. Documentation of all diagnostic tests, which were performed during routine subject care to document the diagnosis of GERD whether or not they supported the diagnosis. These included: pH probe, gastroesophageal endoscopy, esophageal histology, radionuclide milk study, and upper gastrointestinal (GI) series.

e. Complete physical examination included growth parameters (weight, height/length, head circumference) as well as review of body systems including respiratory, cardiovascular, GI, and musculoskeletal.

f. Vital signs including tympanic or core temperature, supine blood pressure, supine pulse rate, and supine respiration rate.

g. The prestudy GSQ-I was performed at Visit 1 and Visit 2 to fulfill inclusion and exclusion criteria (subjects must have had a Score >16).

h. Routine laboratory test evaluations included hematology, blood chemistry, optional urinalysis, and an optional serum gastrin.

i. For Baseline assessment, the optional serum gastrin specimen (performed after a 3-4 hour fast, if possible) and ECG could have been obtained at either Week –2 or Week 0. Tests were completed before the first dose of test article.

j. Subjects started taking open-label pantoprazole the day of Visit 2 (ie, Day 1 of Week 0) and restarted taking test article the day after Visit 4 (ie, Day 1 of Week 5).

k. At Visits 3, 4, 5, and 6 used and unused pouches of test article were collected and compliance assessed; in addition the amount of study antacid was assessed.

l. Parents returned empty bottles to receive a new bottle. At the end of treatment, all bottles were returned to the site. Empty and partial bottles were discarded after drug accountability was completed. At the end of the study, any remaining unopened bottles were returned to Sponsor.

m. Review eDiary only.

**Number of Subjects (Planned and Analyzed):** A total of 154 subjects with symptomatic GERD were screened for the study and a total of 129 subjects entered the study and received at least 1 dose of study medication with 69 in the US; 25 in South Africa; 13 in Spain; 11 in Poland; 6 in Canada; 2 each in Belgium and Latvia. .One subject had a protocol violation so the number of subjects who entered the open-label population were 128 subjects.

**Diagnosis and Main Criteria for Inclusion:** Male and female term or post term infants beyond the neonatal period of an age >28 days but ≤11 months, with clinical diagnosis of GERD and weight >2.5 kg or ≤15 kg were enrolled in the study. Subjects with a known history of upper gastrointestinal anatomic disorders, history of acute life-threatening medical conditions, or clinically significant medical conditions or laboratory abnormalities were excluded from the study.

**Study Treatment:** Study medication was provided as pouches containing 5-mg and 10-mg pantoprazole sodium delayed-release granules for oral suspension, using an inactive powder blend and mixing with water. Placebo was provided as granules for oral suspension in pouches.

During the screening phase, all subjects received 2 weeks of conservative treatment (hypoallergenic formula with rice cereal, instructions on feeding and positioning). At the beginning of the 4-week open-label phase, subjects were assigned by their weight to receive either 5- or 10-mg pantoprazole granules for suspension to achieve a daily dose of approximately 1.2 mg/kg. Upon completion of the open-label phase, eligible subjects were randomly assigned in a 1:1 ratio to receive either pantoprazole oral suspension (1.2 mg/kg) or matching placebo daily and stratified by weight. Study medication was to be administered at least 30 minutes before the morning meal.

**Efficacy Endpoints:**

Primary Endpoint: The primary endpoint was the withdrawal rate due to lack of efficacy during the placebo-controlled withdrawal phase. Lack of efficacy was defined as 1 or more of the following:

- Significant worsening of GERD symptoms frequency (ie, weekly GERD symptom score [WGSS] returned to Baseline or above on 2 consecutive weekly evaluations not related to an intercurrent illness). The WGSS was derived as the sum of the 5 selected individual GERD symptom weekly mean frequencies or;
- A diagnostic test such as endoscopy demonstrating worsening of esophagitis or;
- Maximal antacid use for ≥7 days continuous days or;
- Severe GERD symptoms based on physician's judgment not related to intercurrent illness as documented at an unscheduled or scheduled visit.

Secondary Endpoints:

- Time to withdrawal due to lack of efficacy and time to withdrawal for any reason;
- Individual mean frequency for each symptom;
- The amount of antacid taken during each week as well as number of subjects taking antacids;
- Results of endoscopic and histologic assessments, if performed, as standard of care (ie, not study required);
- Respiratory symptoms, eg, frequency of cough, aspiration, wheezing, stridor, and apnea collected in the eDiary.

**Safety Evaluations:** Throughout the study, routine safety and tolerability were evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, height and weight, 12-lead electrocardiogram (ECG) recordings, and clinical laboratory test results.

**Statistical Methods:** Efficacy data was analyzed separately for the open-label treatment run-in phase and the double-blind placebo-controlled treatment-withdrawal phases. Three efficacy populations were defined as follows:

- The open-label (OL) population during the treatment run-in phase consisted of all the subjects who took at least 1 non-zero dose of study medication in the open-label treatment run-in phase. The population for efficacy analyses during the open-label treatment run-in phase was the OL population.
- The modified intent-to-treat (mITT) population for the double-blind, placebo-controlled treatment-withdrawal phase consisted of all the subjects who completed the 4-week open-label treatment run-in phase (requiring at least 21 days on test article during the open-label treatment run-in phase), were randomized into the double-blind placebo-controlled treatment-withdrawal phase, and took at least 1 non-zero dose of double-blind treatment. This was the primary population for efficacy analyses during the double-blind, placebo-controlled treatment-withdrawal phase.
- The Valid for Efficacy (VFE)-1 population comprised a subset of the mITT that included: subjects with at least 80% compliance with study medication during the double-blind, placebo-controlled treatment-withdrawal phase, and subjects that did not violate the protocol in a major way. The VFE-2 population, a subset of the VFE-1 population, had 1 additional characteristic, including subjects who were at least 80% compliant with recording eDiary symptoms in the open-label phase.

