DIVISION OF GASTROENTEROLOGY PRODUCTS
MEDICAL OFFICER REVIEW

Application Type:	NDA
Submission Number:	20-406/067 21-281/024 21-428/017
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PDUFA Goal Date:	10-28-08
Reviewer Name:	Ali Niak, M.D.
Reviewer Completion Date:	10-27-08
Established Name:	Lansoprazole
(Proposed) Trade Name:	Prevacid Pediatric Suspension
Therapeutic Class:	Proton Pump Inhibitor
Applicant:	TAP Pharmaceutical Products, Inc.
Priority Designation:	Standard
Formulation:	Oral Suspension
Dosing Regimen:	0.2-0.3 mg/kg/day for infants ≤ 10 weeks of age or 1.0-1.5 mg/kg/day > 10 weeks of age
Indication:	treatment of symptomatic GERD patients
Intended Population:	Pediatric patients, > 28 days since birth (preterm infants with corrected age of at least 44 weeks) but < 12 months of age at Dosing Day 1

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1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

Approval of this application is not recommended for the treatment of non-erosive gastroesophageal reflux disease (GERD) in either term or post term infants beyond the neonatal period (> 28 days since birth), but less than 12 months of age or preterm infants with a corrected age of at least 44 weeks, but less than 12 months of age. There was no difference in responder-to-treatment rates between infants treated with once daily administration of lansoprazole pediatric suspension and those given placebo in the treatment of GERD symptoms in infants (aged 1 month to <1 year). Additionally, there were no clinically significant differences in the treatment effects observed for other GERD symptoms assessed in this study. These efficacy results were consistent across all methods of assessment in this study. Crying/fussing and irritability were reduced over time regardless of which treatment the infant received. No statistically significant differences were observed between treatment groups for any baseline demographic characteristics, or in the percentage of subjects with various GERD symptoms reported by diary during baseline.

1.2 Risk Benefit Analysis

The efficacy data did not support the proposal for treatment in the age group 1 month to <1 year.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendation for other Postmarketing Study Commitments

None.

2. INTRODUCTION AND REGULATORY BACKGROUND

Gastroesophageal reflux (GER) implies a functional or physiologic process in a healthy infant with no underlying abnormalities. GER is a common condition that involves regurgitation, or "spitting up," which is the passive return of gastric retrograde into the esophagus. GER peaks between one to four months of age[1], and usually resolves by six to 12 months of age.[2] No definite peak age or gender predilection beyond infancy has been established. Regurgitation has been reported in 40 to 65 percent of healthy infants,[3] but decreases to 1 percent by one year of age.

[1] Orenstein Sr. Infantile reflux: different from adult reflux. Am. Journal of Med. 1997;103:S114-9.
[2] Vandelplas Y, Lifshitz JZ, Orenstein S, Lifshitz CH, Shepherd RW, Casaubon PR, et al. Nutritional management of regurgitation in infants. Journal of Am. Coll. Nutr. 1198;17:308-16.
[3] Hart JJ. Pediatric gastroesophageal reflux. Am. Fam. Physician 1996;54:2463-72.

Gastroesophageal reflux disease (GERD) is a pathologic process in infants that is manifested by poor weight gain, signs of esophagitis, persistent respiratory symptoms, and changes in neurobehavior. Approximately one in 300 infants present with abnormal signs and symptoms that warrant a diagnosis of GERD.[4] GERD is more resistant to complete resolution after the first year of life. A higher prevalence of GERD is noted in children who have the following: a history of esophageal atresia with repair[5], hiatal hernia[6], bronchopulmonary dysplasia[7], asthma[8], and chronic cough.

Table 1.

Clinical Features of GER and GERD in Infants and Children

GER	GERD
Regurgitation with normal weight gain	Regurgitation with poor weight gain
No signs or symptoms of esophagitis	Persistent irritability; pain in infants
	Lower chest pain, dysphagia, and pyrosis in children
	Hematemesis and iron deficiency anemia
No significant respiratory symptoms	Apnea and cyanosis in infants
	Wheezing
	Aspiration or recurrent pneumonia
	Chronic cough
	Stridor
No Neuro behavioral symptoms	Neck tilting in infants (Sandifer's syndrome)

GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease

Initial management of infants diagnosed with GERD is the utilization of the nonpharmacologic approach of Conservative GERD management (CGM). This approach includes feeding modifications, positioning changes, and reduction or elimination of tobacco smoke from the infant's immediate environment. Infants and children that continue to exhibit symptoms even after dietary and lifestyle modifications are candidates for medication intervention.

[4] Behrman RE, Kliegman R, Jenso HB, eds. Nelson Textbook of Pediatrics. 16th ed. Philadelphia: W.B. Saunders, 2000:1125-6.
[5] Faubion WA Jr., Zein NN. Gastroesophageal reflux in infants and children. Mayo Clin Proc 1998;73:166-73
[6] Orentsein SR. Controversies in pediatric gastroeophageal reflux. J Pediatr Gastroenterol Nutr 1992;14:338-48.
[7] Glassman M, George D, Grill B. Gastroeophageal reflux in children. Clinical manifestations, diagnosis, and therapy. Gastroenterol Clin North Am 1995;24:71-98.
[8] Sontag SJ. Gastroeophageal reflux and asthma. Am J Med 1997;103:84S-90S.

Antacids in Pediatric GERD are not generally recommended for long term treatment. Significant aluminum absorption from antacid use can occur in infants approaching levels reported to cause osteopenia and neurotoxicity.

There is insufficient evidence that prokinetic agents, such as metoclopramide, are effective in the treatment of GERD in infants and children. Adverse effects are common with metoclopramide therapy and include extrapyramidal side effects such as dystonic reactions, tardive dyskinesia, parkinsonian reactions, tremor, and irritability.

Sucralfate (carafate) is an aluminum containing surface cytoprotective agent and there is not enough data on its safety of use in children.

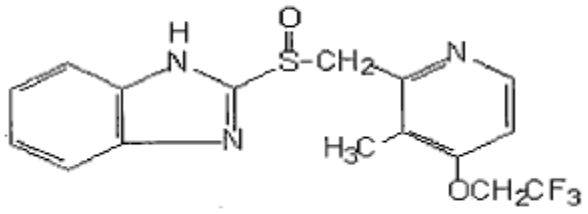
Histamine-2 receptor antagonists (H_2-RAs) are available and are safe and effective. Examples of these are ranitidine, cimetidine, and famotidine[9].

Although proton pump inhibitors (PPI) have not been approved for patients <1 year old, they are used off-label in infants with recurrent vomiting and failure to thrive, and/or irritability that have not responded to H_2-RAs. Additionally, PPI's have also been considered in children with feeding resistance or dysphagia, asthma, recurrent pneumonia, or GERD.

2.1 Product Information

Prevacid (lansoprazole) belongs to a class of antisecretory compounds that do not exhibit anticholinergic or H_2-RA properties, but that suppress gastric acid secretion by specific inhibition of the (H+/K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Since this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

The active ingredient in Prevacid (lansoprazole) is a substituted benzidimazole, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzidimazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_3N_30_3S$ with a molecular weight of 369.37. The structural formula is:



[9] Rudolph C., Mazur L., Liptaq G., et al. Guidelines for Evaluation and Treatment of Gastroesophageal Reflux in Infants and Children: Recommendations for the N. American Society for Ped. Gastro. And Nutrition. Journal of Ped. Gastro. Jan 2001;Vol. 32, Supp 2, S1-S31.

Prevacid (lansoprazole) was approved in the U.S. for use in adults in May 1995, for use in children 1 to 11 years of age in June 2002 and for use in adolescents 12 to 17 years of age in June 2004. Lansoprazole has approved indications for adults that include the short-term treatment of symptomatic, non-erosive GERD (15 mg once daily [QD] up to 8 weeks), the short-term treatment of erosive esophagitis (EE) (30 mg QD up to 8 weeks; patients with unhealed EE after 8 weeks of treatment [5%-10%] may benefit from an additional 8 weeks of treatment), the long term maintenance of healed EE, short-term treatment and maintenance of healed duodenal ulcers, short-term treatment of gastroesophageal ulcers, healing and risk reduction of nonsteroidal anti-inflammatory drug (NSAID)-associated gastroesophageal ulcers, and for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome (60 mg QD).[10]

The investigational formulation, Lansoprazole Microgranules Oral Suspension for Pediatric Use (lansoprazole pediatric suspension) (b) (4)

(b) (4)

(b) (4)

2.2 Currently Available Treatment for Indication

Pharmacokinetic (PK) data for H_2-receptor antagonists, such as ranitidine, is available for children and infants (1 to 12 months of age) for the treatment of GERD. Labeled doses in children are 6-10 mg/kg/day.

PPI's (such as lansoprazole, esomeprazole, and omeprazole) have been approved for treatment of GERD in the pediatric population starting from one year of age. However, the safety and efficacy of these PPIs have not been established in children less than one year of age.

2.3 Availability of Proposed Active Ingredient in the United States

The availability of lansoprazole (Prevacid) in the United States is as follows:

[10] Prevacid Delayed-Release Capsules, Delayed-Release Oral Suspension, and Delayed-Release Orally Disintegrating Tablets [package insert]. Lake Forest, IL: TAP Pharmaceutical Products Inc. July 2007.TAP -07-006591

-on May 10, 1995, the FDA approved lansoprazole for use in adults

-on December 2, 1997, lansoprazole was approved for combination use with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori infections*

-on May 3, 2001, lansoprazole oral extended release suspension was approved

-on July 31, 2002, lansoprazole was approved for symptomatic and erosive GERD in ages 1 to 11 years (inclusive)

-on June 17, 2004, lansoprazole was approved for symptomatic and erosive GERD in ages 12 to years (inclusive)

2.4 Important Issues With Consideration to Related Drugs

Lansoprazole (Prevacid) is the first PPI that has completed a clinical study in the patient age population 1 month to <12 months of age. The safety and effectiveness of PPIs [omeprazole (Prilosec), rabeprazole (Aciphex), pantoprazole (Protonix), lansoprazole (Prevacid), and esomeprazole (Nexium)] are currently approved for several acid-related conditions in adults in the U.S. as of the writing of this document.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

Overall, there were 4 pediatric studies under this FDA pediatric written request. However, before each study is reviewed, a brief summary of the period from the start of the date of the first FDA meeting on Pediatric Exclusivity is listed below.

On January 19, 2000, the protocols for clinical Studies 2 and 3 (listed below) were found to be acceptable.

Discussion of studies for the neonate and infant populations were conducted on February 11, 2003.

On April 1, 2005, discussion of Phase 3 efficacy studies occurred and on July 20, 2005, the Phase 1 neonate study was discussed.

A meeting involving the discussion of Phase 3 safety and efficacy study in infants took place on February 6, 2006, and on December 5, 2006, the FDA CAC approval by the of the dosing for the p53 (+/-) carcinogenicity study occurred.

On June 6, 2007, a discussion regarding the proposed plan for the literature reviews took place. Additionally, the neonatal dog study was accepted and agreements were reached regarding the aspects of commercial formulation development. During that discussion, agreement was achieved regarding the modifications to data sets for Studies 2, 3, and 4 and clarification of the administrative requirements.

There was a supplement to the meeting on June 6, 2007, and additional FDA comments with regards to the commercial formulation were discussed.

On December 5, 2007, the results of the Phase 3 infant study and commercial formulation requirements were discussed.

Overall, there were 4 pediatric studies under this FDA pediatric written request.

