U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - PEDIATRIC

NDA/Serial Number:	22-020/SE05
Drug Name:	Protonix (pantoprazole sodium) delay-release granules
Indication(s):	Treatment of Gastroesophageal reflux disease (GERD)
Applicant:	Wyeth Pharmaceuticals, Inc.
Date(s):	Stamp: November 22, 2008; PDUFA: May 21, 2009
Review Priority:	Priority
Biometrics Division:	Division of Biometrics III
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Keywords: clinical pediatric study, NDA review, treatment withdrawal study

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Among the four studies submitted for a pediatric claim, only Study 3001B3-329-WW was adequate and well-controlled for evaluation of efficacy. The other three studies were double-blind, multiple dose studies not designed or sized to establish efficacy.

This study showed that there was no treatment difference between treatment groups as measured by withdrawal rate due to lack of efficacy, the primary endpoint. A likely cause was lack of treatment efficacy, although it is difficult to interpret the reasons for study failure, inadequate sample size could have been a factor. All results from this study should be considered exploratory.

1.2 Brief Overview of Clinical Studies

1.2.1 Study 3001B3-329-WW

This was a multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of pantoprazole in infants aged 1 through 11 months who had symptomatic GERD.

The primary objective of this study was to assess the efficacy of treatment with 1.2 mg/kg pantoprazole granules administered as an oral suspension in patients aged 1 through 11 months.

The secondary objectives were to assess the safety, tolerability, gastroesophageal reflux disease (GERD) symptoms, respiratory symptoms, antacid use, compliance, and growth parameters in infant patients aged 1 through 11months with symptomatic GERD.

Patients who met the following criteria were eligible to participate:

- Male or female term or postterm infants beyond the neonatal period >28 days but <12 months of age, or preterm infants with a corrected age of ≥44 weeks but <12 months at the time the consent was signed.
- Total GSQ-I (baseline total symptom frequency) mean symptom frequency >16 at screening (week -2) and at baseline.
- A clinical diagnosis of suspected, symptomatic, or endoscopically proven GERD.
- Weight ≥2.5 kg and ≤15 kg.
- Able to take test article orally.

Patients participated for 10 weeks. All patients 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. Patients whose symptoms resolved with the conservative treatment during the screening phase were withdrawn. The remaining patients entered a 4-week treatment run-in phase and received open-label oral pantoprazole granules for suspension daily for 4

weeks. Patients received 1.2 mg/kg pantoprazole sodium enteric-coated granules for suspension in 5- or 10-mg doses, depending on patient's body weight.

The primary endpoint was the withdrawal rate due to lack of efficacy during the double-blind treatment-withdrawal phase. Lack of efficacy was defined as 1 or more of the following:

- Significant worsening of GERD symptom frequency (i.e., Weekly GERD Symptom Score [WGSS] returned to baseline or above on 2 consecutive weekly evaluations not related to an intercurrent illness), or
- A diagnostic test such as endoscopy demonstrating the 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.

1.3 Statistical Issues and Findings

Results from Study 3001B3-329-WW showed that there was no difference between treatment groups in withdrawal rate due to lack of efficacy, the pre-specified primary efficacy endpoint,

The sample size was derived from external information for children aged 5 to 11 years old for pantoprazole. It is unclear whether clinical outcomes for older age children (5 to 11 years old) could be extrapolated for those for infants (1 through 11 months).

With the possibility of inadequate sample size, it is very difficult to interpret the results. So, results from this study should be considered "exploratory."

Since this study failed with no treatment difference for primary efficacy endpoint, results from secondary efficacy endpoint should be considered "exploratory."

2. INTRODUCTION

2.1 Overview

Protonix (pantoprazole sodium) delayed-release oral suspension was approved on November 14, 2007. The Pediatric Written Request (PWR) was original issued on December 31, 2001 pantoprazole sodium delayed-release tablets and pantoprazole sodium for injection. The PWR was amended on July 03, 2002, December 18, 2002, May 07, 2004, and March 15, 2006 and most recently revised on May 17, 2007 with a time frame for submission of the response to the PWR of December 31, 2008.

The sponsor has conducted four pediatric clinical studies to evaluate the efficacy of pantoprazole sodium granules, delayed-release tablets, and pantoprazole sodium IV in the pediatric population. These studies were conducted with oral pantorpazole in response to the PWR letter. These studies were conducted in infants 1 through 11 months (study

3001B3-329-WW), children 1 through 11 years (studies 3001B3-328-NA and 3001A1-322-US), and adolescents 12 through 16 years of age (study 3001A1-326-US).

Among four studies, only study 3001B3-329-WW was a double-blinded, placebo-controlled, treatment-withdrawal study. The other three studies did not employ a placebo control but were double-blind studies of the clinical outcomes, safety and tolerability of multiple doses (studies 3001B3-328-NA and 3001A1-322-US) and two doses (20 and 40 mg) (study 3001A1-326-US).

Study 3001A1-322-US: A Multicenter, Randomized, Double-Blind Study of the Safety, Tolerability, and Clinical Outcomes of Multiple Doses (10, 20, and 40 mg) of Oral Pantoprazole in Children (5 to 11 Years Old) with Symptomatic GERD

Study 3001A1-326-US: A Multicenter, Randomized, Double-Blind Study of the Safety, Tolerability, and Clinical Outcomes of 2 Doses (20 and 40 mg) of Oral Pantoprazole in Children (12 to 16 Years Old) with Symptomatic GERD

Study 3001B3-328-NA: A Multicenter, Randomized, Double-Blind Study of the Clinical Outcomes, Safety, Tolerability, and of Multiple Doses of Oral Pantoprazole Sodium Enteric-Coated Spheroids in Children Ages 1 to 5, with Endoscopically Proven Symptomatic GERD

Study 3001B3-329-WW: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Treatment-Withdrawal Study of the efficacy and Safety of Oral Pantoprazole Sodium Enteric-Coated Granules in Infants (1 Through 11 Month) with Symptomatic GERD

Only study 3001B3-329-WW was well-controlled with adequate sample size and will be statistically reviewed. The other three studies might have inadequate sample sizes, since the number of patients was based on regulatory and practical needs and was not set by statistical power.

2.2 Data Sources

In support of the pediatric claim, the sponsor had submitted one pivotal trial designed to compare pantoprazole to placebo:

Study 3001B3-329-WW: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Treatment-Withdrawal Study of the efficacy and Safety of Oral Pantoprazole Sodium Enteric-Coated Granules in Infants (1 Through 11 Month) with Symptomatic GERD

The sponsor submitted the eCTD submission dated November 21, 2008.

3. STATISTICAL EVALUATION

3.1 **Evaluation of Efficacy**

3.1.1 **Study 3001B3-329-WW**

3.1.1.1 **Study Design**

This was a multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of pantoprazole in infants aged 1 through 11 months who had symptomatic GERD.

The primary objective of this study was to assess the efficacy of treatment with 1.2 mg/kg pantoprazole granules administered as an oral suspension in patients aged 1 through 11 months.

The secondary objectives were to assess the safety, tolerability, gastroesophageal reflux disease (GERD) symptoms, respiratory symptoms, antacid use, compliance, and growth parameters in infant patients aged 1 through 11months with symptomatic GERD.

Patients who met the following criteria were eligible to participate:

- Male or female term or postterm infants beyond the neonatal period >28 days but <12 months of age, or preterm infants with a corrected age of ≥44 weeks but <12 months at the time the consent was signed.
- Total GSQ-I (baseline total symptom frequency) mean symptom frequency >16 at screening (week -2) and at baseline.
- A clinical diagnosis of suspected, symptomatic, or endoscopically proven GERD.
- Weight ≥2.5 kg and ≤15 kg.
- Able to take test article orally.

Patients participated for 10 weeks. All patients 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. Patients whose symptoms resolved with the conservative treatment during the screening phase were withdrawn. The remaining patients entered a 4-week treatment run-in phase and received open-label oral pantoprazole granules for suspension daily for 4 weeks. Patients received 1.2 mg/kg pantoprazole sodium enteric-coated granules for suspension in 5- or 10-mg doses, depending on patient's body weight.

During the screening period and throughout the study, parents used an electronic diary (eDiary) to record the following GERD symptoms during the previous 24-hour period:
- Vomiting/regurgitation
- Choking/gagging
- Arching back
- Irritability/fussiness

• Refusal to feed

WGSS was calculated from 5 selected symptoms (vomiting/regurgitation, irritability/fussiness, choking/gagging, arching back, and refusal to feed). WGSS was the sum of the weekly mean frequencies of these 5 symptoms (GERD questions 1a, 2b, 3a, 4a, and max (5a, 5b)). In addition, the eDiary was used to assess the frequency of respiratory symptoms based on the presence/absence of the following items: cough, noisy breathing when breathing out, breathing with a wheezy or whistling sound, noisy breathing when breathing in, breathing with a croupy or barky sound, and stopping breathing or turning blue or purple, in the absence of a cold or fever. After the 2-week screening phase, the eDiary was also used to track compliance with test article.

Patients who were at least 80% compliant with the test article regimen and eDiary completion entered a 4-week, double-blind, placebo-controlled, treatment-withdrawal phase. Patients were stratified by body weight and randomly assigned to receive either pantoprazole or matching placebo daily for 4 weeks.