For the primary efficacy endpoint, the withdrawal rate due to lack of efficacy for each treatment group was defined as the ratio of the number of subjects who withdrew due to lack of efficacy during the double-blind phase over the total number of subjects who entered into

the double-blind phase. Withdrawal rates between treatment groups were compared by a Fisher exact test.

For secondary endpoints, a paired t-test was used for within-group comparison of change from Baseline to the end of the open-label phase, Baseline to the end of the double-blind phase, and from the end of the open-label phase to the end of double-blind phase. For the treatment-withdrawal phase, the changes from Baseline to the end of double-blind phase were analyzed by an analysis of covariance (ANCOVA) that included treatment and age group (≤6 months, >6 months) as factors and antacid use and the value of the endpoint at the end of the open-label phase as covariates. For time to event data, Kaplan-Meier estimates and p-values from the log-rank test were reported.

The safety population consisted of all the subjects who took at least 1 non-zero dose of study medication. The number of subjects with adverse events (AEs), treatment-emergent AEs (TEAEs), abnormal or potentially clinically important (PCI) laboratory test results and vital sign measurements were summarized and compared by treatment group, if appropriate, using a Fisher exact test.

**RESULTS**

**Subject Disposition and Demography:** The subject disposition is presented in Table 2. Due to 1 subject with a protocol violation, the number of subjects in the open-label population was 128.

## Table 2. Subject Disposition

| Characteristic | Total Subjects (N=154) n (%) |
|---|---|
| All screening subjects | 154 (100) |
| Screen failure | 25 (16.2) |
| Safety population | 129 (83.8) |
| Open label population | 128 (83.1) |
| Open label withdrawal | 21 (13.6) |
| Adverse event | 4 (2.6) |
| Failed to return | 1 (0.6) |
| Investigator request | 1 (0.6) |
| Noncompliance | 9 (5.8) |
| Parent/legal guardian request | 4 (2.6) |
| Protocol violation | 1 (0.6) |
| Unsatisfactory response - efficacy | 1 (0.6) |
| Randomized population | 108 (70.1) |
| Modified intent-to-treat population | 106 (68.8) |
| Study completed in double blind phase | 88 (57.1) |
| Double blind withdrawal | 20 (13) |
| Failed to return | 1 (0.6) |
| Noncompliance | 2 (1.3) |
| Parent/legal guardian request | 1 (0.6) |
| Protocol violation | 4 (2.6) |
| Unsatisfactory response - efficacy | 12 (7.8) |
| Valid for efficacy 1 population | 96 (62.3) |
| Valid for efficacy 2 population | 77 (50.0) |

Percentages are based on the total number of subjects screened.
N = total number of subjects; n = number of subjects meeting criteria.

Demographic characteristics are presented in Table 3.

## Table 3. Demographic and Baseline Characteristics – mITT Population

| Characteristic | Double-Blind Treatment | | |
|---|---|---|---|
| | Pantoprazole 1.2 mg/kg N=52 | Placebo N=54 | Total N=106 |
| Type of birth n (%) | | | |
| Full term (≥37 weeks) | 43 (82.69) | 44 (81.48) | 87 (82.08) |
| Preterm (<37 weeks) | 9 (17.31) | 10 (18.52) | 19 (17.92) |
| Age (month) | | | |
| Mean | 5.15 | 5.04 | 5.09 |
| Standard deviation | 2.81 | 2.81 | 2.8 |
| Minimum | 1.3 | 1 | 1 |
| Maximum | 11.7 | 12 | 12 |
| Sex, n (%) | | | |
| Female | 18 (34.62) | 20 (37.04) | 38 (35.85) |
| Male | 34 (65.38) | 34 (62.96) | 68 (64.15) |

mITT = modified intent-to-treat; N = total number of subjects; n = number of subjects in each observation.

**Efficacy Results:**

Primary Efficacy Endpoint - Withdrawal due to Lack of Efficacy: A comparison of withdrawal rates for lack of efficacy during the double-blind phase are shown in Table 4 for the mITT population. There was no difference between treatment groups in withdrawal rates due to lack of efficacy.

**Table 4. Summary of Actual Withdrawal due to Lack of Efficacy During the Double-Blind Phase – mITT Population**

| Double-Blind Treatment | Event[a]/Total | Percent | p-Value[b] (Pantoprazole vs Placebo) |
|---|---|---|---|
| Placebo | 6/54 | 11 | 1.000 |
| Pantoprazole | 6/52 | 12 | |

mITT = modified intent-to-treat; vs = versus.