Study 1: Pharmacokinetic, Pharmacodynamic, Efficacy, and Safety Study in Pediatric Patients Less Than 12 Months of Age.

Study 2: Clinical Outcome, Pharmocokinetic and Pharmcodynamic Study of Age-Appropriate Formulation(s) of Lansoprazole in Pediatric Patients With Symptomatic and/or Endoscopically Proven GERD Aged 1 to 11 Years Inclusive: multicenter, open-label, 8 to 12-week study in at least 60 patients.

Study 3: Pharmocokinetic, Pharmcodynamic, and Symptom Assessment Study of Lansoprazole in Pediatric Patients Aged 12 to 17 Years Inclusive: multicenter, randomized, double-blind, 5-day study in at least 30 patients with symptomatic and/or endoscopically proven GERD per treatment group.

Study 4: Clinical Outcome Study of Lansoprazole in Pediatric Patients Aged 12 to 17 Years Inclusive: multicenter, open-label, parallel group, 8 to 12-week study in at least 80 patients of both sexes with GERD symptoms for at least three months in whom gastrointestinal endoscopy has been performed.

Study 1: proposed labeling submitted 4-25-08
- **Part A :** study report submitted 11-20-07
- **Part B:** study report submitted 11-20-07
- **Part C:** study report submitted 04-25-08

Study 2: submitted 11-20-07 and label expansion approved 7-31-02
Study 3: submitted 12-19-03 and label expansion approved 6-17-04
Study 4: submitted 12-19-03 and label expansion approved 6-17-04

All written fulfillments were met and on July 15, 2008, the Pediatric Exclusivity Board granted exclusivity to lansoprazole.

2.6 Other Relevant Background Information

As of this writing, Lansoprazole has not been approved for treating GERD in infants between the ages of 1 month and <1 year in any country throughout the world.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

Overall, the submission was organized in a clear and concise fashion. The information was readily available. No DSI inspection site requests were made for this study.

3.2 Compliance with Good Clinical Practices

The study was conducted in accordance with the protocol, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP) guidelines, Food and Drug Administration (FDA) regulations, ethical principles that have their origin in the Declaration of Helsinki, and all applicable local regulations, whichever offered the greater protection for the subject.

3.3 Financial Disclosures

TAP Pharmaceutical Products, Inc., has disclosed financial arrangements with clinical investigators, as recommended in the FDA guidance for industry.

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls/Clinical Microbiology

The CMC information supported the use of the drug product during the clinical trials (pediatric-neonatal) cited in the supplement. The drug product used for these trials (clinical supplies) may be considered to be of acceptable quality, potency, and stability. Again, it is noted that the drug product is not intended to be developed commercially. It appears that this supplement was utilized in order to gain pediatric exclusivity. However, it also appears that the applicant made a good-faith effort to actually develop a neonate-appropriate formulation, but results indicated that the treatment was NOT effective. For complete details, please refer to Dr. David Lewis', chemist at DGP/ODE III/CDER/FDA, review dated September 9, 2008.

4.2 Preclinical Pharmacology/Toxicology

One new study involving a 26 week carcinogenicity study in Heterozygous p53 +/- Trangenic Mice was submitted as part of this written request. This study was not positive. Please refer to Dr. Niraj Mehta's (pharmacology division) review for details.

4.3 Clinical Pharmacology

4.3.1 Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but that suppress gastric acid secretion by specific inhibition of the (H^+,K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Due to the fact that this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

4.3.2 Pharmacodynamics

According to Dr. PeiFan Bai's (clinical pharmacologist) review, dated April 25, 2008, there was no exposure/response relationship.

Intragastric pH, intraesophageal pH, and integrated acidity were assessed in 6 infants on Days -1, 1, and 5. Measurement of pH occurred at baseline and every 15 minutes over the 24-hour dosing interval. From this data, the investigators calculated the percentage of time that intragastric pH was >3, >4, >5, and >6 for each two-hour interval and the mean pH overall for the entire 24-hour dosing interval. The percentage of time that the intraesophageal pH was <4 over the 24-hour dosing interval was also calculated. The high-dose group was not better than the low-dose group when measuring the percent time; the intragastric pH exceeded the 3, 4, 5, and 6 over a 24-hour period on either Day 1 or Day 5. Both dose groups showed increases in the percent time that the pH exceeded 3, 4, 5, and 6 on Day 5 relative to Day 1.

4.3.3 Pharmacokinetics

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by (H^+,K^+)-ATPase within the parietal cell canaliculus, but are not present in the systemic circulation. The plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion. Thus, the plasma elimination half-life is less than two hours, while the acid inhibitory effect lasts more than 24 hours.

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 μg/mL.

According to Dr. PeiFan Bai's review dated 10-01-08, the pharmaockinetics of lansoprazole were studied in pediatric patients with GERD aged < 28 days and 1 to 11 months. Compared to healthy adults receiving a 30 mg dose, exposures in neonates were

higher (mean AUCs 2.4 to 4.4 fold higher at doses of 0.5 and 1 mg/kg/day, respectively). Infants ≤ 10 weeks old had clearance and exposure values that were similar to neonates. Infants > 10 weeks old who received 1 mg/kg/day had mean AUC values that were similar to adults who received a 30 mg dose.

Lansoprazole in neonates showed approximate dose proportionality for both cmax and AUC between 0.5 and 1 mg/kg/day. The 0.5/mg/kg/day group had more physical maturity, and was <1 week older, than the 1 mg/kg/day group. Following repeated dosing, the 2-hr post-dose concentrations were 37% and 34% higher on day 5 than on day 1 for 0.5 mg/kg/day and 1 mg/kg/day, respectively. The 6-hr post dose concentrations were similar on days 1 and 5 for both dose regimens.

Single and Multiple Dose PK: On Day 1, Cmax values for the two dose groups were approximately dose-proportional; however, mean AUC values were higher than dose-proportional between 1 and 2 mg/kg/day. This disproportionate result with regard to AUC was driven by two 6-week-old subjects who have significantly higher exposure per kg relative to older subjects. There appears to be no accumulation by Day 5, a finding that is different for infants relative to neonates. The 2-hour (approximate Coax), and 6-hour lansoprazole plasma concentrations were similar on Days 1 & 5 for both dose regimens.

Neonates vs. older children, adolescent and adults: Adults had much lower AUC than neonates based on an equivalent dose per body weight; as did the adolescent group and children ages 1 to 17. Based on an equivalent dose, lansoprazole AUC decreased dramatically from neonates to children ages 1-11 and then slightly to adolescents, and then increased from adolescents to adults to a small extent. According to the literature about the ontogenic development of 2C19 (Clin Pharmacokinet 2005; 44 (5):441 & Pediatr Clin North Am 1997; 44: 55-77), its activity is low in the first few weeks of life, reaches the adult level by 6-12 months of age, and then exceeds the adult level between 1 and 4 years old and then gradually declines to the adult level by puberty. The aforementioned results are in agreement with the literature. Please refer to Dr. Bai's review for details.

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

The clinical source of data was a Phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel group study assessing the safety and efficacy of lansoprazole microgranules oral suspension in infants (ages 1 month to 11 months) with symptomatic GERD.

5.1 Tables of Clinical Studies

The clinical study in this NDA is listed below:

Table 2. Clinical Study

Study	Description	Age	Date of Submission
1C	**Efficacy & Safety Evaluation**	**1 to 11 months**	**04-25-08**

A detailed discussion of this clinical study is included in the following sections.

5.2 Review Strategy

This medical officer was responsible for the entire safety and efficacy reviews for the GERD indication in the infant population (ages 1 month to <12 months). This study was a Phase 3 study involving 162 subjects diagnosed with GERD in the already stated age group. The collected data comprised of symptoms noted during and after the treatment period. The data, efficacy, and safety results were submitted electronically and were thoroughly evaluated. Since this investigational product is not marketed for this age group anywhere in the world, foreign post-marketing reports was not part of the sources of information for this review.

5.3 Discussion of Individual Studies

PK/PD studies are to be reviewed by the clinical pharmacology reviewers. This NDA includes one clinical efficacy and safety study which is a phase 3, randomized, double-blind, placebo-controlled, multicenter (several sites in the U.S. and Poland), parallel group study comprised of 162 patients (ages 1 month to less than 12 months) with symptomatic GERD. The date of first dose for this study was July 6, 2006, and the date of the last procedure was February 29, 2008.

6.0 INTEGRATED REVIEW OF EFFICACY

Of the 162 subjects that were enrolled in the study, all were included in efficacy analyses.

6.1 (b) (4) Indication

The objectives of this study were to assess the safety and efficacy of once-daily administration of lansoprazole pediatric suspension (0.2-0.3 mg/kg/day in infants ≤10 weeks of age or 1.0-1.5 mg/kg/day in infants >10 weeks of age) with symptomatic GERD.

The primary objectives were:

1. To assess the efficacy of lansoprazole compared to placebo in the reduction in the number of, or duration of episodes of crying, fussing, or

2. To assess the safety of lansoprazole pediatric suspension compared to placebo in infants with symptomatic GERD.

The secondary objectives were:

1. To assess the efficacy of lansoprazole compared to placebo, in:

• Decreasing the prevalence of other GERD symptoms collected by daily diary, including vomiting/spitting up, arching back, feeding refusal or stopping shortly after starting a feeding, wheezing, coughing, and hoarseness.

• Improving global assessments of GERD symptom severity made by the investigator and by the parent/primary caregiver.

• Improving wheezing symptoms as assessed by the investigator through physical examination.

2. To assess the effect of lansoprazole pediatric suspension compared to placebo on weekly measurements of the growth parameters body length and weight.

6.1.2 Methods/Study Design

All prior diagnostic tests (if any) used to establish the clinical diagnosis of suspected, symptomatic, or endoscopy-proven GERD regardless of whether they supported the final clinical diagnosis or not, were documented. The following diagnostic tests were employed for a diagnosis/evaluation of GERD:

• Upper gastrointestinal (GI) Series (i.e. the use of swallowed barium as a contrast medium for radiographic examination)
• Esophageal pH monitoring
• Endoscopy and biopsy of the esophageal mucosa
• Scintigraphy

This was a Phase 3, randomized, double-blind, placebo-controlled, multicenter, parallel group study with 3 periods: Pretreatment (Screening Visit and CGM, 7 to 14 days), Treatment (dosing with double-blind or open-label study drug as per protocol, up to 4 weeks), and Post-treatment (Follow-Up Telephone Calls and Visit, 30 days).