The primary endpoint was the withdrawal rate due to lack of efficacy during the double-blind treatment-withdrawal phase. Lack of efficacy was defined as 1 or more of the following:

- Significant worsening of GERD symptom frequency (i.e., Weekly GERD Symptom Score [WGSS] returned to baseline or above on 2 consecutive weekly evaluations not related to an intercurrent illness), or
- A diagnostic test such as endoscopy demonstrating the 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.

Investigators determined whether to withdrew a patient for lack of efficacy.

Based on a previous study (3001A1-322-US) for children 5 to 11 years treated with pantoprazole only 1/53 (1.9%) dropped out due to lack of efficacy. From the Orenstein and colleagues' article comparing famotidine to placebo in infants, the dropout rate in placebo group was 3 out of 11 (27%).

Assuming that the withdrawal rates in the pantoprazole group and the placebo group in the current study are 3% and 27%, respectively, a sample size of 38 patients per group entering the placebo-controlled withdrawal phase is needed to detect the assumed difference using two-sided Fisher's exact test at the 0.05 level with at least 80% power.

Sufficient patients will be screened (approximately 136) to ensure that at least 76 patients (38 patients per treatment group) enter the 4-week placebo-controlled withdrawal phase.

3.1.1.2 **Sponsor's Analysis**

A total of 154 patients with symptomatic GERD were screened for the study at

31 investigative sites. A total of 25 patients were screen failures; the remaining 129 patients entered the study, received at least 1 dose of the test article, and made up the safety population.

Of these, 128 patients participated in the open-label treatment run-in phase of the study. A total of 108 patients were randomly assigned to the pantoprazole 1.2-mg/kg group or the placebo group in the double-blind phase. Two (2) randomly assigned patients did not meet the mITT criteria and were withdrawn because of protocol violations. One of these patients was inadvertently assigned to double-blind treatment before entering the open-label phase. Twenty-one patients withdrew during the open-label phase, the most common reason being parental noncompliance with maintaining the eDiary. The remaining 106 patients participated in the double-blind treatment-withdrawal phase and constituted the modified intent-to-treat (mITT) population, the primary efficacy analysis population. Within the mITT population, 96 patients met the criteria for the VFE-1 population, and 77 patients met the criteria for the VFE-2 population.

The number and percentage of patients in each efficacy analysis population are summarized by treatment group is given below.

Table 9-1: Summary of Analysis Populations by Treatment Group

		------ Double-blind Treatment[a] ------		
Study Population	Withdrew From Open-label Phase	Pantoprazole 1.2 mg/kg	Placebo	Totals
Open-label Population	21 (100)	53 (98.1)	54 (100)	128 (99.2)
mITT Population	0	52 (96.3)	54 (100)	106 (82.2)
VFE-1 Population	0	48 (88.9)	48 (88.9)	96 (74.4)
VFE-2 Population	0	37 (68.5)	40 (74.1)	77 (59.7)

Abbreviations: mITT=modified intent-to-treat; VFE=valid-for-efficacy.
a. Treatment as randomized at week 4. All patients received 1.2 mg/kg pantoprazole in the open-label phase.
Source: Extracted from/CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3001B3/ 329/FINAL/3001-329 POP4 – 18MAR08 17:20.

The primary reasons for discontinuation of patients during the double-blind treatment-withdrawal phase are shown in below.

Table 8-2: Summary of Reasons for Conclusion of Patient Participation During the Double-Blind Phase – Randomized Patients

	---------- Double-blind Treatment ----------		
	Pantoprazole 1.2 mg/kg n=54	Placebo n=54	Total n=108
Total			108 (100)
Study Completed	43 (79.6)	45 (83.3)	88 (81.5)
Discontinued[a]	11 (20.4)	9 (16.7)	20 (18.5)
Failed to Return	1 (1.9)	0	1 (0.9)
Noncompliance	1 (1.9)	1 (1.9)	2 (1.9)
Parent/Legal Guardian Request	0	1 (1.9)	1 (0.9)
Protocol Violation	3 (5.6)	1 (1.9)	4 (3.7)
Unsatisfactory Response–Efficacy	6 (11.1)	6 (11.1)	12 (11.1)

a. Total discontinued is the sum of individual reasons since they are mutually exclusive by patient.
Source: /CLINICAL R&D/CLINICAL PROGRAMMING SAS REPORTS/3001B3/ 329/FINAL/3001-329 CPP5_DB – 26MAR08 14:18.

Twenty (20; 18.5%) randomized patients were discontinued from the study during the double-blind phase. The most common primary reason for discontinuation was an unsatisfactory response to treatment, which was reported for 12 (11.1%) patients: 6 in the pantoprazole 1.2-mg/kg group and 6 in the placebo group. In addition, 4 (3.7%) patients had a protocol violation as their primary reason for discontinuation from the study, 2 (1.9%) patients were not in compliance with the study protocol, and 1 (0.9%) patient each were discontinued because of parental request or failure to return to the study site.

3.1.1.2.1 **Planned Analysis**

The modified intent-to-treat (mITT) population was the primary analysis population and consisted of all patients who had a clinical diagnosis of GERD, completed the 4-week open-label treatment with a minimum 21 days of test article, entered the double-blind treatment-withdrawal phase, and received at least 1 dose of double-blind treatment.

Two (2) subsets of the mITT population were considered valid-for-efficacy (VFE).

- The VFE-1 population was included in all efficacy analyses and had the following characteristics:
  - Patients were ≥80% compliant with test article during the double-blind treatment-withdrawal phase.
  - The patients were ≥60% compliant with completing eDiary symptoms in the double-blind phase.
  - The patients did not violate the protocol in a major way.
  - The patients participated for at least 21 days in the open-label phase.
- The VFE-2 population, a subset of the VFE-1 population, was included in only those analyses involving withdrawal endpoints and had 1 additional characteristic:
  - Patients were ≥80% compliant with recording eDiary symptoms in the open-label phase.

As mentioned above, the primary efficacy endpoint was the withdrawal rate due to lack of efficacy. The secondary endpoints were 1) time to withdrawal due to lack of efficacy and time to withdrawal for any reason; 2) WGSS and individual mean frequency for each GERD symptom; 3) the amount of antacid taken during each week; 4) the number of patients taking antacids; 5) change in the amount of antacids used; and 6) respiratory symptoms collected in the eDiary.

Baseline demographic and other baseline characteristics were summarized to evaluate the comparability of treatment groups. Descriptive summary statistics and test p-values between treatment groups were presented. The p-values were calculated from the Fisher exact test or chi-square test for discrete variables and from an analysis of variance (ANOVA) model with treatment group as a factor for continuous variables.

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 patients who withdrew due to lack of efficacy during the double-blind phase over the total number of patients entered into the double-blind phase. Withdrawal rates between treatment groups were compared by a Fisher exact test. The primary analysis population was the mITT population.

Additional sensitivity analyses were conducted for the primary endpoint and included comparisons of the number of patients with lack of efficacy per withdrawal criteria or who withdrew for any reason.

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.

When calculating WGSS and individual GERD symptom mean scores, if all values of frequency scores were missing in 7 days within a week, the last-observation-carried-forward (LOCF) imputation method was used. The change in amount of antacids used was analyzed in the same way as WGSS was analyzed. The selected respiratory symptoms were summarized by treatment group.

3.1.1.2.2 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline for double-blind phase is given in Appendix Table 1.

As seen from Appendix Table 1, no statistically significant differences between the two treatment groups were observed for demographic and base characteristics.

3.1.1.2.3 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy parameter of the study was the difference in withdrawal rates between the 2 treatment groups during the double-blind phase because of a lack of efficacy. A lack of efficacy was ascribed if there were a significant worsening of GERD symptom frequency, a diagnostic test showing worsening esophagitis, maximal antacid use for ≥7 days continuous days, or severe GERD symptoms in the judgment of the investigator not related to intercurrent illness. Investigators determined if a patient should be withdrawn for lack of efficacy and recorded their determination as an unsatisfactory response on the "Conclusion of Participation" eCRF. Investigators could report unsatisfactory response at the final visit even for patients who completed the study.

A comparison of withdrawal rates for lack of efficacy during the double-blind phase are given below for the mITT population.

Table 9-10: 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	

Abbreviation: mITT=modified intent-to-treat.

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

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

Source: /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3001B3 PANTOPRAZOLE/P329/ 3001-P329 tab01_1 – 21MAR08 17:29.

As seen from table above, there was no difference between treatment groups in withdrawal rates due to lack of efficacy.

The sponsor performed additional analyses for primary efficacy endpoint: lack of efficacy per withdrawal criteria and withdrawal for any reason during the double-blind phase. The results from these two analyses are given Appendix Table 2 and Table 3, respectively.

As seen from Appendix Tables 2 and 3, there was no difference between treatment groups in lack of efficacy per withdrawal criteria and withdrawal for any reason during the double-blind phase.