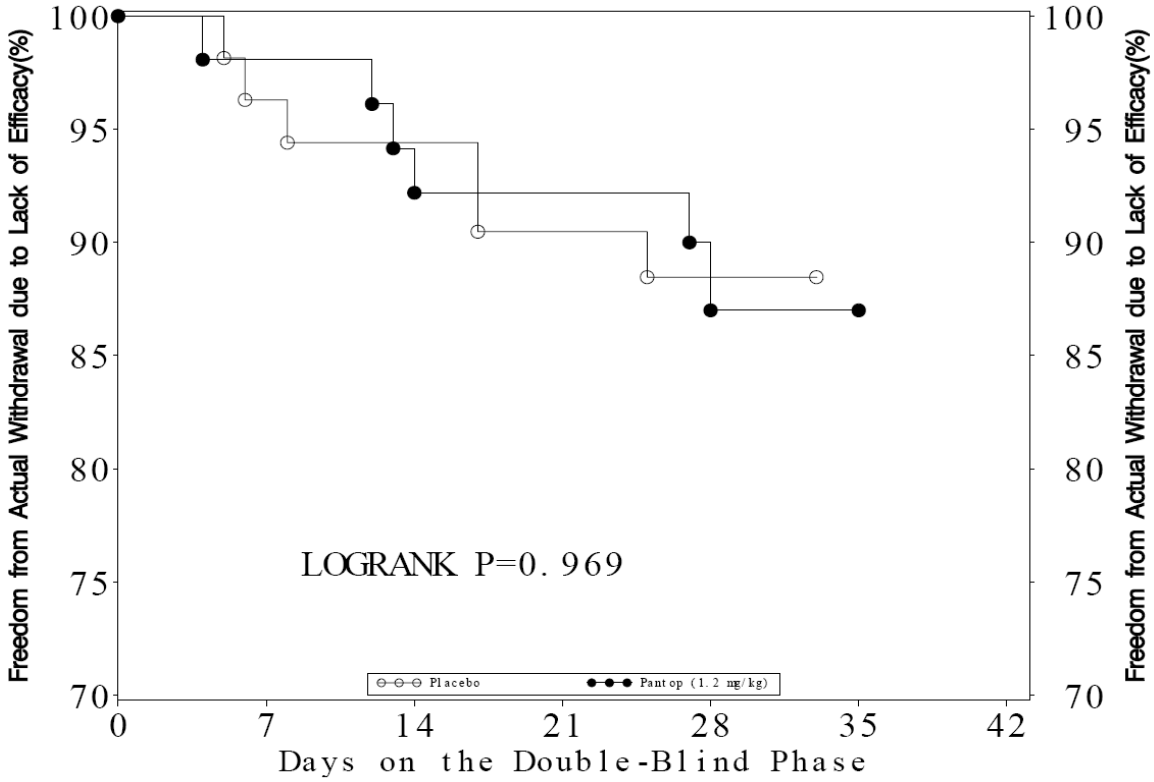
a. An event was defined as a subject who withdrew from the study due to lack of efficacy. Subjects were allowed to withdraw at final week if they met withdrawal criteria.

b. p-Value obtained from the 2-sided Fisher exact test.

Secondary Efficacy Endpoints:

Time to Withdrawal due to Lack of Efficacy: The estimated time to withdrawal from the study due to lack of efficacy is presented for the mITT population in Figure 1. There was no significant difference between the pantoprazole-treated subjects and the placebo-treated subjects in the time to withdrawal due to a lack of efficacy of the study medication.

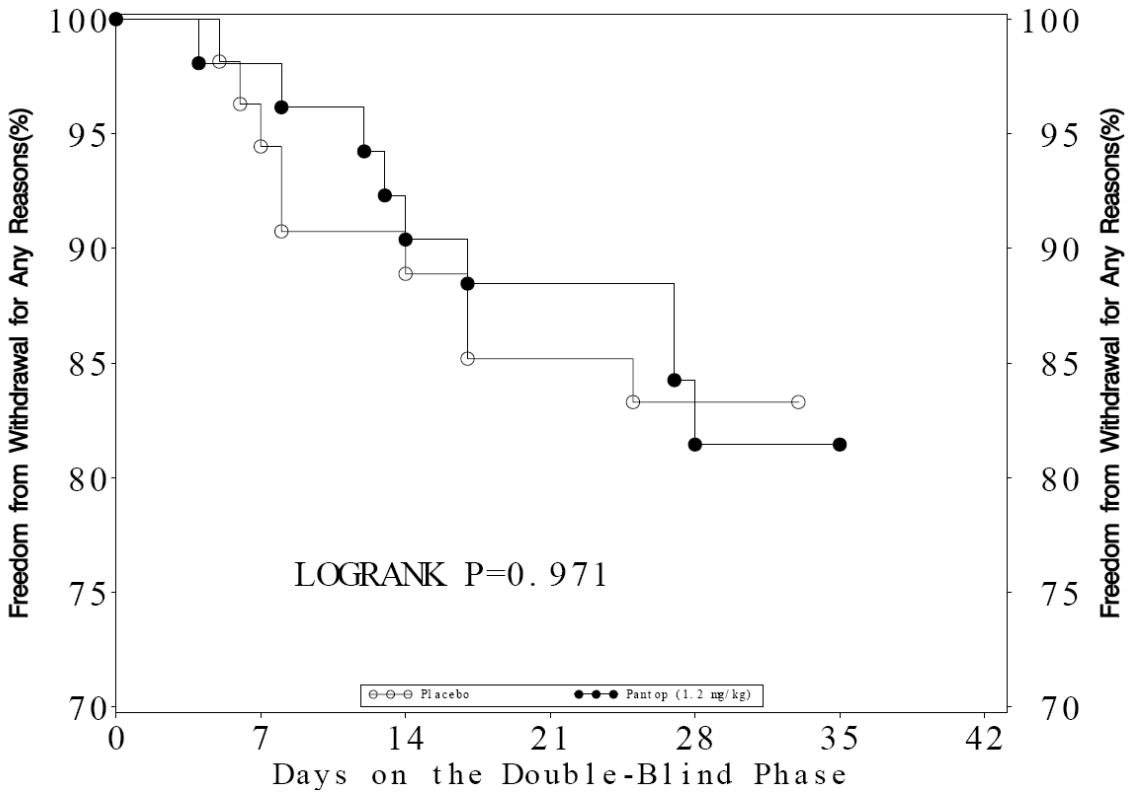
**Figure 1. Kaplan-Meier Plot of Time to Actual Withdrawal due to Lack of Efficacy During the Double-Blind Phase – mITT Population**




mITT = modified intent-to-treat; Pantop = pantoprazole.