Pretreatment Period
Conservative GERD Management consisted of non-pharmacologic strategies. Tobacco smoke exposure was to have been reduced or eliminated from the immediate environment of the subject and at least 1 positioning strategy and 1 feeding strategy were to be utilized

and documented in the daily diary for 7 to 14 days prior to randomization into the Double-Blind Treatment Period. The parent/primary caregiver also recorded daily each feeding, including date and time of feeding, occurrence/amount of vomit or "spit-up," occurrence/duration of crying, fussing, or irritability during or within one hour after feeding, and whether the subject experienced any episodes of feeding refusal, arching back, wheezing, coughing, or hoarseness in a diary. Conservative GERD Management consisted of the following strategies:

• Positional Strategies:
  - Positional treatment (minimizing supine position while subject was awake, quietly holding the subject in semi-upright position for at least 30 minutes after each feeding, avoiding rigorous rocking, dressing or undressing, bathing or other activities than could cause reflux after eating)
  - Minimizing the placement of the baby in seated position (infant seat, car seat, or infant swing)
• Feeding Strategies:
  - Burping baby frequently (after every ½ to 1 oz [15-30 mL] of formula)
  - Offering smaller feedings more frequently to avoid overfilling the stomach.
  - Formula-Fed Infants:
    ◦ Hydrosylate (hypoallergenic) formula for all feedings, if the infant was thought to be allergic to cow's milk protein
    ◦ Formula, not already thickened by the manufacturer, was thickened with dry rice cereal at a ratio as determined by the investigator; parent/primary caregiver was instructed to cross-cut the bottle nipple to ease formula flow of thickened feedings
  - Breast-Fed Infants:
    ◦ Mothers had avoided/limited consumption of dairy products
    ◦ Breast milk was expressed/pumped and thickened with dry rice cereal at a ratio as determined by the investigator; parent/primary caregiver was instructed to cross-cut the bottle nipple to ease formula flow of thickened feedings.
• Other Strategies:
  - Avoidance of tight diapers or elastic waistbands;
  - Instruction was given to family members to make all attempts to eliminate tobacco smoke exposure to the infant. This included smoking outside and ideally changing their shirt prior to holding the baby if smoking cessation was not possible.

Double-Blind Treatment Period

Subjects who met all of the study criteria as outlined in the inclusion criteria and exclusion criteria were eligible for randomization to 1 of 2 study regimens: lansoprazole pediatric suspension (0.2-0.3 mg/kg/day for infants ≤10 weeks of age or 1.0-1.5 mg/kg/day for infants >10 weeks of age) or placebo. The dose was calculated based on the subject's age and body weight at Dosing Day 1 of the Double-Blind Treatment

Period. The subject's dose was not to have been changed for the entire duration of the Double-Blind Treatment Period. The investigator or designee contacted (b) (4) to register a subject entering the Double-Blind Treatment Period, and at each study visit during the Double-Blind Treatment Period. The Double-Blind Treatment Period consisted of 4 weeks of study drug with study visits at Dosing Day 1 (Study Visit 2), and at Weeks 1, 2, 3, and 4 (Study Visits 3, 4, 5, and 6, respectively).

Inclusion Criteria

Subjects who met the following criteria were eligible for randomization into the Double-Blind Treatment Period:

1. Prior to any study-specific procedures being performed, the subject's parent(s)/legally Authorized representative voluntarily signed an IRB/ Central Ethics Committee (CEC) approved ICF and any privacy statement/authorization form required by the region in which the subject was participating, after having its contents fully explained and all questions answered.
2. A hospitalized or outpatient male or female who was either a term or post term infant beyond the neonatal period (>28 days since birth), but less than 12 months of age or a preterm infant with a corrected age of at least 44 weeks, but less than 12 months of age at Dosing Day 1 of the Double-Blind Treatment Period.
3. At least 7 days postsurgery at the time of the Screening Visit and no anticipated need for surgery during the study.
4. Subject had a medical history consistent with clinical manifestations of GERD (regurgitation, vomiting or "spitting up," fussing/irritability, feeding refusal, crying during feeding, arching back, poor weight gain, or extraesophageal manifestations) or endoscopy-proven GERD.
5. Tobacco smoke exposure must have been reduced/eliminated from the immediate environment and at least one positioning strategy and one feeding strategy must have been utilized and documented in the daily diary for the last 7 days of the Pretreatment Period, prior to randomization into the Double-Blind Treatment Period.
6. Subject continued to be symptomatic for GERD based on whether the subject exhibited crying, fussing, or irritability during or within 1 hour after feeding in >25% of all feedings during the last 4 days of the Pretreatment Period, documented in the daily diary.

Exclusion Criteria

A subject was ineligible for study participation if the subject met any of the following criteria:

1. Body weight <2.0 kilogram at Dosing Day 1 of the Double-Blind Treatment Period.
2. Unstable, congenital or acquired, clinically significant disease of any major organ system (cardiovascular, respiratory, renal, hepatic, metabolic, etc) as determined by the investigator, including suspected and/or documented culture-

proven sepsis, or any other condition that suggested to the investigator that participation in this placebo-controlled study was inappropriate. Subjects with neurological deficit associated with cerebral palsy, and often associated with GERD, were not excluded as long as the subject was medically stable.

3. Coexisting disease affecting the esophagus (e.g., eosinophilic esophagitis, viral, bacterial or fungal infection) or caustic or physiochemical trauma to the esophagus.

4. Any congenital anomaly of the upper gastrointestinal tract that might have interfered with gastrointestinal motility, pH, absorption, or active or known history of necrotizing enterocolitis that had been surgically corrected.

5. Participation in any other drug research study at any time prior to the study or any time during the study.

6. Use of a PPI within 30 days prior to Dosing Day 1 of the Double-Blind Treatment Period.

7. Use of an H_2RA within 7 days prior to Dosing Day 1 of the Double-Blind Treatment Period.

8. Known allergy to any component or excipient of any PPI.

9. Use of prokinetics (e.g., metoclopramide) unless on a stable dose for at least 3 days prior to entering the Pretreatment Period, and the reason for use must be documented.

10. Continuous treatment with theophylline derivatives, digoxin, phenytoin, phenobarbital, or carbamazepine unless the serum drug levels are stable within the 7 days prior to Dosing Day 1 of the Double-Blind Treatment Period. The serum drug levels must have been monitored during the study to ensure that appropriate levels of these drugs were maintained, as per standard practice.

11. Requirement for continuous feeding. The presence of nasogastric (NG), orogastric (OG) or gastrostomy (G) tube did not disqualify a subject if all feedings were provided as bolus and the tube was >5 French.

12. Unwillingness or inability of parent/legally authorized representative, in the judgment of the investigator, to comply with study-related activities, such as measures associated with Conservative GERD Management, reconstitution of the study drug, returning to the study site for study visits, completion of the questionnaires, and daily diary.

13. Subjects with histories of acute life-threatening events due to manifestations of GERD.

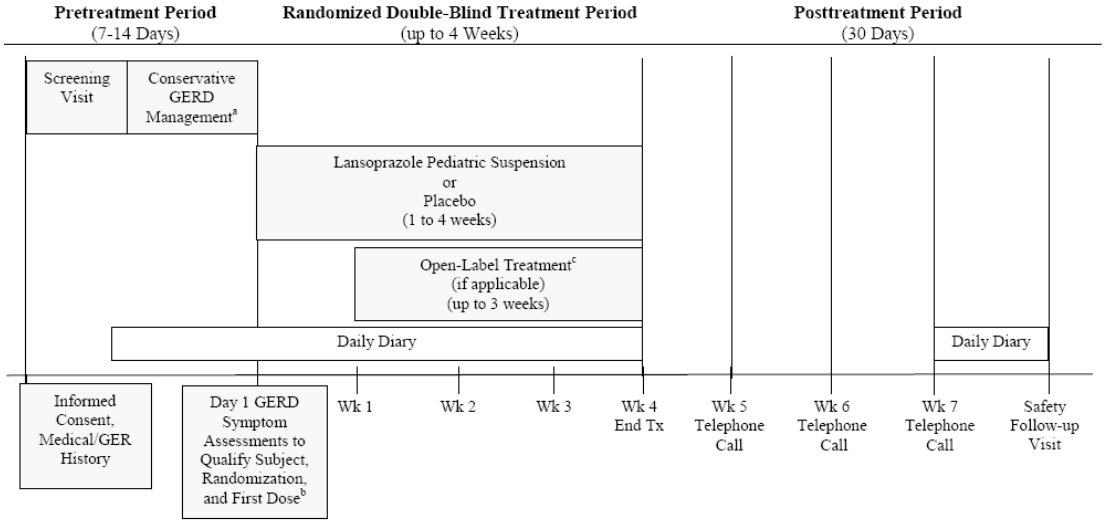
14. Results from laboratory test performed within the 14 days prior to Dosing Day 1 of the Double-Blind Treatment Period indicated a clinically significant abnormality in chemistry (including electrolytes, blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin), hematology (complete blood count [CBC], including differential), or urinalysis (urinalysis to be completed only if standard of care).

Open-Label Treatment

Open-Label Treatment was available for subjects who prematurely discontinued from the

Double-Blind Treatment Period due to lack of efficacy of study drug and not due to safety concerns. Entrance into the Open-Label Treatment Period was determined after completing at least one week in the Double-Blind Treatment Period, at the discretion of the investigator, and with parent(s) or legally authorized representative consent. Open-label treatment consisted of lansoprazole pediatric suspension (0.2-0.3 mg/kg/day for infants ≤10 weeks of age or 1.0-1.5 mg/kg/day for infants >10 weeks of age). The dose was calculated based on the subject's age and body weight at Day 1 of the Open-Label Treatment Period. The subject's dose was not changed for the entire duration of open-label treatment. Before starting open-label treatment, subjects underwent the Termination Visit procedures of the Double-Blind Treatment Period. Upon completion of the Termination Visit procedures from the Double-Blind Treatment Period and after the subject's parent(s)/legally authorized representative voluntarily signed an informed consent form and any privacy statement/authorization form required by the region in which the subject participated, the subject was enrolled in the Open-Label Treatment Period. Subjects who enrolled in the Open-Label Treatment Period completed only those visits not already completed during the Double-Blind Treatment Period. The total treatment duration with study drug, including the Double-Blind and Open-Label Treatment Periods, was not to have exceeded 4 weeks. The investigator or designee contacted (b) (4) at each study visit during the Open-Label Treatment Period. The study design schematic is shown below in Figure 1.

Figure 1. Study Design and Schematic



Tx = treatment; Wk = Week.

a Conservative GERD Management consisted of nonpharmacologic strategies. Tobacco smoke exposure was to be reduced/eliminated from the subject's immediate environment and at least one positioning strategy and one feeding strategy was to be utilized and documented. Conservative GERD Management continued during the Double-Blind Treatment Period and Open-Label Treatment, unless the investigator determined these strategies were of no benefit.

b Subjects met eligibility criteria for randomization into the Double-Blind Treatment Period.

c Open-label treatment was available for subjects who prematurely discontinued from the Double-Blind Treatment Period (after ≥1 week of treatment) due to lack of efficacy of study drug and not due to safety concerns. Subjects met eligibility criteria to enter the Open-Label Treatment Period.

Subjects who met all eligibility criteria were randomized in a 1:1 ratio to receive 1 of 2 treatments (lansoprazole pediatric suspension [0.2-0.3 mg/kg/day for infants ≤10 weeks of age or 1.0-1.5 mg/kg/day for infants >10 weeks of age] or placebo) administered orally as a single daily dose for 4 weeks.

162 subjects with symptomatic GERD who were either term or post-term infants beyond the neonatal period (>28 days since birth), but less than 12 months of age or preterm infants with a corrected age of at least 44 weeks, but less than 12 months of age at Dosing Day 1 of the Double-Blind Treatment Period were enrolled at approximately 20 investigative sites in the US and Poland.