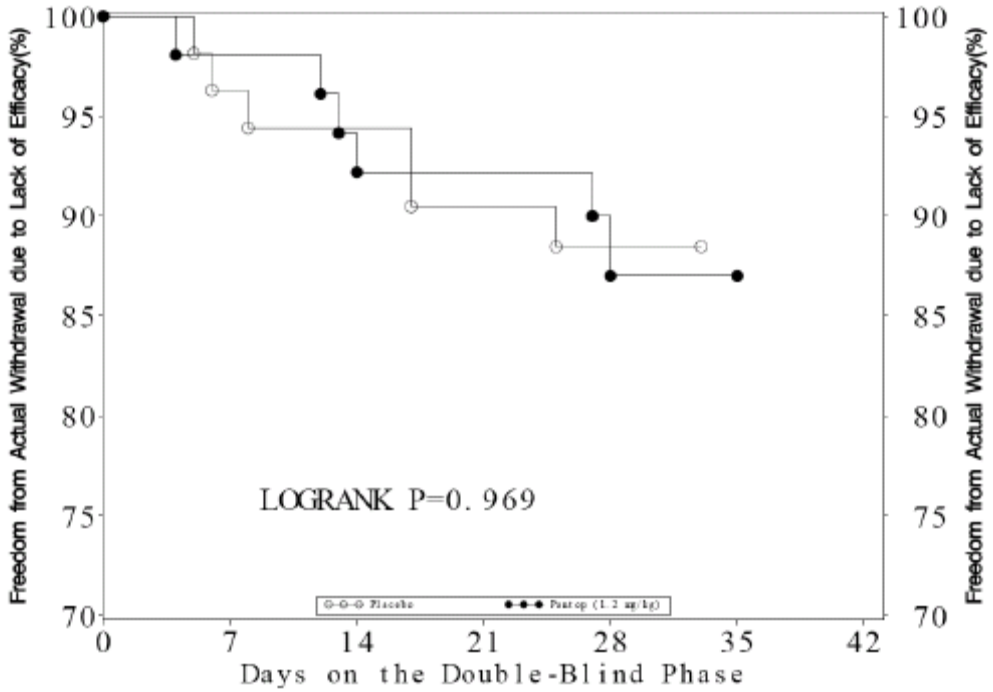
3.1.1.2.4 **Sponsor's Analysis of Secondary Efficacy Parameters**

Secondary efficacy parameters included the time to withdrawal from the study due to lack of efficacy, time to withdrawal from the study for any reason, the individual mean frequency of each GERD symptom, the amount of antacid taken each week, the number of patients taking antacids, and the presence of respiratory symptoms associated with GERD.

3.1.1.2.4.1 **Time to Actual Withdrawal due to Lack of Efficacy**

Kaplan-Meier estimates and log-rank tests were used to compare the time to actual withdrawal from the study due to lack of efficacy between treatment groups. The estimated time to withdrawal from the study is given below for the mITT population.

Figure 9-3: Kaplan-Meier Plot of Time to Actual Withdrawal Due to Lack of Efficacy During the Double-Blind Phase – mITT Population



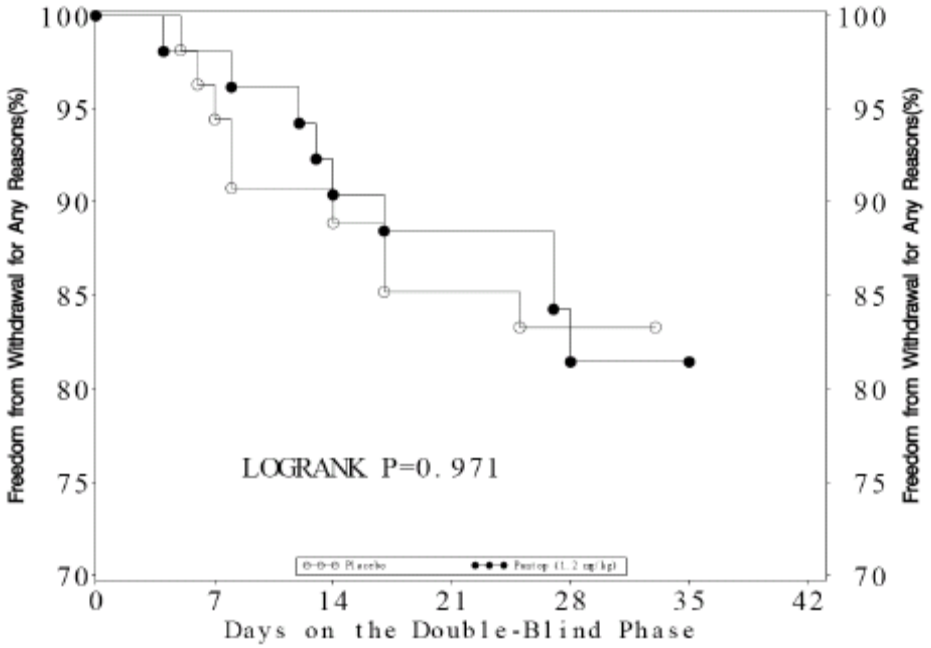
As seen from figure above, there was no significant difference between the pantoprazole-treated patients and the placebo-treated patients in the time to withdrawal due to a lack of efficacy. The withdrawal-free rate at day 28 was 87.0% in the pantoprazole 1.2 mg/kg group and 88.5% in the placebo group.

The sponsor performed similar analyses of time to withdrawal from the study because of lack of efficacy for VFE-1 and VFE-2 populations. In VFE-1, the withdrawal-free rate at day 28 was 86.2% in the pantoprazole 1.2-mg/kg group and 91.4% in the placebo group (p=0.522). In VFE-2, the withdrawal-free rate at day 28 was 87.7% in the pantoprazole 1.2-mg/kg group and 92.4% in the placebo group (p=0.627).

3.1.1.2.4.2 **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; see below.

Figure 9-5: Kaplan-Meier Plot of Time to Withdrawal for Any Reason During the Double-Blind Phase – mITT Population



As seen from Figure above, the time to withdrawal for any reason was similar between the 2 treatment groups. The withdrawal-free rate at day 28 was 81.4% in the pantoprazole 1.2-mg/kg group and 83.3% in the placebo group (p=0.971).

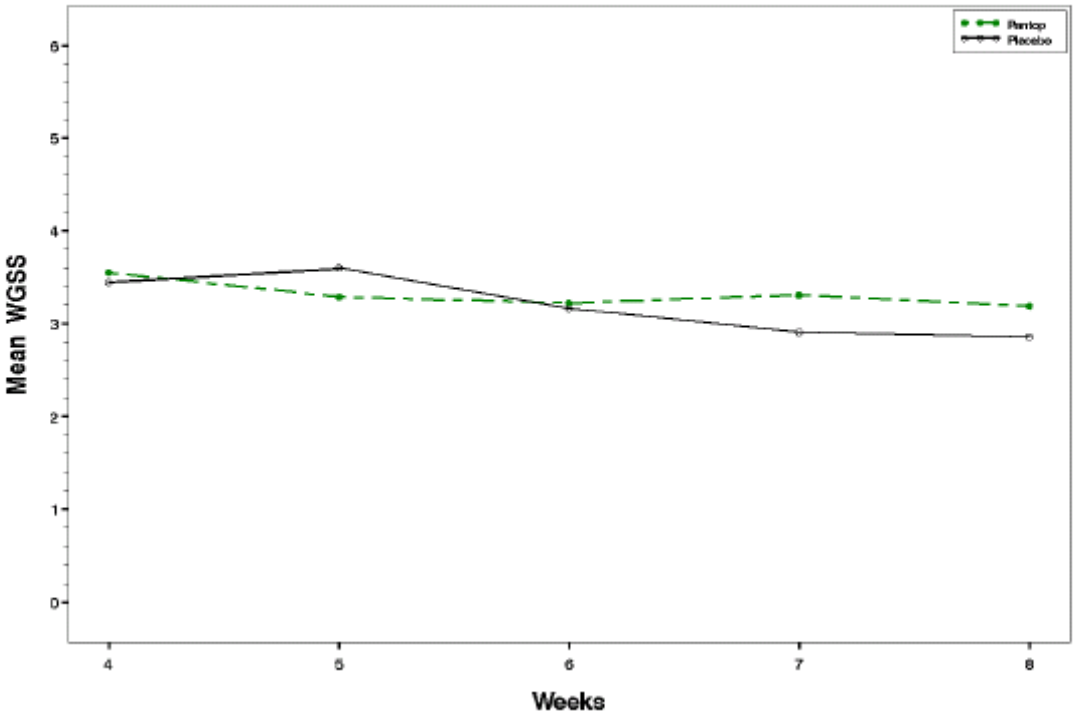
The sponsor also performed similar analyses of time to withdrawal from the study for any reason are provided for the VFE-1 population in and for the VFE-2 population. In VFE-1, the withdrawal-free rate at day 28 was 82.4% in the pantoprazole 1.2-mg/kg group and 87.5% in the placebo group (p=0.583). In VFE-2, the withdrawal-free rate at day 28 was 85.3% in the pantoprazole 1.2-mg/kg group and 90.0% in the placebo group (p=0.648).

3.1.1.2.4.3 **Mean Weekly GERD Symptom Score (WGSS) During Double-Blind Phase**

Weekly GERD symptom score (WGSS) is defined as the sum of the 5 weekly mean frequency scores for items 1a, 2b, 3a, 4a, and the maximum frequency of (5a and 5b).