Time to Withdrawal for Any Reason: The Kaplan-Meier estimates and log-rank tests compared the 2 treatment groups by the time to withdrawal from the study for any reason during the double-blind phase, as presented in Figure 2. The time to withdrawal for any reason was similar between the 2 treatment groups.

**Figure 2. Kaplan-Meier Plot of Time to Withdrawal for any Reason During the Double-Blind Phase – mITT Population**




mITT = modified intent-to-treat; Pantop = pantoprazole.

WGSS and Individual Mean Frequency for Each Symptom: Between-group comparisons of the change from Baseline in WGSS are summarized in Table 7 for the mITT population.

**Table 5. Descriptive Statistics and Between-Treatment Comparison for Change From Baseline in Weekly GERD Symptom Score During the Double-Blind Phase – mITT Population**

| Study Week | Treatment | N | Mean (SD) | Change From Baseline | | |
|---|---|---|---|---|---|---|
| | | | | LS Mean (SE) | LS Mean Diff (SE) (Pantop-Placebo) | p-Value |
| Week -1 (Baseline) | Placebo | 54 | 5.25 (2.928) | | | |
| | Pantop (1.2 mg/kg) | 52 | 5.72 (2.727) | | | |
| Week 4 (open-label) | Placebo | 54 | 3.44 (2.366) | | | |
| | Pantop (1.2 mg/kg) | 52 | 3.55 (2.437) | | | |
| Week 5 (double-blind) | Placebo | 54 | 3.60 (2.444) | -1.76 (0.309) | -0.71 (0.416) | 0.092 |
| | Pantop (1.2 mg/kg) | 52 | 3.29 (2.315) | -2.47 (0.307) | | |
| Week 6 (double-blind) | Placebo | 54 | 3.16 (2.215) | -2.24 (0.342) | -0.33 (0.460) | 0.482 |
| | Pantop (1.2 mg/kg) | 52 | 3.22 (2.353) | -2.57 (0.340) | | |
| Week 7 (double-blind) | Placebo | 54 | 2.91 (1.874) | -2.56 (0.331) | 0.04 (0.446) | 0.924 |
| | Pantop (1.2 mg/kg) | 52 | 3.31 (2.300) | -2.52 (0.329) | | |
| Week 8 (double-blind) | Placebo | 54 | 2.86 (2.095) | -2.61 (0.364) | -0.02 (0.490) | 0.960 |
| | Pantop (1.2 mg/kg) | 52 | 3.19 (2.594) | -2.63 (0.362) | | |
| Final week (double-blind) | Placebo | 54 | 2.88 (1.976) | -2.59 (0.361) | 0.08 (0.486) | 0.865 |
| | Pantop (1.2 mg/kg) | 52 | 3.31 (2.572) | -2.51 (0.359) | | |

Weekly GERD Symptom Score was defined as the sum of the 5 weekly mean frequency scores for GERD Questions 1a, 2b, 3a, 4a and Max (5a, 5b).
Final week was the last 7 days of symptom scores collected during the double-blind phase.
LS Mean and p-value were obtained from the ANCOVA model (change = baseline age group + Week 4 symptom score + Week 4 antacid intake + treatment).
ANCOVA = analysis of covariance; GERD = gastroesophageal reflux disease; LS = least square; mITT = modified intent-to-treat; N = number of subjects; pantop = pantoprazole; SD = standard deviation; SE = standard error.

The number and percentage of subjects with 5 selected GERD symptoms are provided in Table 6 for the mITT population in the double-blind phase.

