CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	22-020 SE-5 S-001/002
Priority or Standard	Priority
Submit Date(s)	November 21, 2008
Received Date(s)	November 21, 2008
PDUFA Goal Date	May 21, 2009
Reviewer Name(s)	Ii-Lun Chen, M.D.
Review Completion Date	Aug 10, 2009
Established Name	pantoprazole sodium for delayed-release oral suspension
(Proposed) Trade Name	Protonix for Delayed-Release Oral Suspension
Therapeutic Class	Proton Pump Inhibitor
Applicant	Wyeth Pharmaceuticals, Inc.
Formulation(s)	Oral suspension
Dosing Regimen	Once daily
Indication(s)	Short-term GERD
Intended Population(s)	Pediatric ages 1 year to 5 years

CLINICAL REVIEW

Application Type	NDA Efficacy Supplement
Application Number(s)	20-987 SE-5 S-036/S037
Priority or Standard	Priority
Submit Date(s)	November 21, 2008
Received Date(s)	November 21, 2008
PDUFA Goal Date	May 21, 2009
Reviewer Name(s)	Ii-Lun Chen, M.D.
Review Completion Date	Aug 10, 2009
Established Name	Pantoprazole sodium for delayed-release tablet
(Proposed) Trade Name	Protonix Delayed-Release Tablet
Therapeutic Class	Proton Pump Inhibitor
Applicant	Wyeth Pharmaceuticals, Inc.
Formulation(s)	Tablet
Dosing Regimen	Once daily
Indication(s)	Short-term GERD
Intended Population(s)	Pediatric ages 5 years to 16 years

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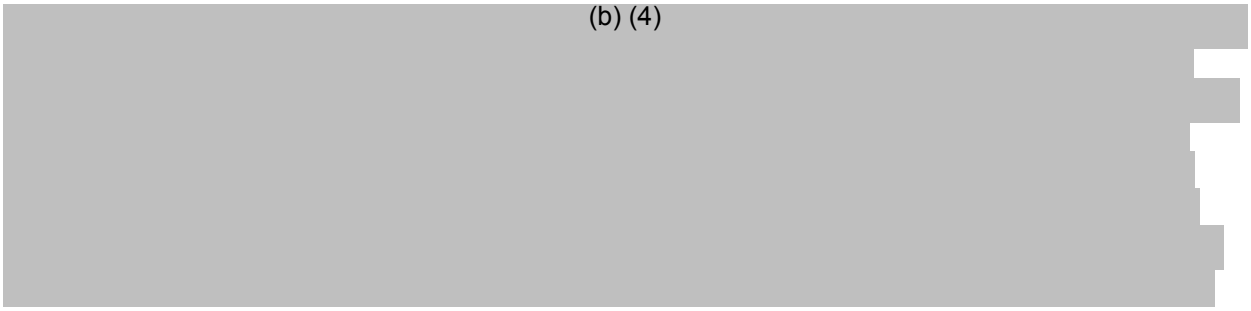
1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of Protonix for Delayed-Release Oral Suspension for the short-term treatment (up to eight weeks) of erosive esophagitis (EE) associated with gastroesophageal reflux disease (GERD) for pediatric patients age 1 year through 5 years. I also recommend approval of Protonix Delayed-Release Tablets for the short-term treatment of EE associated with GERD for pediatric patients age 5 years through 16 years. Efficacy of Protonix is extrapolated from the adult indication as the pathophysiology of EE associated with GERD is believed to be the same in adults and pediatric patients older than one year. There are sufficient pharmacokinetic (PK) and pharmacodynamic (PD) studies and evidence of safety provided by three clinical trials to support this indication and to provide adequate directions for use. Evidence of safety is based on a database of approximately 600 pediatric patients with symptomatic GERD including 8 patients with EE.



These two efficacy supplements (sNDA 22-020 S-001/002 and sNDA 20-987 S-036/037) were submitted in response to a Written Request (WR) originally dated December 31, 2001. The pediatric trials per the WR were designed to study the effectiveness of Protonix in *short-term treatment of symptomatic GERD*. The Applicant fairly met the requirements of the WR and received exclusivity on Feb 17, 2009. However, it appears that when the WR was issued, the pediatric trials were designed with the assumption that efficacy could be extrapolated from the adult indication to the pediatric indication. There is a fundamental flaw in this assumption, as the adult indication for Protonix is *short-term healing of erosive esophagitis (EE)*, which is considered a distinct entity from *short-term treatment of symptomatic GERD*.

The adult trials to support the indication for treatment of EE studied a distinct patient population in which healing of EE lesions was used as the primary endpoint. Whereas in the pediatric trials, relief of symptoms was studied. In adults, relief of GERD symptoms was studied as a secondary endpoint, however, the assessment technique was different and can not be used to directly compare the data between adults and children.