The mean WGSS during the double-blind phase, week 4 to week 8, is shown by treatment group in Figure below.

Figure 9-7: Mean WGSS During Double-Blind Phase, by Treatment Group – mITT Population



As seen from Figure above, in the patients randomly assigned to continue on therapy with pantoprazole, the maximum treatment effect in favor of the pantoprazole 1.2-mg/kg group occurred by week 5. In the patients randomly assigned to placebo, there was a slight increase (worsening) in the WGSS at week 5 (1 week after treatment withdrawal), after which there was catch-up improvement. The WGSS for the placebo group matched that of the pantoprazole 1.2-mg/kg group at week 6.

A summary of the weekly mean changes from baseline and from week 4 at week 5 through 8 for patients in the mITT population is given Appendix Table 4.

As seen from Appendix Table 4, no relapse of symptoms was seen in the placebo group at the completion of the double-blind phase. At week 8, the mean WGSS in the placebo group was 2.86 compared with 3.44 at week 4. Symptom improvement was maintained in both the pantoprazole 1.2-mg/kg group and the placebo group throughout the double-blind phase. At week 8, the mean WGSS in the pantoprazole 1.2-mg/kg group was 3.19 compared with 3.55 at week 4.

Significant reductions in WGSS were observed each week in the pantoprazole 1.2 mg/kg and the placebo groups from baseline to week 8 ($p<0.001$ for both groups). However, most of the improvement in WGSS from week 0 to week 8 was attained during the open-label phase.

The sponsor also performed between-group comparisons for the changes in WGSS from baseline as well as from week 4 to the end of the double-blind phase, using an ANCOVA model with treatment and postnatal age group as factors and weekly antacid used at week 4 and WGSS at week 4 as covariates.

The between-group comparisons of changes from week 4 in mean WGSS are summarized in Appendix Table 5 for the mITT population.

As seen from Appendix Table 5, in the pantoprazole 1.2-mg/kg group, the mean WGSS decreased from 3.55 at week 4 to 3.19 at week 8. In the placebo group, the mean WGSS decreased from 3.44 at week 4 to 2.86 at week 8, indicating that withdrawal of pantoprazole did not result in any loss of the symptomatic improvement that occurred during the 4 weeks of open-label treatment with pantoprazole. The difference between the 2 treatment groups was not statistically significant.

3.1.1.2.4.3.1 **Individual Weekly Mean GERD Symptom Frequency Score**

3.1.1.2.4.3.1.1 **Vomiting/Regurgitation**

Items 1a, 1b, and 1c covered the frequency, amount, and discomfort of vomiting/regurgitation.

Item 1a asked, *how many times did the baby spit up?* Responses were scored 0 to 3, with 0=none; 1=1 to 3 times; 2=4 to 6 times; and 3=more than 6 times. Item 1b asked, *how much did the baby spit up?* Responses were scored 0 to 3, with 0=less than 1 tablespoon; 1=1 tablespoon to 2 fluid ounces; 2=more than 2 fluid ounces to half the feed; and 3=more than half the feed. Item 1c asked, *did the spitting up seem uncomfortable for the baby?* Responses were scored 0 for "no" and 1 for "yes."

In general, patients vomited approximately 4 to 6 times per day at baseline; the average amount was 1 tablespoon to 2 ounces; and discomfort was associated with vomiting approximately 65% of the time.

3.1.1.2.4.3.1.1.1 **Frequency of Spitting up (item 1a)**

During the open-label phase, the weekly mean frequency score for spitting up decreased significantly every week, from a baseline mean of 1.90 to 1.48 at week 4 ($p<0.001$).

During the double-blind phase, the improvements in the weekly mean frequency score achieved during open-label treatment with pantoprazole were maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. Between-group comparisons showed no significant differences at any week in the double-blind phase. Between-group comparisons in the mITT population are provided for changes from week 4 in Appendix Table 6.

3.1.1.2.4.3.1.1.2 **Amount of Spitting up (item 1b)**

During the open-label phase, the weekly mean frequency score for amount of spitting up decreased significantly at every week ($p<0.001$), from a baseline mean of 1.16 to 0.75 at week 4.

During the double-blind phase, the improvements in the amount of vomiting/regurgitation achieved during open-label treatment with pantoprazole were maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. Between-group comparisons showed no significant differences at each week in the double-blind phase. Between-group comparisons in the mITT population are provided for changes from week 4 in Appendix Table 7.

3.1.1.2.4.3.1.1.3 **Discomfort of Spitting up (item 1c)**

During the open-label phase, the weekly mean score of discomfort of spitting up decreased significantly every week ($p<0.001$), from a baseline mean of 0.64 to 0.39 at week 4.

During the double-blind phase, the significant improvements in the discomfort of regurgitation achieved during open-label treatment with pantoprazole were maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. Between-group comparisons in the mITT population are provided for changes from week 4 in Appendix Table 8.

3.1.1.2.4.3.2.1. **Irritability/Fussiness**

Items 2b and 2c asked about the frequency and duration of irritability/fussiness. Item 2b asked, *how many times did the baby cry or fuss during or within 1 hour after a feeding?* Responses were scored 0 to 3, with 0=none; 1=1 to 3 times; 2=4 to 6 times; and 3=more than 6 times. Item 2c asked, *how much of the time did the baby cry or fuss?* Responses were scored 0 to 4, with 0=less than 10 minutes; 1=10 minutes to 1 hour; 2=more than 1 hour but less than 3 hours; 3=3 or more hours; and 4=all of the time.

In general, crying or fussing within 1 hour of a feeding occurred about 1 to 3 times per day at baseline, and the patients tended to cry or fuss between 10 minutes and 1 hour.

3.1.1.2.4.3.2.1 **Frequency of Fussiness (item 2b)**

During the open-label phase, the weekly mean frequency score for irritability/fussiness decreased significantly each week, from a baseline mean of 0.99 to 0.57 at week 4 ($p<0.001$).

During the double-blind phase, the improvements in the weekly mean frequency score achieved during open-label treatment with pantoprazole were maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. Between-group comparisons

showed no significant differences at any week in the double-blind phase in the mITT population.

Between-group comparisons in the mITT population are provided f for changes from week 4 in Appendix Table 9.

3.1.1.2.4.3.2.2 **Duration of Fussiness (item 2c)**

During the open-label phase, weekly mean frequency scores for duration of irritability/fussiness decreased significantly each week, from a baseline mean of 0.92 to 0.50 at week 4 ($p<0.001$).

During the double-blind phase, the improvements in weekly mean frequency score achieved during open-label treatment with pantoprazole were maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. None of the between-group differences were statistically significant. Between-group comparisons in the mITT and VFE-1 populations are provided for changes from week 4 in Appendix Table 10.

3.1.1.2.4.3.3 **Choking/Gagging**

Item 3a asked, *during how many feedings did the baby choke or gag?* Responses were scored 0 to 3, with 0=none; 1=a few; 2=about half; and 3=all or almost all. In general, choking and gagging occurred after a few feedings at baseline.

During the open-label phase, the weekly mean frequency score for choking/gagging decreased significantly each week, from a baseline mean of 0.76 to 0.43 at week 4 ($p<0.001$).

During the double-blind phase, the improvements in the weekly mean frequency scores for choking/gagging achieved during open-label treatment with pantoprazole were maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. Between-group comparisons showed no significant differences at each week in the double-blind phase, in the mITT population. Between-group comparisons in the mITT for changes from week 4 are given in Appendix Table 11.

3.1.1.2.4.3.4 **Arching Back**

Item 4a asked, *how many times did the baby have episodes of arching back?* Responses were scored 0 to 3, with 0=none; 1=1 to 3 times; 2=4 to 6 times; and 3=more than 6 times. In general, arching back occurred 1 to 3 times per day at baseline.

In the open-label phase, the weekly mean frequency scores for arching back decreased significantly ($p<0.001$) from baseline.

During the double-blind phase, the improvements in the weekly mean frequency scores for arching back achieved during open-label treatment with pantoprazole were

maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. Between-group comparisons showed no significant differences at any week in the double-blind phase in the mITT population. Between-group comparisons in the mITT for changes from week 4 in Appendix Table 12.

3.1.1.2.4.3.5 **Refusal to Feed**

Item 5a asked, *how many times did the baby refuse feedings even when hungry?* Item 5b asked, *how many times did the baby stop eating even when hungry?* Responses were scored 0 to 3, with 0=none; 1=1 to 3 times; 2=4 to 6 times; and 3=more than 6 times. The maximum of 5a and 5b was used as the score for refusal to feed. Weekly mean frequency scores at baseline indicated that refusal to feed was reported approximately 1 to 3 times per day.

During the open-label phase, the weekly mean frequency scores for refusal to feed decreased significantly ($p<0.001$) from a baseline mean of 0.66 to 0.44 at week 4.

During the double-blind phase, the improvements in the weekly mean frequency scores for refusal to feed achieved during open-label treatment with pantoprazole were maintained in both the pantoprazole 1.2-mg/kg group and the placebo group. Between-group comparisons showed no significant differences at each week in the double-blind phase in the mITT population. Between-group comparisons in the mITT for changes from week 4 in Appendix Table 13.