**Table 6. Number (%) of Subjects With GERD Symptom by Week in Double-Blind Phase – mITT Population**

| Week | Symptom | Placebo n/N (%) | Pantoprazole n/N (%) |
|---|---|---|---|
| Week 5 | Vomiting/regurgitation - Q:1a | 53/54 (98.1) | 52/52 (100.0) |
| | Irritability/fussiness - Q:2b | 37/54 (68.5) | 32/52 (61.5) |
| | Choking/gagging - Q:3a | 33/54 (61.1) | 22/52 (42.3) |
| | Arching back - Q:4a | 33/54 (61.1) | 30/52 (57.7) |
| | Refusal to feed - maximum (5a, 5b) | 33/54 (61.1) | 32/52 (61.5) |
| Week 6 | Vomiting/regurgitation - Q:1a | 46/49 (93.9) | 48/50 (96.0) |
| | Irritability/fussiness - Q:2b | 31/49 (63.3) | 26/50 (52.0) |
| | Choking/gagging - Q:3a | 24/49 (49.0) | 24/50 (48.0) |
| | Arching back - Q:4a | 29/49 (59.2) | 27/50 (54.0) |
| | Refusal to feed - maximum (5a, 5b) | 22/49 (44.9) | 30/50 (60.0) |
| Week 7 | Vomiting/regurgitation - Q:1a | 46/47 (97.9) | 44/47 (93.6) |
| | Irritability/fussiness - Q:2b | 26/47 (55.3) | 28/47 (59.6) |
| | Choking/gagging - Q:3a | 27/47 (57.4) | 23/47 (48.9) |
| | Arching back - Q:4a | 22/47 (46.8) | 26/47 (55.3) |
| | Refusal to feed - maximum (5a, 5b) | 23/47 (48.9) | 25/47 (53.2) |
| Week 8 | Vomiting/regurgitation - Q:1a | 40/45 (88.9) | 40/45 (88.9) |
| | Irritability/fussiness - Q:2b | 24/45 (53.3) | 21/45 (46.7) |
| | Choking/gagging - Q:3a | 22/45 (48.9) | 19/45 (42.2) |
| | Arching back - Q:4a | 22/45 (48.9) | 22/45 (48.9) |
| | Refusal to feed - maximum (5a, 5b) | 19/45 (42.2) | 23/45 (51.1) |
| Entire DB phase | Vomiting/regurgitation - Q:1a | 53/54 (98.1) | 52/52 (100.0) |
| | Irritability/fussiness - Q:2b | 42/54 (77.8) | 41/52 (78.8) |
| | Choking/gagging - Q:3a | 40/54 (74.1) | 37/52 (71.2) |
| | Arching back - Q:4a | 37/54 (68.5) | 37/52 (71.2) |
| | Refusal to feed - maximum (5a, 5b) | 37/54 (68.5) | 39/52 (75.0) |

DB = double blind; GERD = gastroesophageal reflux disease; N = number of subjects evaluated; n = number of subjects meeting criteria; Q = question.

Amount of Antacid Taken During Each Week: The change from Baseline in the amount of antacid taken weekly is summarized and compared between treatment groups during the double-blind phase in the mITT population in Table 7. There were no statistically significant differences between the treatment groups.

**Table 7. Descriptive Statistics and Between Treatment Comparison for Change From Baseline in Amount (mL) of Study Antacid Taken Weekly During the Double-Blind Phase – mITT Population**

| Study Week | Double-Blind Treatment | N | Mean (SD) | Change From Baseline | | |
|---|---|---|---|---|---|---|
| | | | | LS Mean[a] (SE) | LS Mean Diff (SE) (Pantop-Placebo) | p-Value[a] |
| Week -1 (baseline) | Placebo | 54 | 13.45 (18.428) | | | |
| | Pantoprazole | 52 | 13.33 (17.802) | | | |
| Week 4 (open-label) | Placebo | 54 | 6.62 (11.695) | | | |
| | Pantoprazole | 52 | 7.99 (14.173) | | | |
| Week 5 (double-blind) | Placebo | 54 | 6.33 (11.752) | -7.09 (2.169) | 0.61 (2.934) | 0.836 |
| | Pantoprazole | 52 | 6.88 (12.177) | -6.48 (2.164) | | |
| Week 6 (double-blind) | Placebo | 51 | 5.70 (11.028) | -7.59 (2.460) | 0.13 (3.325) | 0.969 |
| | Pantoprazole | 51 | 6.08 (11.205) | -7.47 (2.424) | | |
| Week 7 (double-blind) | Placebo | 48 | 5.21 (9.769) | -7.58 (2.532) | -0.29 (3.469) | 0.934 |
| | Pantoprazole | 47 | 6.17 (13.241) | -7.87 (2.535) | | |
| Week 8 (double-blind) | Placebo | 46 | 4.09 (7.819) | -8.63 (2.514) | -0.71 (3.430) | 0.838 |
| | Pantoprazole | 46 | 5.06 (10.893) | -9.34 (2.485) | | |

ANCOVA = analysis of covariance; diff = difference; LS Mean = least squares mean; mITT = modified intent-to-treat; Pantop = pantoprazole; SD = standard deviation; SE = standard error.

a. LS mean and p-value are obtained from the ANCOVA model (change = baseline age group + Week 4 antacid intake + treatment).

Number of Subjects Taking Antacids During Each Week: The number and percentage of subjects using antacids weekly during the double-blind phase are summarized in Table 8 for subjects in the mITT population. The number of subjects taking study antacid decreased from Baseline to Week 8 in each of the treatment groups.

**Table 8. Summary of Number of Subjects Taking Study Antacid Weekly – mITT Population**

| Study Week | Double-Blind Treatment | | | | p-Value[a] (Pantoprazole vs Placebo) |
|---|---|---|---|---|---|
| | Placebo | | Pantoprazole 1.2 mg/kg | | |
| | Event/Total | Percent | Event/Total | Percent | |
| Week -1 (baseline) | 33/54 | 61.11 | 37/52 | 71.15 | 0.310 |
| Week 1 (open-label) | 32/54 | 59.26 | 37/52 | 71.15 | 0.226 |
| Week 2 (open-label) | 25/54 | 46.30 | 31/52 | 59.62 | 0.180 |
| Week 3 (open-label) | 26/54 | 48.15 | 28/52 | 53.85 | 0.567 |
| Week 4 (open-label) | 25/54 | 46.30 | 27/52 | 51.92 | 0.698 |
| Week 5 (double-blind) | 27/54 | 50.00 | 28/52 | 53.85 | 0.703 |
| Week 6 (double-blind) | 26/51 | 50.98 | 22/51 | 43.14 | 0.552 |
| Week 7 (double-blind) | 18/48 | 37.50 | 21/47 | 44.68 | 0.535 |
| Week 8 (double-blind) | 15/46 | 32.61 | 18/46 | 39.13 | 0.664 |

mITT = modified intent-to-treat; vs = versus.

a. p-Value was obtained from the 2-sided Fisher exact test.