Table 3. Efficacy and Safety Measurements and Flow Chart

	Pretreatment Period		Double-Blind Treatment Period/Open-Label Treatment[a]					Posttreatment Period				
Procedures	Screening Visit (Prior to Conservative GERD Management)	Conservative GERD Management (-7 to -14)[b]	Dosing Day 1 (Randomization)	Wk 1 Visit	Wk 2[c] Visit	Wk 3[c] Visit	Wk 4/ Termination Visit[d]	Wk 5[c] Phone Call	Wk 6[c] Phone Call	Wk 7[c] Phone Call	Week 8/ Safety Follow-Up Visit[c]	Unscheduled Visit[e] (Anytime during the study)
Study Visit Number	1		2	3	4	5	6				7	
Informed Consent PRIOR to any Study Related Procedures	X[f]											
[redacted] Contact	X		X	X	X	X	X				X	
Medical History	X[g]											
Infant Gastroesophageal Reflux Medical History	X											
Complete Physical Examination	X						X				X	X
Brief Physical Examination			X	X	X	X						
Vital Signs and Growth Parameters	X		X	X	X	X	X				X	X
Clinical Laboratory Analysis	X[h]						X				X[n]	X
Adverse Events			X[i]	X	X	X	X	X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X
Study Drug Compliance and Accountability Reviewed				X	X	X	X					
Physician Global Assessment of GERD Severity			X	X	X	X	X				X[p]	
Parent Global Assessment of GERD Severity			X	X	X	X	X				X[p]	
Parent Global Assessment of Change in GERD Symptoms							X[m,n]				X[o,p]	
Conservative GERD Management		X	X[j]	X[j]	X[j]	X[j]	X[j]					
Daily Diary		X	X	X	X	X	X			X	X[p]	
Study Drug Dispensed			X[k]	X[k,l]	X[k,l]	X[k,l]						

a Subjects enrolled in open-label treatment completed only those visits not already completed during the Double-Blind Treatment Period. The total treatment duration, including the Double-Blind Treatment Period and open-label treatment, should not have exceeded 4 weeks.
b Pretreatment Period consists of 7 to 14 days of Conservative GERD Management.
c Visit/Telephone Call Windows: ± 2 days of the scheduled visit/telephone call, relative to Dosing Day 1 of the Double-Blind Treatment Period.
d Prior to beginning open-label treatment, subjects underwent the Double-Blind Termination Visitl procedures.
e At the Unscheduled Visits, additional procedures were performed when judged medically necessary by the investigator.
f Parent(s) or legally authorized representative written informed consent was obtained prior to the Screening Visit procedures and prior to beginning open-label treatment.
g Including documentation of prior diagnostic tests (if any) used to establish the diagnosis of suspected, symptomatic, or endoscopically proven GERD.
h Screening clinical laboratory analysis was to be completed within the 14 days prior to Dosing Day 1 of the Double-Blind Treatment Period.
i Adverse events reported from Screening through the Pretreatment Period were recorded.
j Conservative GERD Management continued through the Double-Blind Treatment Period and open-label treatment, unless the investigator determined these strategies were of no benefit.
k The dose was calculated based on the subject's age and body weight at Dosing Day 1 of the Double-Blind Treatment Period. The subject's dose was not to be changed for the duration of the Double-Blind Treatment Period.
l The dose was calculated based on the subject's age and body weight at Day 1 of open-label treatment. The subject's dose was not to be changed for the duration of open-label treatment.
m The parent/primary caregiver rated the observed global change of the subject's GERD symptoms at the Week 4/Termination Visit compared to Dosing Day 1 of the Double-Blind Treatment Period.
n Abnormal laboratory values at the Week 4 or at the Termination Visit, considered by the investigator to be clinically significant, must be repeated. Other laboratory analyses may also have been performed, if judged medically necessary by the investigator.
o The parent/primary caregiver rated the observed global change of the subject's GERD symptoms at the Posttreatment Period Safety Follow-Up Visit compared to the Week 4/Termination Visit.
p Only subjects who completed 4 weeks of treatment with study drug.

This study used accepted methods of daily diary recording of various GERD symptoms by the parent/caregiver and global ratings of symptom severity to assess GERD symptoms at weekly time-points during treatment with study drug by the investigator and parent/caregiver. A subject was considered a responder to treatment if the subject had a reduction from Baseline (Day -7 to -1) to the end of the Double-Blind Treatment Period of ≥50% in the percentage of feedings for which crying/fussiness/irritability episodes occurred during or within 1 hour after feeding or ≥50% reduction in average duration of episodes.

Efficacy was assessed using data from the daily diaries and global symptom assessments made by the parent/primary caregiver and from the physical examination and global symptom assessments made by the investigator. Baseline diary-based information was derived from diary entries during the last 7 days of the Pretreatment Period prior to the start of the Double-Blind Treatment Period.

The parent/primary caregiver was given a daily diary on the first day of the Pretreatment Period, and at every study visit during the Double-Blind and Open-Label Treatment Periods, if applicable. Throughout the Pretreatment Period, Double-Blind Treatment Period, open-label treatment (if applicable), and for the 7 days prior to the Post-treatment Period Safety Follow-Up Visit, the parent/primary caregiver recorded daily each feeding, including date and time of feeding, occurrence/amount of vomit or "spit-up," occurrence/duration of crying, fussing, or irritability during or within one hour after feeding, and whether the subject experienced any episodes of feeding refusal, arching back, wheezing, coughing, or hoarseness. The daily diary was returned to the site, reviewed for completeness by the investigator or designee, and recorded at each study visit. For consistency, the same parent/primary caregiver was urged to complete the daily diary assessments throughout the study. The daily diary assessments for the 4 days prior to randomization were used to determine if the subject qualifies to enter the Double-Blind Treatment Period. The daily diary assessments for the 7 days prior to randomization into the Double-Blind Treatment Period were considered the baseline assessments for all efficacy comparisons.

On Dosing Day 1 of the Double-Blind Treatment Period, health and physical evaluations were performed, the investigator completed the Physician Global Assessment of GERD Severity, and the parent/primary caregiver completed the Parent Global Assessment of GERD Severity. A subject's dose was also calculated at this visit and was based on his/her age and body weight; this dose remained unchanged for the entire duration of the Double-Blind Treatment Period. The study site personnel demonstrated to the parent/primary caregiver the reconstitution and administration of the study drug and, on Dosing Day 1 of the Double-Blind Treatment Period, provided them with the first 2 kits of study drug. At all subsequent study visits, study site personnel verified that the parent/primary caregiver was correctly reconstituting and administering the study drug and provided study drug kits to the parent/primary caregiver. Study drug was administered by the parent/caregiver within 45 minutes of reconstitution. Subjects were fasting for 30 minutes before dosing. The subject was not fed for at least 30 minutes post-dosing.

During the Double-Blind Treatment Period, visits occurred weekly for 4 weeks. During this period, the parent/primary caregiver recorded in the daily diary each feeding, including date and time of each feeding; occurrence/amount of vomit or "spit up"; occurrence/duration of crying, fussing, or irritability during or within one hour after feeding; whether the baby experienced any episodes of feeding refusal, arching back, wheezing, coughing, or hoarseness and whether the baby received study drug. Conservative GERD Management was continued throughout the Double-Blind Treatment

Period, unless the investigator determined that these strategies were of no benefit to the subject. The status (continued or discontinued) of CGM was documented at each study visit. Open-label treatment with lansoprazole pediatric suspension (0.2-0.3 mg/kg/day for infants ≤10 weeks of age or 1.0-1.5 mg/kg/day for infants >10 weeks of age) was available for subjects who prematurely discontinued from the Double-Blind Treatment Period because of lack of efficacy of study drug (GERD symptoms persisted) and not due to safety concerns, i.e., subjects were not permitted to switch to open-label treatment if there were any safety concerns. Entrance into the Open-Label Treatment Period was allowed after the subject completed at least 1 week of the Double-Blind Treatment Period; the switch to open-label treatment was at the discretion of the investigator and with the consent of the subject's parent(s) or legally authorized representative. All subjects who switched to open-label treatment underwent assessments during the Double-Blind Treatment Period Termination Visit and proper informed consent was obtained from the parent(s) or legally authorized guardian before the subject was enrolled in the Open-Label Treatment Period.

The first dose of open-label treatment was administered at the study site on Day 1 of the Open-Label Treatment Period unless a dose from the Double-Blind Treatment Period had already been administered that day. The subject's study drug dose was calculated based on the subject's age and body weight at Day 1 of the Open-Label Treatment Period and was not changed for the entire duration of the Open-Label Treatment Period. Information regarding the administration of the dose (if applicable) was recorded in the eCRF. The total treatment duration with study drug, including the Double-Blind and Open-Label Treatment Periods, was not to have exceeded 4 weeks. Subjects who were enrolled in open-label treatment had weekly visits and completed only those visits not already completed during the Double-Blind Treatment Period. The parent(s)/primary caregiver continued to make daily diary entries and CGM strategies were continued throughout Open-Label Treatment Period. The CGM strategies were discontinued at any point during the study if the investigator determined that these strategies were of no benefit to the subject. Efficacy assessments were based on changes in GERD symptoms documented in the daily diary, Physician Global Assessment of GERD Severity, Parent Global Assessment of GERD Severity, and the Parent Global Assessment of Change in GERD Symptoms.

Primary and secondary endpoints are specified in Sections 6.1.5 and 6.1.6, respectively. Safety was monitored via physical examinations (including assessment of aspiration and/or wheezing), laboratory analyses, vital signs, concomitant medication use, and adverse event (AE) reports (including aspiration). Subjects continued to be evaluated for safety throughout the Post-treatment Period with safety follow-up telephone calls that were conducted weekly from Week 5 to Week 7. If a subject prematurely discontinued from the Double-Blind Treatment Period and was not enrolled in the Open-Label Treatment Period or was prematurely discontinued from Open-Label Treatment Period, the site contacted the parent/primary caregiver via telephone 14 days after the last dose of study drug to assess adverse events and concomitant medications. All subjects were to return to the study site 30 days after the last dose of study drug for the Post-treatment Period Safety Follow-Up Visit. For subjects who completed 4 weeks of treatment, the

parent/primary caregiver was asked to complete the daily diary for the 7 days immediately preceding the Safety Visit. The investigator or designee then reviewed the daily diary for completeness and entered the diary data. The investigator completed the Physician Global Assessment of GERD Severity. The parent/primary caregiver completed the Parent Global Assessment of GERD Severity and the Parent Global Assessment of Change in GERD Symptoms.

6.1.3 Demographics

Baseline demographic characteristics are summarized by treatment group in Table 4. Overall, the subjects in this study were primarily white (79.6%) and were not Hispanic or Latino (96.9%). There were equal percentages of male and female subjects (50.0% of each). Fifty-eight percent of subjects were enrolled at sites in Poland and 42.0% of subjects were enrolled at sites in the US. Two-thirds of the subjects (66.7%) were >10 weeks of age, the remaining subjects (33.3%) were ≤10 weeks. Demographic characteristics of subjects were similar across treatment groups.

Table 4.

Demographic and Baseline Characteristics

Variable	Lansoprozole (N=81)	Placebo (N=81)	All Subjects (N=162)	P-value@
Gender				0.530
Male	38 (46.9%)	43 (53.1%)	81 (50.0%)	
Female	43 (53.1%)	38 (46.9%)	81 (50.0%)	
Ethnicity				0.059
Hispanic or Latino	5 (6.2%)	0	5 (3.1%)	
Not Hispanic or Latino	76 (93.8%)	81 (100.0%)	157 (96.9%)	
Race				>0.999
American Indian/Alaska Native	0	0	0	
Asian	0	1 (1.2%)	1 (0.6%)	
Black of African Heritage	13 (16.0%)	14 (17.3%)	27 (16.7%)	
Native Hawaiian or other Pacific Islander	0	0	0	
White	65 (80.2%)	64 (79.0%)	129 (79.6%)	
Multiracial	3 (3.7%)	2 (2.5%)	5 (3.1%)	
Country				0.152
POLAND	42 (51.9%)	52 (64.2%)	94 (58.0%)	
USA	39 (48.1%)	29 (35.8%)	68 (42.0%)	
Age Stratum for Dosing #				0.243
<=10 Weeks	31 (38.3%)	23 (28.4%)	54 (33.3%)	
>10 Weeks	50 (61.7%)	58 (71.6%)	108 (66.7%)	

At baseline
@ For categorical variables, p-values are from Fisher's Exact tests. The test for race uses Caucasian vs Black vs Other. For ages, weight, and length, p-values are from one-way analyses of variance using treatment as the factor.