3.1.1.2.4.4. **Amount of Antacid Taken Each Week**

Study antacid was dispensed during the screening phase and subsequent visits. Antacid use and amount were documented in the eDiary. Patients were allowed to take study antacid concomitantly with the test article during the open-label and double-blind treatment phases.

The amount of antacid taken weekly decreased from a mean of 11.86 mL at baseline to 6.64 mL at week 4, a statistically significant change ($p<0.001$). Statistically significant declines in the amount of antacid taken were observed at Week 2, 3, and 4 of the open-label phase.

The amount of antacid taken weekly decreased from a mean of 13.33 mL at baseline to 7.99 mL at week 4 ($p=0.015$) and 5.06 mL at week 8 ($p=0.001$) in the pantoprazole 1.2-mg/kg group. In the placebo group, the amount of antacid taken weekly decreased from a mean of 13.45 mL at baseline to 6.62 mL at week 4 ($p=0.003$) and 4.09 mL at week 8 ($p=0.002$).

The changes from week 4 in the amount of antacid taken weekly are summarized below for comparison between treatment groups in the double-blind phase in the mITT population below.

Table 9-20: Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Amount (mL) of Study Antacid Taken Weekly During the Double-Blind Phase –mITT Population

				---------- Change from Week 4 ----------		
Study Week	Double-blind Treatment	N	Mean (SD)	LSMEAN[a] (SE)	LSMEAN 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)	-0.01 (0.928)	-0.60 (1.256)	0.633
	Pantoprazole	52	6.88 (12.177)	-0.61 (0.926)		
Week 6 (Double-blind)	Placebo	51	5.70 (11.028)	-1.11 (1.082)	-0.56 (1.463)	0.703
	Pantoprazole	51	6.08 (11.205)	-1.67 (1.066)		
Week 7 (Double-blind)	Placebo	48	5.21 (9.769)	-1.61 (1.287)	0.04 (1.763)	0.980
	Pantoprazole	47	6.17 (13.241)	-1.56 (1.288)		
Week 8 (Double-blind)	Placebo	46	4.09 (7.819)	-2.35 (1.045)	-0.42 (1.426)	0.769
	Pantoprazole	46	5.06 (10.893)	-2.77 (1.033)		

Abbreviations: mITT=modified intent-to-treat; SD=standard deviation; LSMEAN=least squares mean; SE=standard error; diff=difference; Pantop=pantoprazole.

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

As seen from Table above, there were no statistically significant differences between treatment groups.

3.1.1.2.4.4 **The Number of Patients Taking Antacids**

At baseline, 80 (62.5%) of 128 patients used study antacid at least once a week. At week 4, the number was reduced to 58 (47.93%) of 121 patients.

The number and percentage of patients using antacids weekly during the double-blind phase are summarized below for patients in the mITT population.

Table 9-22: Summary of Number of Patients Taking Study Antacid Weekly – mITT Population

	---------- Double-blind Treatment ----------				p-Value[a]
	Placebo		Pantoprazole 1.2 mg/kg		(Pantoprazole
Study Week	Event/Total	Percent	Event/Total	Percent	vs Placebo)
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

Abbreviation: mITT=modified intent-to-treat.

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

As seen from Table above, the number of patients taking study antacid declined from baseline to week 8 in each of the treatment groups. Among patients in the pantoprazole

1.2-mg/kg group, the number declined from 37 (71.15%) of 52 at baseline to 18 (39.13%) of 46 at week 8. Among patients in the placebo group, the number declined from 33 (61.11%) of 54 at baseline to 15 (32.61%) of 46 at week 8. There were no statistically significant differences between the treatment groups.

3.1.1.3 **Reviewer' Comments and Evaluation**

3.1.1.3.1 **Comments on Study Design**

This study is the only placebo controlled clinical study performed by the sponsor.Its primary objective was to assess the efficacy of treatment with 1.2 mg/kg pantoprazole granules administered as an oral suppression in patients aged 1 through 11 months.

Sample size was derived from external information for children aged 5 to 11 years old for pantoprazole. It is unclear whether clinical outcomes for older age children (5 to 11 years old) could be extrapolated for those for infants (1 through 11 months).

This study showed that there was no treatment difference between treatment groups in withdrawal rates due to lack of efficacy, pre-specified primary efficacy endpoint.

With the possibility of inadequate sample size, it is very difficult to interpret the results. Results from this study should be considered "exploratory."

3.1.1.3.2 **Comments on Study Population**

At baseline, more patients in the pantoprazole 1.2-mg/kg group (32 [61.54%] of 52) than in the placebo group (28 [51.85%] of 54) had taken solid food.

3.1.1.3.3 **Comments on GSQ-I Symptom Frequency and WGSS**

The entry criteria, total GSQ-I (baseline total symptom frequency) mean symptom frequency >16, was used at screening (week -2) and at baseline.

But, overall, the mean GSQ-I symptom score was 109.95 at baseline. In the pantoprazole 1.2-mg/kg group, the mean GSQ-I symptom score was 113.35, and in the placebo group, it was 106.54.

Furthermore, the secondary efficacy endpoint was the change from baseline in mean WGSS. The sponsor stated that the baseline GSQ-I score was highly correlated with the baseline WGSS ($r=0.747$, $p<0.0001$). The high correlation coefficient indicates that the development of the daily eDiary from the GSQ-I was successful in capturing the same symptoms and should therefore have similar discriminant validity in distinguishing patients with GERD from healthy patients. However, WGSS has not been used to distinguish physiologic reflux (GER) from pathologic reflux (GERD). After 8 weeks of PPI treatment, the WGSS does not go to 0 but reaches a plateau at a score of 3, which corresponds to a GSQ-I score of approximately 65 (estimated from the regression line).

The sponsor's finding suggests that the study eligibility cutoff point of 16 on the GSQ-I was perhaps too low or that residual GERD symptoms should be expected in this population.

3.1.1.3.4 **Weekly GERD Symptom Score (WGSS)**

Since this study failed for the primary efficacy endpoint, results from secondary efficacy endpoints should be considered "exploratory."

Weekly GERD Symptom Score (WGSS) consists of item 1a, 2b, 3a, 4a, and max(5a,5b).

Furthermore, patients who were randomly assigned to pantoprazole 1.2 mg/kg in the double-blind phase had slightly higher baseline scores than the patients who were randomly assigned to receive placebo in the double-blind phase. At week 4, which was the baseline for the double-blind phase, the WGSS means for the 2 groups were close: 3.55 and 3.44 in the pantoprazole 1.2-mg/kg group and the placebo group, respectively, representing changes from baseline of -2.17 and -1.81, respectively.

The descriptive statistics for WGSS for individual items are given in Appendix Table 14. As seen from Appendix Table 14, average at baseline, at Week 4, and at Week 8 for Items [1a,2b,3a,4a,max(5a,5b] were:

- Average at baseline –
- 1a – 2.04 for pantoprazole; 1.85 for placebo
- 2b – 1.09 for pantoprazole; 0.92 for placebo
- 3a – 0.72 for pantoprazole; 0.79 for placebo
- 4a – 1.23 for pantoprazole; 0.98 for placebo
- Max(5a,5b) – 0.64 for pantoprazole; 0.71 for placebo
- Average at Week 4 –
- 1a – 1.63 for pantoprazole; 1.40 for placebo
- 2b – 0.54 for pantoprazole; 0.53 for placebo
- 3a – 0.34 for pantoprazole; 0.43 for placebo
- 4a – 0.65 for pantoprazole; 0.64 for placebo
- Max(5a,5b) – 0.39 for pantoprazole; 0.44 for placebo
- Average at Week 8 –
- 1a – 1.55 for pantoprazole; 1.23 for placebo
- 2b – 0.45 for pantoprazole; 0.43 for placebo
- 3a – 0.30 for pantoprazole; 0.39 for placebo
- 4a – 0.51 for pantoprazole; 0.48 for placebo
- Max(5a,5b) – 0.38 for pantoprazole; 0.33 for placebo

There was a light improvement for both pantoprazole 1.2-mg/kg and placebo groups at Week 4 from baseline for each item. However, those improvements might not be clinical meaningful.

3.2 **Evaluation of Safety**

3.2.1 **Study 301B33-329-WW**

A total of 84 (65.6%) of 128 patients had 1 or more treatment-emergent adverse events (TEAEs) during the open-label phase. The most common TEAEs were upper respiratory infection (25; 19.5%), fever (13; 10.2%), and diarrhea (13; 10.2%). Other TEAEs that occurred in at least 5% of patients were otitis media (12; 9.4%), rhinitis (11; 8.6%), oral moniliasis (7; 5.5%), vomiting (7; 5.5%), and cough increased (7; 5.5%).