Other than the pediatric trial involving infants, birth to 11 months old, all other pediatric trials were dose ranging studies without an active comparator or placebo-control. The pediatric trials relied on being able to extrapolate efficacy from the adult data. The trials were not powered to detect dose response. Nor was there a clear dose response within the patients studied to support efficacy on its own. (b) (4)

1.2 Risk Benefit Assessment

Overall, there were no major safety signals and Protonix (pantoprazole) appears to be well tolerated in the pediatric population.

Pediatric Patients Less than One Year of Age

According to my review of the clinical data, the efficacy data did not support the proposal for treatment in the age group one month to less than one year. There was no difference in withdrawal rates between infants treated with once daily administration of pantoprazole pediatric suspension and those given placebo in the treatment of GERD symptoms in infants (age 1 month to 11 months). These efficacy results were consistent across all methods of assessment in this trial. No statistically significant differences were observed between treatment groups for any baseline demographic characteristics, or in the percentage of patients with various GERD symptoms reported by diary during baseline.

After the initial four week open-label treatment phase, the mean symptoms score improved from baseline score of 5.38 to 3.58. Although this was a statistically significant improvement, we do not have a clear understanding of the clinical meaningfulness of this change in symptom score. The placebo-control is valuable in allowing us to understand that Protonix, as studied in these infants, does not appear to be any more effective than placebo. It could be argued that the short four-week course of treatment had a lasting effect such that the withdrawal rates after the open-label treatment is not expected to be vastly different between those on continued treatment and those randomized to placebo.

To date, we do not have approval of PPI use in the young infant population less than one year of age. However, PPIs are commonly used in this age group despite lack of known effectiveness. Pharmacodynamic studies to date do demonstrate that acidity is suppressed in infants when treated with PPIs, despite this, efficacy has not been adequately demonstrated in a clinically meaningful manner. Previous trial designs for other PPIs have varied from a four week, double-blind, randomized, placebo-controlled and a treatment-withdrawal type design. We need better understanding of why efficacy has not been demonstrated in the infant population prior to

pursuing more PPI studies in this age group. It is possible that there are a few infants who have acid-induced esophageal damage and respond to PPI treatment, but overall true erosive esophagitis is uncommon in the infants, likely that it takes time for this to develop. It is possible that in young infants the pathogenesis for most feeding associated regurgitation and irritability is not related to acidity, and thus we do not see difference in responder rates between PPI treatment and placebo. Uncomplicated reflux in infants is known to spontaneously resolve in over 95% of cases by 18 months of age.[1]

Challenges of studying this patient population include need for more specific and sensitive assessment tools for this age group with an increased understanding if the pathophysiology and pathogenesis of gastrointestinal discomfort/regurgitation in this age group is similar to GERD in adults, whether behavioral conditioning is a factor, the role of maturation and ability of infant to start solids and feed sitting in improvement of symptoms, ethical considerations with use of invasive diagnostic procedures such as endoscopy to obtain more objective findings, and designing a trial to capture treatment effect appropriately.

Pediatric Patients Ages One Year through Sixteen Years

The clinical outcome trials were not powered to detect treatment differences between the dosages studied. The results from the clinical trials provide supportive data that pediatric patients ages 1 year through 16 years old improve on treatment, and PK/PD trials in the same age groups also provide support of treatment effect similar to that seen in adults on pantoprazole treatment. Although there were only eight patients with EE in this submission, all these patients healed with Protonix treatment as demonstrated by endoscopic findings. This was for me the most convincing evidence that Protonix has effectiveness in children as in adults, although I would have preferred to have a larger sample size and age distribution. Given the combined supportive evidence of effectiveness for short-term improvement of EE associated with GERD in pediatric patients older than 1 year of age and the lack of new safety signals, the use of pantoprazole is warranted.

1.3 Recommendations for Postmarket Risk Management Activities

Routine surveillance for adverse events is recommended.

1.4 Recommendations for Postmarket Studies/Clinical Trials

There exists a complicating factor in this submission in that all the pediatric patients were not studied using the same Protonix formulation (see Section 2.1 for more details). Pediatric patients 1 year through 5 years were studied using newly developed pediatric granules (distinct from the currently marketed adult granules in both chemistry and pharmacokinetics) and patients 5 years through 16 years were studied using the currently marketed adult tablets. From the review of the submission, it was determined that the pediatric granules and adult granules are not bioequivalent

1 Orenstein SR, Shalaby TM, Kelsey SF, et al. Natural History of infant reflux esophagitis: symptoms and morphometric histology during one year without pharmacotherapy. *J Gastroenterol 2006;* 101:628-40.

in terms of Cmax, whereas the formulations are bioequivalent in terms of AUC. (b) (4)

(b) (4)

There are no outstanding PREA requirements for NDA 22-020 or NDA 20-987.