Demographic and Baseline Characteristics

Variable	Lansoprozole (N=81)	Placebo (N=81)	All Subjects (N=162)	P-value@
Weight (kg) #				
N	81	81	162	
Mean	6.1	6.4	6.2	0.309
SD	1.48	1.65	1.57	
Median	5.9	6.2	6.0	
Min-Max	4-9	4-11	4-11	
Length (cm) #				
N	81	81	162	
Mean	62.4	63.4	62.9	0.316
SD	5.86	6.76	6.33	
Median	61.0	62.0	61.5	
Min-Max	53-78	52-80	52-80	

At baseline
@ For categorical variables, p-values are from Fisher's Exact tests. The test for race uses Caucasian vs Black vs Other. For ages, weight, and length, p-values are from one-way analyses of variance using treatment as the factor.

6.1.4 Patient Disposition

Two-hundred sixteen subjects were screened, and 54 subjects were screening failures; thus 162 were eligible for enrollment and randomization (by remaining symptomatic during the Pretreatment CGM Period). These subjects were randomized in a 1:1 ratio to double-blind treatment of lansoprazole pediatric suspension or placebo. The mean duration of double-blind treatment was 22 days for lansoprazole and 21 days for placebo.

A total of 66 subjects prematurely discontinued treatment during the study. During the Double-Blind Treatment Period, 39.5% of subjects prematurely discontinued from the lansoprazole pediatric suspension group and 42.0% of subjects prematurely discontinued from the placebo group. Three of these subjects were discontinued from double-blind treatment primarily due to adverse events (2 lansoprazole and 1 placebo). Most subjects (n=57) discontinued double-blind treatment primarily due to therapeutic failure (34.6% and 35.8% of subjects in the lansoprazole and placebo groups, respectively). Fifty-five of these subjects (26 from the lansoprazole pediatric suspension group and 29 from the placebo group) then entered the Open-Label Treatment Period and were treated with lansoprazole. Two subjects prematurely discontinued from lansoprazole open-label treatment.

Please refer to Section 7.3.3 for a discussion of patients who dropped out of the study secondary to adverse events.

6.1.5 Analysis of the Primary Endpoint(s)

The primary endpoint of this study was the percentage of subjects in each treatment group who were classified as responders to treatment at Week 4 of the Double-Blind Treatment Period (or at time of premature termination from the Double-Blind Treatment Period).

A subject was considered a responder to treatment if the subject had a reduction from Baseline (Day -7 to 1, prior to dosing) to the end of the Double-Blind Treatment Period of ≥50% in the percentage of feedings in which crying/fussiness/irritability episodes occurred during or within 1 hour after feeding or ≥50% reduction in average duration of episodes.

The percentages of subjects who responded to treatment in the lansoprazole pediatric suspension and placebo groups were the same (54.32%). A summary of the results is provided in Table 5.

Table 5. Percentage of Subjects Responding to Double-Blind Treatment

Variable	Lansoprazole Pediatric Suspension % (n/N)	Placebo % (n/N)
Responders	54.32 (44/81)	54.32 (44/81)

Note: If a subject was prematurely discontinued from the study with <4 weeks of treatment, then the last available week with data was used.

There are several issues involved with the above primary endpoint that affect the interpretation of the obtained data. The diagnosis of GERD in this age group is questionable; obtaining a patient history is only possible through the parents' observations of possible symptoms due to GERD. Secondly, using the stomach pH to determine whether an infant is suffering from GERD is inaccurate, in that, changes in stomach pH in this age group are highly variable at different times[11]. Thirdly, using behavior patterns (such as crying, fussing, or irritability) for labeling infants with GERD is highly subjective and can affect the patient population, which in turn, can significantly affect the final outcome of the study. A fourth point is that the decrease in the number of occurrences of the behavior patterns (crying, fussing, or irritability) after the administration of lansoprazole to the infants does not necessarily signify that there was positive response to the GERD treatment; behavior-based criteria can be affected by many other factors which could, ultimately, affect the interpretation of results.[12] ,[13] All the above points can affect the interpretation of the results, which can in turn, seriously affect the efficacy results of the medication.

Table 6. Primary efficacy responder analysis and associated sensitivity analyses of the primary endpoint

Efficacy Analysis	Analysis Performed	Lansoprazole Pediatric Suspension % (n/N)	Placebo % (n/N)
Primary	Responders to treatment	54.32 (44/81)	54.32 (44/81)
Secondary: Sensitivity analyses on the primary efficacy variable	Responders to treatment with noncompleters considered treatment failures	45.68 (37/81)	40.74 (33/81)
	Responders to treatment with Baseline derived over Days -4 to -1	58.02 (47/81)	50.62 (41/81)
	Responders to treatment for subjects with ≤10 Days CGM pretreatment	52.94 (36/68)	52.24 (35/67)
	Responders to treatment for subjects with >10 Days CGM pretreatment	61.54 (8/13)	64.29 (9/14)

[11] Buret, Andre G., How stress induces intestinal hypersensitivity. American Journal of Pathology. 2006;168:3-5.

[12] Buret, Andre G. How stress induces intestinal hypersensitivity. American Journal of Pathology. 2006;168:3-5.

[13] Crill, Catherine M., Bugnitz, Mark C., & Hak, Emily B. Evaluation of gastric pH and guaiac measurements in neonates receiving acid suppression therapy during extracorporeal membrane oxygenation. Pharmacotherapy. 2004;24(9):1130-1136.

As per Table 6, the percentage of responders to treatment in both the LPS and placebo groups were the same (54.32%). The percentage of responders to treatment for subjects with less than or equal to 10 days of CGM pretreatment for the LPS Group was 52.94% and 52.24% for the placebo group. In fact, the percentage of responders to treatment for subjects with greater than 10 day of CGM pretreatment was slightly larger in the placebo group (64.29%) than the LPS Group (61.54%).

Table 7. Efficacy Results

Variable	Lansoprazole Pediatric Suspension (N=81)		Placebo (N=81)	
	Baseline Mean % (SD)	**Week 4** Mean Change from Baseline (SD)	**Baseline** Mean % (SD)	**Week 4** Mean Change from Baseline (SD)
% of Feedings With Symptom (during or within 1 hour after feeding)				
Crying, Fussing, or Irritability	51.0 (20.4)	-19.9 (23.1)	52.4 (20.5)	-19.9 (22.8)
Stopping Feeding Soon after Starting	21.4 (23.4)	-6.8 (19.8)	19.3 (20.5)	-7.5 (14.8)
Spitting-up /Vomiting	53.7 (24.0)	-14.1 (24.4)	47.8 (24.8)	-11.4 (17.3)
% of Feedings With Spitting-Up/Vomiting (by amount vomited)				
Vomited:				
<1/2 Feeding	73.5 (28.5)	3.9 (29.3)	76.1 (26.6)	3.5 (28.5)
>1/2 but <Full Feeding	13.4 (19.2)	-1.9 (24.7)	12.7 (18.7)	-3.8 (17.6)
Full Feeding	4.8 (11.9)	-1.2 (13.6)	3.3 (8.2)	-0.5 (10.1)
% of Days With Symptom (24-hour recall)				
Feeding Refusal	40.4 (39.9)	-13.8 (33.5)	32.7 (33.4)	-10.1 (24.2)
Arching of Back	67.9 (34.9)	-19.6 (31.8)	67.9 (37.1)	-18.0 (32.1)
% of Days With Symptom for Subjects With the Symptom at Baseline (24-hour recall)				
Coughing	72.8 (30.9) n=61	-9.3 (38.2)	76.7 (28.4) n=58	-13.8 (33.6)
Wheezing	53.8 (29.3) n=32	-17.0 (34.7)	69.6 (29.8) n=36	-16.4 (39.2)
Hoarseness	51.6 (35.0) n=18	-12.0 (41.2)	61.7 (29.7) n=25	-30.1 (38.5)

As per Table 7, no clinical significance was noted between the two groups in Week 4 when looking at the crying, fussing, or irritability symptoms one hour after feeding.

By adhering to the primary endpoints of this study and based on the obtained data, it can be concluded that Lansoprazole Pediatric Solution did not show any efficacy in either term or postterm infants beyond the neonatal period (> 28 days since birth), but less than 12 months of age.

6.1.6 Secondary Endpoint(s)

The secondary endpoints in this study are as follows:

1. To assess the efficacy of lansoprazole pediatric suspension compared to placebo in:

    • Decreasing the prevalence of other GERD symptoms collected by daily diary, including vomiting/spitting up, arching back, feeding refusal or stopping shortly

after starting a feeding, wheezing, coughing, and hoarseness. Please refer to Table 7 for the presenting data.

• Improving global assessments of GERD symptom severity made by the investigator and by the parent/primary caregiver. Please refer to Table 8 for the data.

• Improving wheezing symptoms as assessed by the investigator through physical examination. Please refer to Table 7 for the data.

2. To assess the effect of lansoprazole pediatric suspension compared to placebo on weekly measurements of the growth parameters of body length and weight. Please refer to the data in Table 9.

There was no clinical significance amongst the two groups when monitoring the symptoms of feeding stoppage, spitting-up, and vomiting after 4 weeks (Table 7).

Additionally, no clinical significance was noted when comparing arching of back on week 4 in the two groups. Furthermore, there was 30.1% improvement in hoarseness in week 4 in the placebo group as compared to the LPS Group (12.0%). The symptom of wheezing showed no clinical significance in week 4 amongst the two groups.

Table 8. Summary of secondary endpoints based on global assessment of GERD severity at Week 4 of Double-Blind Treatment Period

Variable	Lansoprazole Pediatric Suspension (N=81)			Placebo (N=81)		
	Parent/ Primary Caregiver		Investigator	Parent/ Primary Caregiver		Investigator
Baseline Severity Grade: n/N (%)	≥mod	73/81 (90.1)	72/80 (90)	66/81 (81.5)		64/81 (79)
	≥sev	28/81 (34.6)	21/80 (26.2)	30/81 (37)		26/81 (32.1)
% of Subjects Improved ≥1 Grade Level at Week 4	55.6%		55.0%	50.6%		49.4%
Parent Assessment of Symptom Change from Baseline: n (%)	Much better	26 (32.1)	not applicable	Much better	23 (28.4)	not applicable
	Slightly Better	18 (22.2)		Slightly Better	21 (25.9)	
	No Change	17 (21)		No Change	24 (29.6)	
	Slightly worse	11 (13.6)		Slightly worse	9 (11.1)	
	Much worse	2 (2.5)		Much worse	1 (1.2)	
	Missing	7 (8.6)		Missing	3 (3.7)	

As per Table 8, there is little to no clinical significance between the LPS and the placebo groups when reviewing the percentages of subjects with improvement at Week 4 (55.6 and 50.6, respectively) as determined by the parent/primary caregiver. Similarly, the same can be said for subject improvement as per the investigator at Week 4 in the LPS and placebo groups. In addition, the parent assessment of symptom change from baseline in both groups was quite similar and there were no clinical differences.