Altogether, 49 (45.4%) of 108 randomized patients had 1 or more TEAEs during the double-blind phase, including 25 (46.3%) of 54 patients from the pantoprazole 1.2-mg/kg group and 24 (44.4%) of 54 patients from the placebo group. There were no significant differences between the 2 treatment groups. The most common TEAE was upper respiratory infection, which was reported in 7 (13.0%) patients in each of the treatment groups. TEAEs that occurred in at least 5% of patients in the pantoprazole 1.2-mg/kg group were fever, otitis media, vomiting, and creatine phosphokinase increased (3 patients each; 5.6% each). The only TEAE other than upper respiratory infection reported in more than 5% of patients in the placebo group was cough increased, which was reported in 4 (7.4%) patients.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATION

4.1 **Gender, Race and Age**

No conclusion on race can be drawn due to lack of representation of Black and other races.

5. SUMMARY AND CONCLUSIONS

5.1 **Statistical Issues and Collective Evidence**

Sample size was derived from external information for children aged 5 to 11 old for pantoprazole. It is unclear whether clinical outcomes for older age children (5 to 11 old) could be extrapolated for those for infants (1 through 11 months).

With the possibility of inadequate sample size, it is very difficult to interpret the results. So, results from this study should be considered “exploratory.”

This study showed that there was no difference between treatment groups in withdrawal rates due to lack of efficacy, pre-specified primary efficacy endpoint.

Since this study failed with no treatment difference for primary efficacy endpoint, results from secondary efficacy endpoint analyses should be considered “exploratory.”

5.2 **Conclusions and Recommendations**

This study showed that there was no difference between treatment groups in withdrawal rates due to lack of efficacy, pre-specified primary efficacy endpoint.

Since this study failed with no treatment difference for primary efficacy endpoint, results from secondary efficacy endpoint analyses should be considered “exploratory.”

6. Appendix

Table 1 Summary of Demographic and Baseline Characteristics --- Protocol 3001B3-329-WW

Characteristics	Pantoprazole (N=54)	Placebo (N=54)	Between Treatment p-value
Sex			0.8412
Male	35 (64.8%)	34 (63.0%)	
Female	19 (35.2%)	20 (37.0%)	
Race			0.7077
White	36 (66.7%)	35 (64.8%)	
Black	11 (20.4%)	10 (18.5%)	
Asian	6 (11.1%)	5 (9.3%)	
American Indian or Alaska Native		1 (1.9%)	
Other	1 (1.9%)	3 (5.6%)	
Ethnic			0.6959
Hispanic or Latino	4 (7.4%)	3 (5.6%)	
Age (months)			0.6918
Mean (SD)	5.19 (2.79)	5.04 (2.81)	
Age			0.5309
≤ 6 months	36 (66.7%)	39 (72.2%)	
> 6 months	18 (33.3%)	15 (27.8%)	
Head Circumference (cm)			0.5464
Mean (SD)	42.13 (3.06)	42.42 (2.99)	
Height (cm)			0.8897
Mean (SD)	64.16 (6.43)	64.09 (5.82)	
Weight (kg)			0.8634
Mean (SD)	7.10 (1.86)	6.90 (1.66)	
Weight			0.4402
≥ 2.5 kg < 7 kg	27 (50.0%)	31 (57.4%)	
≥ 7 kg ≤15 kg	27 (50.0%)	23 (42.6%)	
GSQ-I Score			
Mean (SD)	113 (72.83)	106.54 (72.49)	0.5491

Compiled by this reviewer. P-values were obtained by this reviewer.
Chi-square test was used for sex, age group and race. Wilcoxon method was used for head circumference, age, height, weight, GSQ-I score.

Table 2 Summary of Lack of Efficacy Per Withdrawal Criteria During the Double-Blind Phase – mITT Population --- 3001B3-329-WW

Summary of Lack of Efficacy Per Withdrawal Criteria During the Double-Blind Phase – mITT Population --- 3001B3-329-WW

Double-blind Treatment	Event[a] / Total	Percent	p-Value[b] (Pantoprazole vs Placebo)
Placebo	8/54	15	1.000
Pantoprazole	8/52	15	

Abbreviation: mITT=modified intent-to-treat.

a. An event is defined as a patient lack of efficacy per withdrawal criteria (see section 6.6.1.1). A patient might or might not have been actually withdrawn due to lack of efficacy per the withdrawal criteria.

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

Table 3 Summary of Withdrawal for Any Reason During the Double-Blind Phase – mITT Population --- 3001B3-329-WW

Summary of Withdrawal for Any Reason During the Double-Blind Phase
mITT Population --- 3001B3-329-WW

Double-blind Treatment	Event[a] / Total	Percent	p-Value[b] (Pantoprazole vs Placebo)
Placebo	9/54	17	1.000
Pantoprazole	9/52	17	

Abbreviation: mITT=modified intent-to-treat.

a. An event is defined as a patient withdrawal for any reason.

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

Table 4 Descriptive Statistics and Within-Treatment Comparisons to Baseline for Weekly GERD Symptom Score --- mITT Population

Table 9-15: Descriptive Statistics and Within-Treatment Comparisons to Baseline for Weekly GERD Symptom Scores – mITT Population

		------- Double-blind Treatment --------	
Study Week	WGSS[a] Statistics	Placebo n=54 [b]	Pantoprazole 1.2 mg/kg n=52 [b]
Week -1 (Baseline)	Mean (SD) score	5.25 (2.928)	5.72 (2.727)
Week 4 (Open-label)	Mean (SD)	3.44 (2.366)	3.55 (2.437)
	Change from Baseline		
	Mean (SD)	-1.81 (2.333)	-2.17 (1.722)
	p-Value[c]	< 0.001	< 0.001
Week 5 (Double-blind)	Mean (SD)	3.60 (2.444)	3.29 (2.315)
	Change from Baseline		
	Mean (SD)	-1.65 (2.345)	-2.43 (1.982)
	p-Value[c]	< 0.001	< 0.001
	Change from Week 4		
	Mean (SD)	0.15 (1.282)	-0.26 (1.309)
	p-Value[c]	0.384	0.155
Week 6 (Double-blind)	Mean (SD)	3.16 (2.215)	3.22 (2.353)
	Change from Baseline		
	Mean (SD)	-2.09 (2.135)	-2.49 (2.633)
	p-Value[c]	< 0.001	< 0.001
	Change from Week 4		
	Mean (SD)	-0.28 (1.437)	-0.33 (1.864)
	p-Value[c]	0.155	0.212
Week 7 (Double-blind)	Mean (SD)	2.91 (1.874)	3.31 (2.300)
	Change from Baseline		
	Mean (SD)	-2.34 (2.407)	-2.41 (2.362)
	p-Value[c]	< 0.001	< 0.001
	Change from Week 4		
	Mean (SD)	-0.54 (1.626)	-0.24 (1.870)
	p-Value[c]	0.018	0.354
Week 8 (Double-blind)	Mean (SD)	2.86 (2.095)	3.19 (2.594)
	Change from Baseline		
	Mean (SD)	-2.39 (2.468)	-2.52 (2.698)
	p-Value[c]	< 0.001	< 0.001
	Change from Week 4		
	Mean (SD)	-0.59 (1.500)	-0.36 (2.095)
	p-Value[c]	0.006	0.222
Final Week[d] (Double-blind)	Mean (SD)	2.88 (1.976)	3.31 (2.572)
	Change from Baseline		
	Mean (SD)	-2.38 (2.464)	-2.41 (2.702)
	p-Value[c]	< 0.001	< 0.001
	Change from Week 4		
	Mean (SD)	-0.57 (1.509)	-0.24 (2.115)
	p-Value[c]	0.008	0.416

Abbreviations: WGSS=weekly GERD symptom score; mITT=modified intent-to-treat; SD=standard deviation.

a. WGSS is defined as the sum of the 5 weekly mean frequency scores for items 1a, 2b, 3a, 4a, and the maximum frequency of (5a and 5b).
b. Last observation carried forward.
c. p-Value is obtained from the 2-sided paired t-test.
d. Final week is the last 7 days of symptom scores collected during the double-blind phase.

Table 5 Descriptive Statistics and Between-Treatment Comparisons for Change from Week 4 in Weekly GERD Symptom Score During the Double-Blind Phase --- mITT Population

Table 9-16: Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly GERD Symptom Score During the Double-Blind Phase – mITT Population, LOCF

				-------- Change From Week 4 --------		
Study Week	Double-blind Treatment	n	Mean (SD)	LSMean[a] (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	p-Value[a]
Week 4 (Open-label)	Placebo	54	3.44 (2.366)			
	Pantoprazole	52	3.55 (2.437)			
Week 5 (Double-blind)	Placebo	54	3.60 (2.444)	0.10 (0.182)	-0.39 (0.245)	0.116
	Pantoprazole	52	3.29 (2.315)	-0.29 (0.181)		
Week 6 (Double-blind)	Placebo	54	3.16 (2.215)	-0.38 (0.219)	-0.01 (0.295)	0.985
	Pantoprazole	52	3.22 (2.353)	-0.39 (0.218)		
Week 7 (Double-blind)	Placebo	54	2.91 (1.874)	-0.70 (0.213)	0.36 (0.288)	0.211
	Pantoprazole	52	3.31 (2.300)	-0.34 (0.212)		
Week 8 (Double-blind)	Placebo	54	2.86 (2.095)	-0.75 (0.240)	0.29 (0.323)	0.364
	Pantoprazole	52	3.19 (2.594)	-0.45 (0.239)		
Final week[b] (Double-blind)	Placebo	54	2.88 (1.976)	-0.73 (0.237)	0.40 (0.320)	0.211
	Pantoprazole	52	3.31 (2.572)	-0.33 (0.236)		

Notes: Weekly GERD symptom score (WGSS) is defined as the sum of the 5 weekly mean frequency scores for items 1a, 2b, 3a, 4a, and the maximum frequency of (5a and 5b).