Results of Endoscopic and Histologic Assessments: No endoscopic or histologic examinations were performed in subjects during the double-blind phase.

Respiratory Symptoms: Respiratory symptoms were not balanced between groups at Baseline. More subjects had cough without a cold and noisy breathing in the pantoprazole 1.2 mg/kg group than in the placebo group. Parents did not differentiate well between

different types of noisy breathing. Contrary to expectations, noisy breathing when breathing out did not correlate with wheezing nor did noisy breathing when breathing in correlate with croupy or barky sound. The improvement in symptoms in the pantoprazole 1.2 mg/kg group was greatest at Week 4, but little change was observed thereafter. Wheezing and croupy cough were similar in both groups. Apnea was very uncommon and unchanged with treatment.

**Safety Results:** TEAEs reported during the open-label phase are summarized in Table 9. A total of 84 subjects (65.6%) had 1 or more TEAEs during the open-label phase. The most common TEAEs were upper respiratory infection, fever, and diarrhea. Other TEAEs that occurred in at least 5% of subjects were otitis media, rhinitis, oral moniliasis, vomiting, and cough increased.

## Table 9. Number (%) of Subjects Reporting Adverse Events During Open-Label Phase – Open-Label Population

| Body System<br>Adverse Event[a] | Sex[b] | Pantoprazole (1.2 mg/kg)<br>N=128<br>N (M)=80 |
|---|---|---|
| Any adverse event | | 84 (65.6) |
| Body as a whole | | 19 (14.8) |
| Abdominal pain | | 1 (0.8) |
| Accidental injury | | 1 (0.8) |
| Fever | | 13 (10.2) |
| Flu syndrome | | 1 (0.8) |
| Hernia | | 1 (0.8) |
| Infection | | 4 (3.1) |
| Injection site reaction | | 1 (0.8) |
| Lab test abnormal | | 1 (0.8) |
| Digestive system | | 36 (28.1) |
| Anorexia | | 3 (2.3) |
| Constipation | | 5 (3.9) |
| Diarrhea | | 13 (10.2) |
| Flatulence | | 1 (0.8) |
| Gastroenteritis | | 2 (1.6) |
| Gastroesophageal reflux disease | | 4 (3.1) |
| Oral moniliasis | | 7 (5.5) |
| Tooth disorder | | 5 (3.9) |
| Vomiting | | 7 (5.5) |
| Metabolic and nutritional | | 4 (3.1) |
| Alkaline phosphatase increased | | 1 (0.8) |
| Creatine phosphokinase increased | | 1 (0.8) |
| Dehydration | | 1 (0.8) |
| Failure to thrive | | 1 (0.8) |
| SGOT increased | | 1 (0.8) |
| SGPT increased | | 1 (0.8) |
| Musculoskeletal system | | 1 (0.8) |
| Muscle cramp | | 1 (0.8) |
| Nervous system | | 6 (4.7) |
| Agitation | | 1 (0.8) |
| Anxiety | | 1 (0.8) |
| Emotional lability | | 2 (1.6) |
| Nervousness | | 1 (0.8) |
| Sleep disorder | | 1 (0.8) |
| Respiratory system | | 46 (35.9) |
| Asthma | | 1 (0.8) |
| Bronchiolitis | | 3 (2.3) |
| Cough increased | | 7 (5.5) |
| Dyspnea | | 1 (0.8) |
| Nasal septum disorder | | 1 (0.8) |
| Pharyngitis | | 2 (1.6) |
| Rhinitis | | 11 (8.6) |
| Sinus congestion | | 1 (0.8) |
| Sinusitis | | 3 (2.3) |
| Upper respiratory infection | | 25 (19.5) |
| Wheezing | | 1 (0.8) |
| Skin and appendages | | 26 (20.3) |
| Contact dermatitis | | 5 (3.9) |

**Table 9. Number (%) of Subjects Reporting Adverse Events During Open-Label Phase – Open-Label Population**

| Body System<br>Adverse Event[a] | Sex[b] | Pantoprazole (1.2 mg/kg)<br>N=128<br>N (M)=80 |
|---|---|---|
| Cutaneous moniliasis | | 5 (3.9) |
| Eczema | | 5 (3.9) |
| Erythema | | 2 (1.6) |
| Fungal dermatitis | | 5 (3.9) |
| Maculopapular rash | | 1 (0.8) |
| Miliaria | | 1 (0.8) |
| Rash | | 4 (3.1) |
| Seborrhea | | 1 (0.8) |
| Skin disorder | | 1 (0.8) |
| Special senses | | 14 (10.9) |
| Conjunctivitis | | 2 (1.6) |
| Otitis media | | 12 (9.4) |
| Urogenital system | | 1 (0.8) |
| Testis disorder | M | 1 (1.3) |

Adverse events and serious adverse events are not separated out in the table.
F = female; M = male; N = total number of subjects; SGOT = aspartate aminotransferase (formerly known as serum glutamicoxaloacetic transaminase); SGPT = alanine aminotransferase (formerly known as serum glutamic-pyruvic transaminase).

a. Body system totals are not necessarily the sum of the individual adverse events since a subject may have reported 2 or more different adverse events in the same body system.
b. F, M, or blank indicates the calculation is based on subjects of either female only, male only, or both.