Table 9. Summaries of treatment-emergent aspiration, wheezing and mean changes in growth parameters (body weight & length) during Double-Blind Treatment Period in both groups

Investigator Assessment of Aspiration Status at Week 4				
Treatment	**Present at Baseline?**	**Number of Subjects with Aspiration Present at Week 4**		
		No	**Yes**	**Total**
Lansoprazole Pediatric Suspension	No	71	6	77
	Yes	2	2	4
Placebo	No	69	2	71
	Yes	2	8	10
Investigator Assessment of Wheezing Status at Week 4				
Treatment		**Improved**	**Same**	**Worsened**
Lansoprazole Pediatric Suspension: n/N (%)		4/6 (66.7%)	75/81 (92.6%)	2/81 (2.5%)
Placebo: n/N (%)		3/5 (60%)	76/81 (93.8%)	2/81 (2.5%)
Growth Parameter Mean Change from Baseline to Week 4				
Treatment	**Parameter**	**Mean Change from Baseline**	**SD**	**p-Value**
Lansoprazole Pediatric Suspension	Weight (kg)	0.5	0.39	0.314
	Length (cm)	2.0	1.47	0.131
Placebo	Weight (kg)	0.6	0.29	not applicable
	Length (cm)	2.6	1.69	
Note: p-values are from one-way analysis of variance with treatment as the factor.				

As per Table 9, no clinical differences (in terms of weight or length gain) were noted in the Lansoprazole Pediatric Suspension (LPS) Group and the placebo group after 4 weeks during the Double-Blind Treatment Period. Additionally, there was no clinical significance in wheezing status after 4 weeks of treatment in either group. Furthermore, no clinical significance emerged after 4 weeks of treatment in the LPS Group in terms of the aspiration status.

6.1.7 Subpopulations

This study encompassed sites in two countries, Poland and the U.S. The numbers of patients in each group and in each country are listed in Table 10. As per the data, no clinically significant effect was noted in the LPS Group in either the U.S. or Poland.

Table 10.

Subgroup Analysis - Percent of Subjects Responding to Double-Blind Treatment
By Country

Country	Treatment	N	Percent Responders	Treatment Difference (S.E.)	95% CI	P-value @
Poland	Lansoprazole	42	24/ 42(57.14%)	3.297% (10.301)	-16.892, 23.485	0.970
	Placebo	52	28/ 52(53.85%)			
USA	Lansoprazole	39	20/ 39(51.28%)	-3.890% (12.221)	-27.842, 20.062	
	Placebo	29	16/ 29(55.17%)			

@ P-Value from CMH analysis (general association statistic), with country as the stratifying factor.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The data in this submission did not show any efficacy for lansoprazole in the age group 1 month to <12 months of age. No delayed effect or tolerance was noted. No efficacy was noted also at different doses (0.2-0.3 mg/kg/day for infants ≤10 weeks of age and 1.0-1.5 mg/kg/day for infants >10 weeks of age).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The data from the LPS Group showed no clinical significance as compared to the placebo group in this age group. No efficacy was noted.

6.1.10 Additional Efficacy Issues/Analyses

For flaws in this study regarding the collection of data, please refer to section 6.1.5. Unfortunately, obtaining meaningful data for the treatment of GERD with PPI's in this age group has been difficult. As of the writing of this NDA, there has not been any clinically significant data supporting the use of PPI's for GERD in this age group. It is the opinion of this writer that the use of PPI's in this infant age group is not warranted since the efficacy of PPI's is not demonstrated in this trial.

7. INTERGRATED REVIEW OF SAFETY

Summary of Safety Results and Conclusions

7.1 Methods

Among the variables being analyzed for safety were adverse events (AE), clinical laboratory results, vital signs, growth parameters, physician/caretaker assessment, and physical examinations. All 162 subjects received at least one dose of study drug and were included in the safety analyses. Study drug exposure is presented by treatment group in Table 11.

Table 11. Study Drug Exposure of Subjects by Study Period

Duration	Lansoprazole Pediatric Suspension (N=81)	Placebo (N=81)
Double-Blind Treatment Period		
N	81	81
Mean±SD (days)	22.2±9.23	21.1±9.81
Median (days)	28.0	28.0
Minimum-Maximum (days)	1-33	3 – 31
Incremental Exposure (n of subjects)		
1-7 days	4	14
8-14 days	19	11
15-21 days	6	5
22-28 days	19	24
29-35 days	33	27
Cumulative Exposure (n of subjects)		
≥1 day	81	81
>7 days	77	67
>14 days	58	56
>21 days	52	51
>28 days	33	27
>30 days	6	2
Open-Label Treatment Period		
N	55	
Mean±SD (days)	18.3±5.11	
Median (days)	21.0	
Minimum-Maximum	2-25	
Incremental Exposure (n of subjects)		
1-7 days	4	
8-14 days	6	
15-21 days	31	
22-28 days	14	
Cumulative Exposure (n of subjects)		
≥1 day	55	
>7 days	51	
>14 days	45	
>21 days	14	
>23 days	2	

Note: Data for duration are number of subjects per duration category.

During the Double-Blind Treatment Period, 40.7% of subjects (33/81) in the LPS Group and 33.3% of subjects (27/81) in the placebo group had a duration of treatment of >28 days. The median duration of treatment during the Double-Blind Treatment Period was 28 days for each of the 2 treatment groups. Maximum double-blind treatment exposure for LPS and placebo was 33 and 31 days, respectively. For those subjects who received LPS during the Double-Blind Treatment Period, 31 subjects received 0.2−0.3 mg LPS and 50 subjects received 1.0−0.5 mg LPS.

Twenty-six subjects in the LPS Group and 29 subjects in the placebo group entered open-label treatment. Forty-five of the 55 subjects who entered open-label treatment had a duration of open-label treatment of 15 to 25 days.

Adverse events were collected from the time that the informed consent was signed through the Post-treatment Period Safety Follow-Up Visit. Treatment-emergent AEs were defined as those that were reported after the first dose of study drug up until 30 days after

the last dose of study drug. Treatment-related AEs were defined as those treatment-emergent events that the investigator considered to be possibly related to study drug.

An AE was defined as any untoward medical occurrence in a patient or clinical trial subject. An AE represented a change from baseline and thus can be any new or worsened untoward and unintended sign, symptom, or disease (including an abnormal laboratory or imaging finding). An untoward finding generally:

• Indicated a new diagnosis
• Necessitated therapeutic intervention
• Required an invasive diagnostic procedure
• Required termination or a change in dose of study drug or a concomitant medication
• Was considered unfavorable by the investigator for any reason
• Repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality was not considered an intervention
• Overdose was also considered an AE
• Some abnormal findings may not have been considered untoward by the investigator and thus were not AEs. Examples include, but were not limited to, small changes in laboratory values or vital signs outside of the normal range, that were not deemed indicative of a new or worsened diagnosis

Adverse events during the Double-Blind Treatment Period were summarized through the last day of double-blind treatment for those subjects who entered open-label treatment. For subjects who did not enter open-label treatment, adverse events during the Double-Blind Treatment Period included those that occurred during dosing and for the 30 days after last dose of study drug. Adverse events that occurred during the Open-Label Treatment Period included those that occurred after first dose of open-label treatment through 30 days after last dose of study drug.

7.1.1 Discussion of Clinical Studies Used to Evaluate Safety

For a detailed review of the composition of the study locations please refer to Section 6.1.3 and the tables within that section. Please refer to Table 3 for a listing of safety measurements. The efficacy results are noted in Tables 6 and 7.

7.1.2 Adequacy of Data

Appropriate safety coding was conducted in this study. MedDRA was the source used for preferred terms and the terms were used appropriately and consistently.

7.1.3 Pooling Data Across Studies and Compare Incidence

The number of patients in the study (162) was adequate. Patients were selected from 20 centers within the U.S. and Poland. Although the patients in the Polish centers were all listed as “white” and the patients in the U.S. centers were composed of different races

and ethnicities, the data noted from centers in both countries did not exhibit any major differences.

7.2 Adequacy of Safety Assessments

The safety evaluations performed were adequate. The doses and durations of exposure were appropriate. All important findings were adequately explored.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

An adequate number of subjects were exposed to lansoprazole. The doses and durations of exposure were adequate to assess safety for the intended use. This was a placebo-control study which yielded results showing no efficacy with regards to lansoprazole in the infant population (ages 1 month to <12 months).

7.2.2 Explorations for Dose Response

There was no difference amongst the different dose levels with regards to adverse events; no pattern was noted in terms of adverse events at different dose levels.

7.2.3 Special Animal and/or In Vitro Testing

As of the writing of this NDA, no new adverse reactions have been noted in preclinical models. The preclinical findings are the same as the findings initially submitted for adults.

7.2.4 Routine Clinical Testing

The routine clinical testing of study subjects was adequate. The methods for acquisition of laboratory, vital signs, and adverse event data in the development program are described in the relevant sections (7.3.4, Significant Adverse Events; 7.4.1, Common Adverse Events; 7.4.3, Vital Signs; and Table 3, Efficacy & Safety Measurements and Flow Chart).

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to Section 4.3 for a full summary.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As of the writing of this NDA, no new side effects have been noted in PPI's. However, safety concerns have been raised regarding a possible association regarding the long-term use off PPI's and osteoporosis, namely risk of hip fractures[14].

[14] Yang, Y; Lewis JD.; Epstein S., Metz, DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA. 2006; 296:2947-2953.

7.3 Major Safety Results and Discussion

For a discussion of significant adverse events, please refer to Section 7.3.4.

Table 13 in Section 7.3.3 lists a summary of adverse events that led to the premature discontinuation of subjects from the study. Additionally, the subject number and gender are listed. For an explanation of each subject's discontinuation from the study, please refer to the above-mentioned section.

7.3.1 Deaths

No deaths occurred during this study.

7.3.2 Nonfatal Serious Adverse Events

During the Double-Blind Treatment Period, 12 subjects (10 subjects in the LPS Group vs 2 subjects in the placebo group, p=0.032) experienced ≥1 treatment-emergent SAE (Table 12); all of these subjects were hospitalized. Ten of the 12 subjects who experienced serious adverse events were at sites in Poland (8 subjects received lansoprazole, 2 subjects received placebo). It should also be noted that 2 of the 10 subjects who experienced serious adverse events in the LPS Group during the Double-Blind Treatment Period had serious adverse events that were considered congenital anomalies (both treated in Poland), while 2 additional subjects (Subjects both treated in Poland) had other potentially relevant medical histories (Table 12a). Two additional subjects at sites in Poland experienced ≥1 treatment-emergent serious adverse event during open-label lansoprazole treatment (or within 30 days following the last dose of open-label treatment). The two subjects with serious adverse events at sites in the US were both in the LPS Group (Statistical Tables 12 and 12b, respectively). None of the serious adverse events reported during the Double-Blind or Open-Label Treatment Periods were assessed by the investigator as related to study drug administration. Details for the serious adverse events that occurred during both treatment periods are presented in Table 12a.