Abbreviations: mITT=modified intent-to-treat; LOCF=last observation carried forward; SD=standard deviation; SE=standard error; LSMEAN=least squares mean; Pantop=pantoprazole.

a. LSMEAN and p-value are obtained from the ANCOVA model (change=baseline age group+week 4 symptom score+week 4 antacid intake+treatment).

b. Final week is the last 7 days of symptom scores collected during the double-blind phase.

Source: Extracted from /CLINICAL R&D/CLINICAL BIOSTATISTICS SAS REPORTS/3001B3 PANTOPRAZOLE/P329/ 3001-P329 tab02_6 –11APR08 12:20.

Table 6 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Vomiting/Regurgitation (Item 1a) During the Double-Blind Phase – m ITT Population

15.49. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency for Vomiting/Regurgitation (Item 1a) During the Double-Blind Phase – mITT Population

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REPORT TAB03_6 Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Vomiting/Regurgitation: Frequency (Question 1a)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

				Change from Week 4		
Study Week	Treatment	N	Mean (SD)	LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	1.85 (0.851)			
	Pantop (1.2 mg/kg)	52	2.04 (0.821)			
WEEK 4 (OPEN-LABEL)	Placebo	54	1.40 (0.833)			
	Pantop (1.2 mg/kg)	52	1.63 (0.950)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	1.41 (0.851)	-0.01 (0.055)	-0.05 (0.074)	0.504
	Pantop (1.2 mg/kg)	52	1.56 (0.880)	-0.06 (0.054)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	1.34 (0.852)	-0.09 (0.074)	0.02 (0.099)	0.807
	Pantop (1.2 mg/kg)	52	1.57 (0.998)	-0.06 (0.072)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	1.32 (0.798)	-0.15 (0.079)	0.11 (0.106)	0.298
	Pantop (1.2 mg/kg)	52	1.60 (0.972)	-0.04 (0.078)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	1.23 (0.877)	-0.26 (0.082)	0.16 (0.110)	0.152
	Pantop (1.2 mg/kg)	52	1.55 (1.009)	-0.10 (0.080)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	1.26 (0.872)	-0.22 (0.078)	0.13 (0.104)	0.213
	Pantop (1.2 mg/kg)	52	1.56 (1.007)	-0.09 (0.076)		

Question 1a: Since last evening how many times did the baby spit up (anything coming into or out of the mouth)?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid intake + treatment).

Table 7 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Vomiting/Regurgitation (Item 1b) During the Double-Blind Phase – m ITT Population

15.56. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Volume for Vomiting/Regurgitation (Item 1b) During the Double-Blind Phase – mITT Population

REPORT TAB04_6

Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Vomiting/Regurgitation: Volume (Question 1b)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

				Change from Week 4		
Study Week	Treatment	N	Mean (SD)	LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	1.06 (0.723)			
	Pantop (1.2 mg/kg)	52	1.30 (0.788)			
WEEK 4 (OPEN-LABEL)	Placebo	54	0.71 (0.565)			
	Pantop (1.2 mg/kg)	52	0.76 (0.715)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	0.71 (0.621)	-0.01 (0.051)	0.01 (0.069)	0.941
	Pantop (1.2 mg/kg)	52	0.76 (0.686)	-0.00 (0.051)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	0.69 (0.654)	-0.03 (0.061)	0.00 (0.082)	0.992
	Pantop (1.2 mg/kg)	52	0.74 (0.728)	-0.03 (0.060)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	0.63 (0.666)	-0.09 (0.072)	0.07 (0.097)	0.477
	Pantop (1.2 mg/kg)	52	0.74 (0.787)	-0.02 (0.072)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	0.54 (0.645)	-0.21 (0.067)	0.12 (0.090)	0.176
	Pantop (1.2 mg/kg)	52	0.70 (0.733)	-0.08 (0.066)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	0.57 (0.669)	-0.17 (0.065)	0.09 (0.088)	0.296
	Pantop (1.2 mg/kg)	52	0.69 (0.693)	-0.08 (0.065)		

Question 1b: Since last evening how much did the baby usually spit up (anything coming into or out of the mouth)?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid intake + treatment).

Table 8 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Vomiting/Regurgitation (Item 1c) During the Double-Blind Phase – m ITT Population

15.63. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequenc for Vomiting/Regurgitation Discomfort (Item 1c) During the Double-Blind Phase – mITT Population

REPORT TAB05_6 Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Vomiting/Regurgitation: Discomfort (Question 1c)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

				Change from Week 4		
Study Week	Treatment	N	Mean (SD)	LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	0.61 (0.413)			
	Pantop (1.2 mg/kg)	52	0.69 (0.370)			
WEEK 4 (OPEN-LABEL)	Placebo	54	0.45 (0.424)			
	Pantop (1.2 mg/kg)	52	0.33 (0.397)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	0.47 (0.429)	0.02 (0.037)	-0.02 (0.050)	0.686
	Pantop (1.2 mg/kg)	52	0.35 (0.394)	-0.00 (0.037)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	0.42 (0.406)	-0.03 (0.039)	0.02 (0.053)	0.705
	Pantop (1.2 mg/kg)	52	0.34 (0.424)	-0.01 (0.039)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	0.36 (0.390)	-0.07 (0.042)	0.05 (0.057)	0.417
	Pantop (1.2 mg/kg)	52	0.32 (0.411)	-0.03 (0.042)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	0.38 (0.436)	-0.07 (0.044)	0.05 (0.060)	0.437
	Pantop (1.2 mg/kg)	52	0.33 (0.445)	-0.02 (0.045)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	0.37 (0.430)	-0.07 (0.043)	0.05 (0.059)	0.428
	Pantop (1.2 mg/kg)	52	0.32 (0.442)	-0.03 (0.043)		

Question 1c: Since last evening, did spitting up (anything coming into or out of the mouth) seem uncomfortable (ie crying, fussiness, irritability) for the baby?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid intake + treatment)

Table 9 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Irritability/Fussiness (Item 2b) During the Double-Blind Phase – m ITT Population

15.70. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequenc for Irritability/Fussiness (Item 2b) During the Double-Blind Phase – mITT Population

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REPORT TAB06_6 Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Irritability/Fussiness: Frequency (Question 2b)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

				Change from Week 4		
Study Week	Treatment	N	Mean (SD)	LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	0.92 (0.758)			
	Pantop (1.2 mg/kg)	52	1.09 (0.758)			
WEEK 4 (OPEN-LABEL)	Placebo	54	0.53 (0.610)			
	Pantop (1.2 mg/kg)	52	0.54 (0.701)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	0.58 (0.675)	0.03 (0.056)	-0.06 (0.076)	0.463
	Pantop (1.2 mg/kg)	52	0.52 (0.674)	-0.02 (0.056)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	0.44 (0.585)	-0.10 (0.056)	-0.04 (0.076)	0.608
	Pantop (1.2 mg/kg)	52	0.41 (0.580)	-0.14 (0.056)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	0.40 (0.564)	-0.16 (0.057)	0.06 (0.077)	0.451
	Pantop (1.2 mg/kg)	52	0.46 (0.597)	-0.10 (0.057)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	0.43 (0.649)	-0.12 (0.061)	0.01 (0.083)	0.871
	Pantop (1.2 mg/kg)	52	0.45 (0.633)	-0.11 (0.061)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	0.42 (0.595)	-0.13 (0.059)	0.05 (0.080)	0.531
	Pantop (1.2 mg/kg)	52	0.47 (0.625)	-0.08 (0.059)		

Question 2b: Since last evening, how many times did the baby either cry a lot during or within 1 hour after a feeding?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid intake + treatment)

Table 10 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Irritability/Fussiness (Item 2c) During the Double-Blind Phase – m ITT Population

15.77. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequenc for Duration of Irritability/Fussiness (Item 2c) During the Double-Blind Phase – mITT Population

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REPORT TAB07_6 Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Irritability/Fussiness: Duration (Question 2c)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

Study Week	Treatment	N	Mean (SD)	Change from Week 4		
				LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	0.89 (0.992)			
	Pantop (1.2 mg/kg)	52	0.97 (0.831)			
WEEK 4 (OPEN-LABEL)	Placebo	54	0.49 (0.690)			
	Pantop (1.2 mg/kg)	52	0.45 (0.596)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	0.53 (0.815)	0.04 (0.058)	-0.09 (0.079)	0.262
	Pantop (1.2 mg/kg)	52	0.41 (0.657)	-0.05 (0.058)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	0.44 (0.741)	-0.06 (0.055)	-0.06 (0.074)	0.447
	Pantop (1.2 mg/kg)	52	0.35 (0.585)	-0.11 (0.055)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	0.45 (0.765)	-0.04 (0.067)	-0.00 (0.091)	0.987
	Pantop (1.2 mg/kg)	52	0.41 (0.670)	-0.04 (0.067)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	0.51 (0.861)	0.00 (0.071)	-0.08 (0.096)	0.433
	Pantop (1.2 mg/kg)	52	0.39 (0.707)	-0.07 (0.071)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	0.49 (0.820)	-0.01 (0.067)	-0.06 (0.091)	0.502
	Pantop (1.2 mg/kg)	52	0.39 (0.696)	-0.07 (0.067)		