TEAEs reported during the double-blind phase are summarized in Table 10. Altogether, 49 subjects (45.4%) had 1 or more TEAEs during the double- blind phase, including 25 subjects (46.3%) from the pantoprazole 1.2 mg/kg group and 24 subjects (44.4%) from the placebo group. The most common TEAE was upper respiratory infection. Other TEAEs that occurred in at least 5% of subjects in the pantoprazole 1.2 mg/kg group were fever, otitis media, vomiting, and creatine phosphokinase increased. The only TEAE other than upper respiratory infection reported in >5% of subjects in the placebo group was cough increased.

## Table 10. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events During the Double-Blind Phase – Randomized Subjects

| Body System<br>Adverse Event[a] | Overall p-Value[b] | Double-Blind Treatment<br>Pantoprazole 1.2 mg/kg N=54 | <br>Placebo N=54 |
|---|---|---|---|
| Any adverse event | 1.000 | 25 (46.3) | 24 (44.4) |
| Body as a whole | 1.000 | 5 (9.3) | 6 (11.1) |
| Accidental injury | 1.000 | 1 (1.9) | 2 (3.7) |
| Fever | 0.618 | 3 (5.6) | 1 (1.9) |
| Flu syndrome | 1.000 | 1 (1.9) | 0 |
| Infection | 1.000 | 0 | 1 (1.9) |
| Lab test abnormal | 1.000 | 0 | 1 (1.9) |
| Moniliasis | 1.000 | 0 | 1 (1.9) |
| Digestive system | 1.000 | 7 (13.0) | 7 (13.0) |
| Anorexia | 1.000 | 1 (1.9) | 1 (1.9) |
| Constipation | 1.000 | 1 (1.9) | 2 (3.7) |
| Diarrhea | 1.000 | 2 (3.7) | 1 (1.9) |
| Oral moniliasis | 1.000 | 1 (1.9) | 0 |
| Tooth disorder | 0.495 | 0 | 2 (3.7) |
| Vomiting | 1.000 | 3 (5.6) | 2 (3.7) |
| Metabolic and nutritional | 0.243 | 3 (5.6) | 0 |
| Creatine phosphokinase increased | 0.243 | 3 (5.6) | 0 |
| Dehydration | 1.000 | 1 (1.9) | 0 |
| Hyperlipidemia | 1.000 | 1 (1.9) | 0 |
| Musculoskeletal system | 1.000 | 1 (1.9) | 0 |
| Muscle cramp | 1.000 | 1 (1.9) | 0 |
| Nervous system | 0.618 | 3 (5.6) | 1 (1.9) |
| Anxiety | 1.000 | 0 | 1 (1.9) |
| Emotional lability | 1.000 | 1 (1.9) | 0 |
| Sleep disorder | 1.000 | 1 (1.9) | 0 |
| Twitching | 1.000 | 1 (1.9) | 0 |
| Respiratory system | 0.817 | 13 (24.1) | 11 (20.4) |
| Asthma | 1.000 | 0 | 1 (1.9) |
| Bronchiolitis | 1.000 | 1 (1.9) | 1 (1.9) |
| Cough increased | 0.678 | 2 (3.7) | 4 (7.4) |
| Laryngitis | 0.495 | 2 (3.7) | 0 |
| Pharyngitis | 1.000 | 1 (1.9) | 0 |
| Rhinitis | 1.000 | 1 (1.9) | 0 |
| Tachypnoea | 1.000 | 0 | 1 (1.9) |
| Upper respiratory infection | 1.000 | 7 (13.0) | 7 (13.0) |
| Wheezing | 1.000 | 0 | 1 (1.9) |
| Skin and appendages | 0.776 | 6 (11.1) | 8 (14.8) |
| Contact dermatitis | 0.495 | 2 (3.7) | 0 |
| Cutaneous moniliasis | 1.000 | 1 (1.9) | 1 (1.9) |
| Eczema | 1.000 | 0 | 1 (1.9) |
| Erythema | 1.000 | 0 | 1 (1.9) |
| Furunculosis | 1.000 | 0 | 1 (1.9) |
| Impetigo | 1.000 | 0 | 1 (1.9) |
| Miliaria | 1.000 | 0 | 1 (1.9) |
| Rash | 1.000 | 2 (3.7) | 2 (3.7) |
| Seborrhea | 1.000 | 1 (1.9) | 0 |
| Special senses | 0.618 | 3 (5.6) | 1 (1.9) |
| Conjunctivitis | 1.000 | 0 | 1 (1.9) |

**Table 10. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events During the Double-Blind Phase – Randomized Subjects**

| Body System<br>Adverse Event[a] | Overall p-Value[b] | Double-Blind Treatment<br>Pantoprazole 1.2 mg/kg N=54 | Placebo N=54 |
|---|---|---|---|
| Otitis media | 0.243 | 3 (5.6) | 0 |
| Urogenital system | 0.495 | 0 | 2 (3.7) |
| Urinary tract infection | 0.495 | 0 | 2 (3.7) |

Adverse events and serious adverse events are not separated out in the table.
N = total number of subjects.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject may have reported 2 or more different adverse events in the same body system.
b. Fisher exact test p-value (2-tailed).

During the open-label phase, 12 (9.4%) subjects had 1 or more TEAEs that were considered to be related to study medication. In the double-blind phase, 5 subjects in the pantoprazole 1.2 mg/kg group and 1 subject in the placebo group had 1 or more TEAEs that were considered to be related to study medication. An overall summary of treatment-related TEAEs is provided in Table 11.