Table 12. Serious Adverse Events During the Double-Blind Treatment Period

MedDRA System Organ Class/ High Level Term/ Preferred Term	Lansoprazole (N=81)	Placebo (N=81)	P-Values @
Total Subjects with at Least One Adverse Event	10 (12%)	2 (2%)	0.032*
GASTROINTESTINAL DISORDERS	3 (4%)	0	
DIARRHOEA (EXCL INFECTIVE)	2 (2%)	0	0.497
DIARRHOEA	2 (2%)	0	
GASTROINTESTINAL STENOSIS AND OBSTRUCTION NEC	1 (1%)	0	>0.999
ILEUS	1 (1%)	0	
INFECTIONS AND INFESTATIONS	7 (9%)	2 (2%)	
BACTERIAL INFECTIONS NEC	1 (1%)	0	>0.999
CELLULITIS	1 (1%)	0	
EAR INFECTIONS	0	1 (1%)	>0.999
OTITIS MEDIA ACUTE	0	1 (1%)	

MedDRA System Organ Class/ High Level Term/ Preferred Term	Lansoprazole (N=81)	Placebo (N=81)	P-Values @
LOWER RESPIRATORY TRACT AND LUNG INFECTIONS	4 (5%)	1 (1%)	0.367
BRONCHITIS	1 (1%)	0	
BRONCHOPNEUMONIA	1 (1%)	1 (1%)	
PNEUMONIA	3 (4%)	0	
MALE REPRODUCTIVE TRACT INFECTIONS	1 (1%)	0	>0.999
EPIDIDYMAL INFECTION	1 (1%)	0	
UPPER RESPIRATORY TRACT INFECTIONS	1 (1%)	0	>0.999
UPPER RESPIRATORY TRACT INFECTION	1 (1%)	0	
METABOLISM AND NUTRITION DISORDERS	1 (1%)	0	
TOTAL FLUID VOLUME DECREASED	1 (1%)	0	>0.999
DEHYDRATION	1 (1%)	0	
NERVOUS SYSTEM DISORDERS	1 (1%)	0	
NERVOUS SYSTEM NEOPLASMS UNSPECIFIED MALIGNANCY NEC	1 (1%)	0	>0.999
ARACHNOID CYST	1 (1%)	0	

Subjects with one or more adverse events within a level of the MedDRA term are counted only once in that level. Adverse events summarized were reported after the first dose of study drug and no more than 30 days after the last dose of study drug for subjects not entering Open-Label. For subjects entering Open-Label, events with onset after the last day of Double-Blind treatment are excluded.
@ P-values for Total Subjects and High Level Terms are from Fisher's Exact Test.

Table. 12a Other Treatment-Emergent Serious Adverse Events During Double-Blind or Open-Label Treatment Periods

Subject No./ Country/ Gender/ Age (wks)	MedDRA High Level Term / *Preferred Term*	Day of Onset[a] Duration (days)[b]	Relationship to Study Drug	Severity	Comments
Events During Double-Blind Treatment (includes events within 30 days after last dose for subjects not entering OL treatment)					
Double-Blind Lansoprazole Pediatric Suspension					
6034/ Poland/F/8[c]	Nervous System Neoplasms Unspecified Malignancy NEC / *Arachnoid Cyst*	19/18	Not Related	Severe	Alt Et: Congenital Anomaly MedHx: Meningitis, GER, Anemia
6065/ Poland/M/7	Lower Respiratory Tract and Lung Infections / *Pneumonia*	15/9	Not Related	Mild	Alt Et: Viral Infection (Antibiotic Therapy) MedHx: Pneumonia, Diarrhoea, GER, UTI, Congenital Defect of Right Kidney, Anemia
6069/ Poland/M/9	Lower Respiratory Tract and Lung Infections / *Bronchopneumonia*	40 (10)/7	Not Related	Severe	Alt Et: Bacterial Infection MedHx: GER, Hydrocele Testis
6122/Poland/F/5[c]	Gastrointestinal Stenosis and Obstruction NEC / *Ileus*	13/21	Not Related	Severe	Alt Et: Congenital Anomaly of Gastrointestinal Malrotation MedHx: Vomiting, Congenital Duodenal Malrotation, Metabolic Alcalosis Due to Vomiting and Dehydratation
6132/ Poland/M/10	Lower Respiratory Tract and Lung Infections / *Pneumonia*	21/11	Not Related	Moderate	Alt Et: Infection MedHx: Rhinitis, GER, Vomiting, Umbilical Hernia, Cow's Milk Allergy, Dermatitis/Eczema
6177/ US/M/24	Total Fluid Volume Decreased / *Dehydration*	17/4	Not Related	Severe	Alt Et: Vomiting MedHx: GER, Ear/Nose/Throat

Subject No./ Country/ Gender/ Age (wks)	MedDRA High Level Term / *Preferred Term*	Day of Onset[a]/ Duration[b]	Relationship to Study Drug	Severity	Comments
Double-Blind Lansoprazole Pediatric Suspension (Cont)					
6184/ Poland/M/21[d]	Diarrhoea (Excl Infective) / *Diarrhoea*	20/8	Not Related	Mild	Alt Et: Bacterial or Viral Infection (Diarrhoea) and Infection (URTI) MedHx: Oral Thrush Retinopathy, Pneumonia, Patent Ductus Arteriousus, GER, Inguinal Hernia, UTI, Premature Birth, Failure to Thrive, Periventricular Leucomalacie, Pulmonary Dysplasia, Osteopenia, Hydrocele, Anemia, Hyperbilirubinemia
	Upper Respiratory Tract Infections / *Upper Respiratory Tract Infection*	20/8	Not Related	Mild	
6185/ US/M/35[d]	Bacterial Infections NEC / *Cellulitis*	47 (18)/2	Not Related	Moderate	Alt Et: Inflammatory Response Resulting in Clinically Apparent Pain, Redness, Warmth, and Swelling MedHx: URI, GER, Premature Birth
6188/ Poland/M/13[c, d]	Lower Respiratory Tract and Lung Infections / *Bronchitis*	24/17	Not Related	Moderate	Alt Et: Bacterial or Viral Infection (Bronchitis and Pneumonia) and Bacterial (Pseudomonas Aeruginosa) and Viral (Rota) Infection (Diarrhoea) MedHx: GER, Failure to Thrive Umbilical Hernia, Neutropenia
	Diarrhoea (Excl Infective) / *Diarrhoea*	24/17	Not Related	Mild	
	Lower Respiratory Tract and Lung Infections / *Pneumonia*	24/17	Not Related	Moderate	
6214/ Poland/M/13	Male Reproductive Tract Infections / *Epididymal Infection*	13/6	Not Related	Severe	Alt Et: Infection MedHx: GER, Pylorostenosis Negativa, Food Allergy

Subject No./ Country/ Gender/ Age (wks)	MedDRA High Level Term / *Preferred Term*	Day of Onset[a]/ Duration[b]	Relationship to Study Drug	Severity	Comments
Double-Blind Placebo					
6085/ Poland/F/46[c]	Lower Respiratory Tract and Lung Infections / *Bronchopneumonia*	3/11	Not Related	Moderate	Alt Et: Indefinite Infection Factor MedHx: GER
6118/ Poland/F/14	Ear Infections / *Otitis Media Acute*	4/9	Not Related	Mild	Alt Et: Probable Complication of GERD MedHx: GER
Events During Open-Label Lansoprazole Treatment (includes events occurring within 30 days after last dose)					
6113/ Poland/F/28	Klebsiella Infections / *Klebsiella Infection*	11/4	Not Related	Mild	Alt Et: Infection MedHx: GER
6199/ Poland/M/29	Seizures and Seizure Disorders NEC / *Febrile Convulsion*	45 (17)/4	Not Related	Severe	Alt Et: Bacterial Infection Within the Ears and resulting Fever MedHx: GER, Birth Prolonged (Forceps Delivery with Intrauterine Infection)
	Ear Infections / *Otitis Media*	45 (17)/9	Not Related	Severe	

Note: All subjects who experienced SAEs were hospitalized.
Alt Et = alternative etiology; DB = Double-Blind Treatment Period; F = female; M = male; MedHx = medical history; Ong = ongoing; OL = Open-Label Treatment Period.

a If onset occurred after the last day of the treatment period, then days postdosing are shown in parentheses.
b If the event was ongoing, the day at which it remained ongoing is shown in parentheses.
c Subject prematurely discontinued from all study drug.
d Subject was premature at birth.

Cross-reference: Appendices 16.2.7.2 and 16.2.4.3

Table 12b. Serious Adverse Events During the Double-Blind Treatment at U.S. Sites

MedDRA System Organ Class/ High Level Term/ Preferred Term	Lansoprazole (N=39)	Placebo (N=29)
Total Subjects with at Least One Adverse Event	2 (5%)	0
INFECTIONS AND INFESTATIONS	1 (3%)	0
BACTERIAL INFECTIONS NEC	1 (3%)	0
CELLULITIS	1 (3%)	0
METABOLISM AND NUTRITION DISORDERS	1 (3%)	0
TOTAL FLUID VOLUME DECREASED	1 (3%)	0
DEHYDRATION	1 (3%)	0

Subjects with one or more adverse events within a level of the MedDRA term are counted only once in that level. Adverse events summarized were reported after the first dose of study drug and no more than 30 days after the last dose of study drug for subjects not entering Open-Label. For subjects entering Open-Label, events with onset after the last day of Double-Blind treatment are excluded.

7.3.3 Dropouts and/or Discontinuations

Four of the 162 study subjects experienced AE's that led, at least in part, to premature discontinuation from the Double-Blind Treatment Period; 3 of these subjects were in the LPS Group and 1 subject was in the placebo group. No subjects prematurely discontinued from the Open-Label Treatment Period due to an AE. Details of the AE's experienced by the 4 subjects during the Double-Blind Treatment Period are presented in Table 13.

Table 13. Summary of Adverse Events Leading to Premature Discontinuation of Subjects From the Study

Subject No./ Gender/Age	MedDRA HLT/ Preferred Term	Day of Onset[a] / Tx Period	Duration	Relationship to Study Drug	Severity	Comments
Lansoprazole Pediatric Suspension						
6034/F/8wks	Nervous System Neoplasms Unspecified Malignancy NEC / *Arachnoid Cyst*	19 / DB	18	Not Related	Severe	Alt Et: Congenital Anomaly MedHx: Meningitis, GER, Anemia
6122/F/5wks	Gastrointestinal Stenosis and Obstruction NEC / *Ileus*	13 / DB	21	Not Related	Severe	Alt Et: Congenital Anomaly of Gastrointestinal Malrotation MedHx: Vomiting, Congenital Duodenal Malrotation, Metabolic Alcalosis Due to Vomiting and Dehydratation
	Anaemias NEC/ *Anaemia*	27 / DB	Ongoing as of Day 33	Not Related	Mild	
6188/M/13wks[a]	Diarrhoea (Excl Infective) / *Diarrhoea*	24 / DB	17	Not Related	Mild	Alt Et: Bacterial or Viral Infection (Bronchitis and Pneumonia) and Bacterial (pseudomonas aeruginosa) and viral (rota) infection (Diarrhoea) MedHx: GER, Failure to Thrive Umbilical Hernia, Neutropenia
Placebo						
6085/F/46wks[a]	Lower Respiratory Tract and Lung Infections / *Bronchopneumonia*	3 / DB	11	Not Related	Moderate	Alt Et: Indefinite Infection Factor MedHx: GER
	Diarrhoea (Excl Infective) / *Diarrhoea*					

Note: For alternatives etiologies for the subjects in this table, see Table 12.3.1.2.a.
Alt Et = alternative etiology; DB = double-blind; F = female; M = male; MedHx = medical history; Tx = treatment; wks = weeks.
a Subject was hospitalized for adverse event.