Question 2c: Since last evening, how much of the time did the baby cry or fuss?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid intake + treatment)

Table 11 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Choking/Gagging (Item 3a) During the Double-Blind Phase – m ITT Population

15.84. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequenc for Choking/Gagging (Item 3a) During the Double-Blind Phase – mITT Population

REPORT TAB08_6
Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Choking/Gagging: Frequency(Question 3a)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

				Change from Week 4		
Study Week	Treatment	N	Mean (SD)	LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	0.79 (0.719)			
	Pantop (1.2 mg/kg)	52	0.72 (0.716)			
WEEK 4 (OPEN-LABEL)	Placebo	54	0.43 (0.516)			
	Pantop (1.2 mg/kg)	52	0.34 (0.569)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	0.50 (0.547)	0.06 (0.038)	-0.14 (0.051)	0.007
	Pantop (1.2 mg/kg)	52	0.28 (0.559)	-0.08 (0.038)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	0.47 (0.561)	0.04 (0.055)	-0.08 (0.074)	0.261
	Pantop (1.2 mg/kg)	52	0.32 (0.550)	-0.05 (0.055)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	0.39 (0.459)	-0.02 (0.053)	-0.01 (0.072)	0.927
	Pantop (1.2 mg/kg)	52	0.33 (0.550)	-0.02 (0.053)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	0.39 (0.483)	-0.04 (0.053)	-0.02 (0.072)	0.773
	Pantop (1.2 mg/kg)	52	0.30 (0.560)	-0.06 (0.053)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	0.40 (0.482)	-0.03 (0.053)	0.00 (0.072)	0.977
	Pantop (1.2 mg/kg)	52	0.33 (0.557)	-0.03 (0.053)		

Question 3a: Since last evening, during how many feeds did the baby choke or gag?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid

Table 12 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Arching Back (Item 4a) During the Double-Blind Phase – m ITT Population

15.91. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequenc for Arching Back (Item 4a) During the Double-Blind Phase – mITT Population

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REPORT TAB09_6

Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Arching Back: Frequency (Question 4a)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

				Change from Week 4		
Study Week	Treatment	N	Mean (SD)	LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	0.98 (0.952)			
	Pantop (1.2 mg/kg)	52	1.23 (1.007)			
WEEK 4 (OPEN-LABEL)	Placebo	54	0.64 (0.850)			
	Pantop (1.2 mg/kg)	52	0.65 (0.820)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	0.67 (0.880)	0.01 (0.062)	-0.11 (0.083)	0.197
	Pantop (1.2 mg/kg)	52	0.56 (0.753)	-0.10 (0.062)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	0.61 (0.795)	-0.08 (0.073)	-0.04 (0.098)	0.691
	Pantop (1.2 mg/kg)	52	0.57 (0.808)	-0.12 (0.073)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	0.50 (0.712)	-0.20 (0.066)	0.06 (0.089)	0.503
	Pantop (1.2 mg/kg)	52	0.55 (0.742)	-0.14 (0.066)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	0.48 (0.694)	-0.21 (0.076)	0.03 (0.102)	0.765
	Pantop (1.2 mg/kg)	52	0.51 (0.758)	-0.18 (0.076)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	0.48 (0.679)	-0.21 (0.075)	0.07 (0.101)	0.505
	Pantop (1.2 mg/kg)	52	0.55 (0.763)	-0.14 (0.075)		

Question 4a: Since last evening, how many times did the baby have episodes of arching back?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid

Table 13 Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequency Score for Refusal to Feed: Initiation and Cessation (Maximum of Items 5a and 5b) During the Double-Blind Phase – m ITT Population

15.98. Descriptive Statistics and Between-Treatment Comparison for Change From Week 4 in Weekly Mean Frequenc for Refusal to Feed (Maximum of Items 5a and 5b) During the Double-Blind Phase – mITT Population

REPORT TAB10_6

Descriptive Statistics and Between Treatment Comparison
For Change from Week 4 in Weekly Mean Frequency Score for Refusal to Feed:
Initiation and Early cessation (Maximum of Questions 5a and 5b)
During the Double-blind Phase
The Modified Intent to Treat Population
Last Observation Carried Forward

				Change from Week 4		
Study Week	Treatment	N	Mean (SD)	LSMEAN (SE)	LSMEAN Diff (SE) (Pantop-Placebo)	P-value
WEEK -1 (BASELINE)	Placebo	54	0.71 (0.750)			
	Pantop (1.2 mg/kg)	52	0.64 (0.643)			
WEEK 4 (OPEN-LABEL)	Placebo	54	0.44 (0.583)			
	Pantop (1.2 mg/kg)	52	0.39 (0.462)			
WEEK 5 (DOUBLE-BLIND)	Placebo	54	0.44 (0.525)	0.02 (0.043)	-0.05 (0.058)	0.436
	Pantop (1.2 mg/kg)	52	0.36 (0.418)	-0.02 (0.043)		
WEEK 6 (DOUBLE-BLIND)	Placebo	54	0.30 (0.460)	-0.11 (0.049)	0.09 (0.066)	0.170
	Pantop (1.2 mg/kg)	52	0.37 (0.470)	-0.02 (0.049)		
WEEK 7 (DOUBLE-BLIND)	Placebo	54	0.30 (0.380)	-0.12 (0.051)	0.10 (0.069)	0.165
	Pantop (1.2 mg/kg)	52	0.37 (0.454)	-0.02 (0.051)		
WEEK 8 (DOUBLE-BLIND)	Placebo	54	0.33 (0.479)	-0.09 (0.062)	0.08 (0.084)	0.370
	Pantop (1.2 mg/kg)	52	0.38 (0.573)	-0.01 (0.062)		
FINAL WEEK (DOUBLE-BLIND)	Placebo	54	0.32 (0.471)	-0.10 (0.062)	0.11 (0.084)	0.212
	Pantop (1.2 mg/kg)	52	0.39 (0.569)	0.01 (0.062)		

Question 5a: Since last evening, how many times did the baby refuse feedings even when hungry?
Question 5b: Since last evening, how many times did the baby stop feeding even when hungry?
Final week is the last 7 days of symptom scores collected during the double-blind phase.
LSMEANS and P-value are obtained from the ANCOVA model (change = baseline age group + week 4 symptom score + week 4 antacid intake + treatment)

Table 14 Descriptive Statistics for Weekly GERD Symptom Score for Individual Items

							Pantoprazole		Placebo	
		Pantoprazole			Placebo		Week 4	Week 8	Week 4	Week 8
Item	Week -1	Week 4	Week 8	Week -1	Week 4	Week 8	– Week -1	– Week 4	- Week -1	-Week 4
1a	2.04 (0.821)	1.63 (0.950)	1.55 (1.007)	1.85 (0.851)	1.40 (0.833)	1.23 (0.877)	-0.41	-0.08	-0.45	-0.17
2b	1.09 (0.758)	0.54 (0.701)	0.45 (0.633)	0.92 (0.758)	0.53 (0.610)	0.43 (0.649)	-0.55	-0.09	-0.39	-0.10
3a	0.72 (0.716)	0.34 (0.569)	0.30 (0.560)	0.79 (0.719)	0.43 (0.516)	0.39 (0.483)	-0.38	-0.04	-0.36	-0.04
4a	1.23 (1.01)	0.65 (0.820)	0.51 (0.758)	0.98 (0.952)	0.64 (0.850)	0.48 (0.679)	-0.58	-0.14	-0.34	-0.16
Max(5a, and 5b)	0.64 (0.643)	0.39 (0.462)	0.38 (0.573)	0.71 (0.750)	0.44 (0.583)	0.33 (0.479)	-0.25	-0.01	-0.27	-0.11
WGSS	5.72 (2.73)	3.55 (2.44)	3.19 (2.59)	5.25 (2.93)	3.44 (2.37)	2.86 (2.10)	-2.17	-0.36	-1.81	-0.58
1b	1.30 (0.788)	0.76 (0.715)	0.70 (0.733)	1.06 (0.723)	0.71 (0.565)	0.54 (0.645)	-0.84	-0.06	-0.35	-0.17
1c	0.69 (0.370)	0.33 (0.397)	0.33 (0.445)	0.61 (0.413)	0.45 (0.424)	0.38 (0.436)	-0.36	-0.00	-0.16	-0.07
2c	0.97 (0.992)	0.45 (0.596)	0.39 (0.707)	0.89 (0.992)	0.49 (0.690)	0.51 (0.861)	-0.52	-0.06	-0.40	0.02

Compiled from Tables 15.39, 15.49, 15.56, 15.63, 15.70, 15.77, 15.84, 15.91, and 15.98.

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Milton Fan
4/17/2009 01:55:03 PM
BIOMETRICS

Mike Welch
4/17/2009 02:10:02 PM
BIOMETRICS
Concur with review.