**Table 11. Number (%) of Subjects Reporting Treatment-Emergent, Treatment-Related Adverse Events - Safety Population**

| Body System[a]<br>Adverse Event | Total Subjects<br>N=129<br>N (F)=48<br>N (M)=81 |
|---|---|
| Any adverse event | 16 (12.4) |
| Body as a whole | 2 (1.6) |
| Fever | 1 (0.8) |
| Lab test abnormal | 1 (0.8) |
| Digestive system | 12 (9.3) |
| Anorexia | 5 (3.9) |
| Constipation | 1 (0.8) |
| Diarrhea | 5 (3.9) |
| Gastroenteritis | 1 (0.8) |
| Vomiting | 4 (3.1) |
| Metabolic and nutritional | 5 (3.9) |
| Creatine phosphokinase increased | 3 (2.3) |
| Dehydration | 2 (1.6) |
| Hyperlipemia | 1 (0.8) |
| SGOT increased | 2 (1.6) |
| SGPT increased | 2 (1.6) |
| Nervous system | 5 (3.9) |
| Anxiety | 1 (0.8) |
| Emotional lability | 1 (0.8) |
| Sleep disorder | 2 (1.6) |
| Twitching | 1 (0.8) |
| Respiratory system | 2 (1.6) |
| Cough increased | 1 (0.8) |
| Upper respiratory infection | 1 (0.8) |
| Skin and appendages | 3 (2.3) |
| Contact dermatitis | 1 (0.8) |
| Rash | 1 (0.8) |
| Seborrhea | 1 (0.8) |

Adverse events and serious adverse events are not separated out in the table.
F = female; M = male; N = total number of subjects; SGOT = aspartate aminotransferase (formerly known as serum glutamicoxaloacetic transaminase); SGPT = alanine aminotransferase (formerly known as serum glutamic-pyruvic transaminase).
a. Body system totals are not necessarily the sum of the individual adverse events since a subject may have reported 2 or more different adverse events in the same body system.

Overall, 8 subjects had a total of 11 serious adverse events (SAEs) at some time during the study, including screening and follow-up, as shown in Table 12.

**Table 12. Serious Adverse Events**

| Serial No. | Body System | Adverse Event (Verbatim) | Treatment-Related | Phase in Which Event Occurred |
|---|---|---|---|---|
| 1 | Metabolic and nutritional | Failure to thrive | No | Open-label |
| | Metabolic and nutritional | Poor weight gain | No | Follow-up |
| 2 | Respiratory system | Status asthmaticus | No | Double-blind |
| 3 | Cardiovascular system | Syncope | No | Follow-up |
| 4 | Respiratory system | Croup | No | Screening |
| | Digestive system | Worsening of GERD | No | Open-label |
| 5 | Respiratory system | Bronchiolitis | No | Follow-up |
| | Special senses | Otitis media | No | Follow-up |
| 6 | Respiratory system | Bronchiolitis | No | Open-label |
| 7 | Digestive system | Worsening of GERD | No | Screening |
| 8 | Digestive system | Gastroenteritis viral | No | Open-label |

GERD = gastroesophageal reflux disease; No. = number.

A total of 5 subjects withdrew from the study because of AEs, 4 during the open-label phase and 1 during the double-blind phase, as presented in the Table 13.

**Table 13. Subjects Reporting Adverse Events Causing Withdrawal From the Study**

| Serial No. | Body System | Adverse Event (Verbatim) | Treatment-Related | Phase in Which Event Occurred |
|---|---|---|---|---|
| 1 | Nervous system | Sleep problems | Yes | Double-blind |
| 2 | Nervous system | Emotional lability | Yes | Open-label |
| 3 | Digestive system | Worsening of GERD | No | Open-label |
| 4 | Digestive system | Worsening of GERD | No | Open-label |
| 5 | Digestive system | Diarrhea | Yes | Open-label |

GERD = gastroesophageal reflux disease; No. = number.

No subjects died during the study.

Laboratory test results did not reveal any treatment-related abnormalities. The medical monitor reviewed all of the AEs and clinical test findings and did not identify any safety signal.

**CONCLUSIONS:** Pantoprazole sodium 1.2 mg/kg was effective in reducing symptoms of GERD in infants with a clinical diagnosis of GERD. After 4 weeks of treatment, the majority of subjects treated with placebo along with conservative treatment and rescue antacids continued to do well and were indistinguishable from those who continued treatment with pantoprazole 1.2 mg/kg. The impact of time on the maturation of these infants was highly likely to have had an impact on these results.

Pantoprazole was safe and well-tolerated. None of the SAEs and few TEAEs were considered to be related to study drug. Changes in laboratory test results, ECG findings, and vital sign measurements were also considered to be minor, with few considered to be AEs by the Investigators. All infants grew normally during the study with no significant differences between groups.

Future studies should consider focusing on infants with more severe GERD. Symptoms alone may not be sufficient to distinguish physiologic GER from GERD. The lack of correlation between symptoms (measured by GSQ-I and I-GERQ) and objective tests as well as the lack of correlation between pH-metry and endoscopy with biopsy are significant concerns for clinicians, as previously reported.

The results of this study suggest that extensive conservative treatment along with rescue antacids plus possibly a 4 to 5 week course of protocol pump inhibitors (PPIs) may be sufficient for the majority of infants with symptomatic GERD. Subjects with more severe symptoms or failure of conservative treatment might benefit from objective testing to assess their disease and to exclude other disorders such as cow's milk allergy, eosinophilic esophagitis, and infantile colic, which are often confused with GERD. Only infants with clinically significant GERD should be considered for longer term pharmacologic therapy.