Of the 3 subjects in the LPS Group that discontinued the study secondary to AE's, no relationship to the study drug was determined by the manufacturer. Upon further study by this writer, it was noted that the one subject who had developed an Arachnoid Cyst during the study had congenital anomalies leading to the development of meningitis, hydrocephalus, and cystis cerebri. The final diagnosis based on surgical results was subarachnoidal cystis. The on-site investigator assessed the event as not related to study procedures. This writer agrees with the investigator's assessment.

The second subject who prematurely discontinued the study had a history of congenital duodenal malrotation and GERD. The patient was diagnosed with severe partial ileus and had to discontinue the study. The manufacturer concluded that there was no relationship between the study and the patient's life-threatening situation. The on-site investigator provided the congenital anomaly as the alternative etiology for the event and the event was assessed as "not related to a study procedure." This writer agrees with the investigator's assessment of the situation.

The third subject had a medical history of failure to thrive and GERD. He was hospitalized for pneumonia that was assessed as moderate in severity. While hospitalized, the subject was also diagnosed with bronchitis (moderate in severity) and diarrhea (mild in severity). A bacteriological fecal culture revealed Pseudomonas aeruginosa and the viral fecal culture revealed Rotavirus and Adenovirus. The study drug was discontinued due to the diarrhea. The manufacturer concluded that there was no relationship between the study and the patient's condition. The on-site investigator's causality assessment for the events of pneumonia, diarrhea, and bronchitis noted "no relationship to the study procedure." This writer is in agreement with that assessment.

7.3.4 Significant Adverse Events

Sixty-two percent (50/81) of subjects in the lansoprazole pediatric suspension group versus 46% (37/81) of subjects in the placebo group experienced ≥1 adverse event during the Double-Blind Treatment Period (p=0.058) as demonstrated in Table 14. The number of subjects with events of Gastrointestinal Atonic and Hypomotility Disorders (Constipation, and GERD) and Febrile Disorders (Pyrexia) were somewhat higher in the LPS Group. There were no statistically significant differences between the treatment groups in the percentage of subjects with treatment-related adverse events by MedDRA HLT during the Double-Blind Treatment Period, overall, or for any individual HLT. The most frequently occurring significant adverse event was Lower Respiratory Tract and Lung Infections, which occurred in 7% of subjects in the LPS Group and 2% of subjects in the placebo group. The percentage of occurrence of upper respiratory tract infections was nearly identical in the LPS Group (22%) and the placebo group (21%). The occurrence of viral infections, NEC (2%) in the LPS Group was decreased as compared to the placebo group (viral infections, NEC @ 6%).

Of the other frequently reported (≥5% of subjects in any treatment group by MedDRA HLT) treatment-emergent AE's during the Double-Blind Treatment Period occurrences of AE's were generally similar between treatment groups and there were no statistically significant treatment differences between individual HLT's. However, there were somewhat more Pyrexia adverse events observed in the lansoprazole group than in the placebo group (10% and 2%, respectively).

Table 14. Most Frequently Reported Treatment-Emergent Adverse Events During the Double-Blind Treatment Period Experienced Within a MedDRA High Level Term by ≥5% of Subjects in Any Treatment Group

MedDRA High Level Term Preferred Term	Lansoprazole Pediatric Suspension N=81 n (%)	Placebo N=81 n (%)	P-Values
Total Subjects With at ≥1 AE During the Double-Blind Treatment Period	50 (62)	37 (46)	0.058

Upper Respiratory Tract Infections Nasopharyngitis Rhinitis Sinusitis Upper Respiratory Tract Infection	18 (22)	17 (21)	>0.999
Gastrointestinal Atonic and Hypomotility Disorders NEC Constipation Gastrooesophageal Reflux Disease	9 (11)	3 (4)	0.131
Dermatitis and Eczema Dermatitis Allergic Dermatitis Atopic Dermatitis Contact Dermatitis Diaper Eczema Seborrhoeic Dermatitis	8 (10)	6 (7)	0.781
Ear Infections Ear Infection Otitis Media Otitis Media Acute	8 (10)	5 (6)	0.565
Febrile Disorders Pyrexia	8 (10)	2 (2)	0.098
MedDRA High Level Term Preferred Term	Lansoprazole Pediatric Suspension N=81 n (%)	Placebo N=81 n (%)	
Lower Respiratory Tract and Lung Infections Bronchitis Bronchopneumonia Pneumonia	6 (7)	2 (2)	0.277
Upper Respiratory Tract Signs and Symptoms Rhinorrhoea	6 (7)	4 (5)	0.746
Candida Infections Candida Nappy Rash Candidiasis Oral Candidiasis	5 (6)	3 (4)	0.720
Diarrhea (Excl Infective) Diarrhea	4 (5)	5 (6)	>0.999
Nausea and Vomiting Symptoms Vomiting Vomiting Projectile	4 (5)	1 (1)	0.367
Tissue Enzyme Analyses NEC Blood Alkaline Phosphatase Increased	2 (2)	5 (6)	0.443
Viral Infections NEC Bronchiolitis Gastroenteritis Viral Viral Infection Viral Rash Viral Upper Respiratory Tract	2 (2)	5 (6)	0.443

Subjects with one or more adverse events within a level of the MedDRA term are counted only once in that level. Adverse events summarized were reported after the first dose of study drug and no more than 30 days after the last dose of study drug for subjects not entering Open-Label. For subjects entering Open-Label, events with onset after the last day of Double-Blind treatment are excluded.
@ P-values for Total Subjects and High Level Terms are from Fisher's Exact Test.

7.3.5 Submission Specific Primary Safety Concerns

No safety concerns were noted.

7.4 Supportive Safety Results and Discussion

Please refer to section 7.3.5.

7.4.1 Common Adverse Events

Please refer to Table 14 for a further listing of common adverse events during the Double-Blind Treatment Period and Table 15 for most frequently reported adverse events during the Open-Label Treatment Period.

Table 15. Most Frequently Reported Treatment-Emergent Adverse Events During the Open-Label Treatment Period Experienced Within a MedDRA High Level Term by ≥5% of Subjects in Any Treatment Group

MedDRA High Level Term Preferred Term	**All Open-Label** N=55 n (%)
Total Subjects With ≥1 AE During the Open-Label Treatment Period	34 (62)
Upper Respiratory Tract Infections Nasopharyngitis, Pharyngitis, Rhinitis, Upper Respiratory Tract Infection	11 (20)
Dermatitis and Eczema Dermatitis, Dermatitis Atopic, Dermatitis Diaper, Eczema	8 (15)
Febrile Disorders Pyrexia	7 (13)
Ear Infections Otitis Media	6 (11)
Viral Infections NEC Bronchiolitis, Respiratory Tract Infection Viral, Viral Upper Respiratory Tract Infection	6 (11)
Diarrhoea (Excl Infective) Diarrhoea	4 (7)
Upper Respiratory Tract Signs and Symptoms Rhinorrhoea	4 (7)
Candida Infections Oral Candidiasis, Skin Candida	3 (5)
Gastrointestinal Atonic and Hypomotility Disorders NEC Constipation, Gastrooesophageal Reflux Disease	3 (5)
Respiratory Tract Disorders NEC Respiratory Tract Congestion	3 (5)
White Blood Cell Analyses White Blood Cell Count Decreased	1 (2)
Mineral and Electrolyte Analyses Blood Bicarbonate Decreased	1 (2)

Note: Subjects with ≥1 AE within a level of a MedDRA term were counted only once in that level.
Excl = excluding; NEC= not elsewhere classified.

The majority of subjects who experienced adverse events during either of the 2 treatment periods had events that were mild or moderate in severity. The most frequently reported treatment-emergent adverse events during the Double-Blind Treatment Period were

Upper Respiratory Tract Infections, Gastrointestinal Atonic and Hypomotility Disorders not elsewhere classified (NEC), Dermatitis and Eczema, Ear Infections, Febrile Disorders, Lower Respiratory Tract and Lung Infections, Upper Respiratory Tract Signs and Symptoms, Candida Infections, Diarrhea (Excluding [Excl] Infective), Tissue Enzyme Analyses NEC, Viral Infections NEC, and Nausea and Vomiting Symptoms. Similar types of adverse events were reported during the Open-Label Treatment Period. There was no statistically significant data between the LPS Group and the placebo group in either the Double-Blind Treatment Period or the Open Label Treatment Period.

7.4.2 Laboratory Findings

No new safety signals (as compared to the label for lansoprazole) were identified upon

review of laboratory data that included urinalysis, liver functions tests, kidney function tests, electrolytes, and other blood chemistries.

7.4.3 Vital Signs

Body temperature (degrees Celsius), blood pressure, pulse, respiratory rate, body length, and weight were measured at the Screening Visit (Study Visit 1), Dosing Day 1 of the Double-Blind Treatment Period (Study Visit 2), and at Weeks 1, 2, 3, and 4 (Study Visits 3, 4, 5, and 6, respectively) or the Termination Visit of the Double-Blind or Open-Label Treatment Periods, the Post-treatment Period Safety Follow-Up Visit (30 days after the last dose of study drug), and at any Unscheduled Visit during the study. Vital signs and growth parameters were measured using the same measurement tools at each study visit.

7.4.4 Electrocardiograms (EKGs)

No EKG's were mentioned in the study, and thus presumably, were not part of the physical exam.

7.4.5 Special Safety Studies

There were no studies designed to evaluate specific safety concerns.

7.4.6 Immunogenicity

Lansoprazole is not a protein and does not demonstrate evidence for immunogenicity.

7.5 Other Safety Explorations

The adverse event profile noted in this study for LPS was similar to the adverse event profile noted lansoprazole for adults. No new clearly drug-related adverse event was noted in this study.

7.5.1 Dose Dependency for Adverse Findings

No dose-dependent adverse findings were noted in this study.

7.5.2 Time Dependency for Adverse Findings

Please refer to section 7.4.1 and Tables 14 and 15 for a listing of common adverse events. No clear associations were evident between any adverse events and the time of the most recent study agent administration.

7.5.3 Drug-Demographic Interactions

No new interactions were noted in this study. Please refer to the existing label of lansoprazole for further discussion.

7.5.4 Drug Disease Interactions

No new drug disease interactions were noted in this study. There were no deviations from the existing label of lansoprazole.

7.5.5 Drug-Drug Interactions

The drug-drug interactions are part of the existing label for lansoprazole. No new drug interactions were noted in this study.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

At recommended human doses, no evidence of carcinogenicity has been noted in lansoprazole.

7.6.2 Human Reproduction and Pregnancy Data

This study involved infants between the ages of one month and <12 months. Therefore, pregnancy was not an issue. With regards to human reproduction, teratology studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day (40 times the recommended human dose based on BSA) and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

7.6.3 Pediatrics and Assessments and/or Effects on Growth

Body length and weight were two parameters used to assess efficacy in this study. Please refer to Table 9 for effects on growth. The use of LPS did not show any significant changes on growth (either height or weight) amongst the test subjects.

7.6.4 Drug Abuse Potential/Withdrawal and Rebound

No drug abuse potential or withdrawal was noted in this study and no rebound phenomenon was noted as well.

7.7 Additional Submissions

As of this writing, no changes in foreign labeling for lansoprazole have been noted.

8. APPENDICES

8.1 Labeling Recommendations

I recommend the following paragraphs to be added to the labeling under Section 8.4:

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ali Niak
10/27/2008 06:03:57 PM
MEDICAL OFFICER

Ruyi He
10/27/2008 06:06:28 PM
MEDICAL OFFICER