There were two PREA PMCs for NDA 22-020:

- "Deferred pediatric study under PREA for the treatment of EE associated with GERD in pediatric patients ages birth to seventeen years." (Commitment ID: 4851) This was fulfilled by submission of the PWR studies.
- "Deferred pediatric study under PREA for the maintenance of healing of EE in pediatric patients ages birth to seventeen years." (Commitment ID: 4853) This was fulfilled by Wyeth completing a literature review as specified by the Agency. At this time, the DGP does not wish to pursue clinical trials to study the maintenance indication in the pediatric population until there is a better understanding of the safety with chronic use of PPIs in the adult population.

There are no outstanding PREA requirements for NDA 20-987:

- There were two non-PREA-related PMCs, one of which (pharmtox study) was fulfilled. The other is a clinical study, “Long-term prospective observational study of the incidence of cancer among pantoprazole users compared to an appropriate control group.” This is ongoing since 2004 and expected completion is in 2011.

2 Introduction and Regulatory Background

Gastroesophageal reflux (GER) is a common condition that involves regurgitation, or "spitting up," which is the passive return of gastric contents into the esophagus. Typical pattern of GER activity in infants peaks between one and four months of age[2], and usually resolves by 6 to 12 months of age.[3] Regurgitation has been reported almost half of infants but is negligible by one year of age.

Gastroesophageal reflux disease (GERD) is a common, chronic gastrointestinal disorder commonly known as "heartburn," is thought to occur in 2% to 7% of children.[4] GERD is known to cause erosive esophagitis (EE) due to the abnormal reflux of acidic gastric fluid into the esophagus when the esophageal sphincter is overly lax. When patients develop EE, their esophageal lining is inflamed and ulcerated. Other complications of GERD are esophageal strictures and Barrett esophagus. Endoscopy is commonly used to diagnose GERD and its severity. GERD is a pathologic process in infants with poor weight gain, signs of esophagitis, persistent respiratory symptoms, and changes in behavior. Approximately 0.3% of infants present with abnormal signs and symptoms that warrant a diagnosis of GERD.[5] GERD appears to be more resistant to complete resolution after the first year of life. A higher prevalence of GERD is noted in children who have co-morbid conditions.

Initial management of infants diagnosed with GERD is a nonpharmacologic approach that includes: feeding modifications, positioning changes, and reduction or elimination of tobacco smoke from the infant's immediate environment. Infants and children that continue to have symptoms after dietary and lifestyle modifications may require medication.

Long-term use of antacid treatment in pediatric GERD is not generally recommended. Aluminum absorption from antacid use, such as in sucralfate, can occur in infants approaching levels reported to cause osteopenia and neurotoxicity. Prokinetic agents, such as metoclopramide, are used in the treatment of GERD in infants and children, but there is not substantial evidence of effectiveness. Adverse effects are common with metoclopramide therapy and include extrapyramidal side effects. Histamine-2 receptor antagonists (H2-RAs) are available and are generally safe and effective. See Table 1 (Sec 2.2) for approved treatments for pediatric GERD.

Although proton pump inhibitors (PPI) have not been approved for patients <1 year old to date, they are used frequently off-label in infants with recurrent vomiting and failure to thrive, and/or

2Orenstein Sr. Infantile reflux: different from adult reflux. Am. Journal of Med. 1997;103:S114-9.
3Vandelplas Y, Lifshitz JZ, Orenstein S, Lifshitz CH, Shepherd RW, Casaubon PR, et al. Nutritional management of regurgitation in infants. Journal of Am. Coll. Nutr. 1998;17:308-16.
4 Gilger MA, El-Serag HB, God BD et al. Prevalence of endoscopic findings of erosive esophagitis in children: a population based study. J Pediatr Gastroenterol Nutr. 2008:Aug;47(2):141-6.
5 Behrman RE, Kliegman R, Jenso HB, eds. Nelson Textbook of Pediatrics. 16th ed. Philadelphia: W.B. Saunders, 2000:1125-6.

irritability that have not responded to H2-RAs. PPI's have also been used in pediatric patients with feeding resistance or dysphagia, asthma, recurrent pneumonia, or GERD.

2.1 Product Information

Pantoprazole sodium sesquihydrate, 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl) methyl]sulfinyl]-1Hbenzimidazole, monosodium salt, sesquihydrate, which may also be referred to as pantoprazole or pantoprazole sodium, is a substituted benzimidazole derivative that binds covalently to the gastric acid pump H+, K+-ATPase. Pantoprazole, a PPI, is an acid-activated, irreversible inhibitor of the H+, K+-ATPase of parietal cells and produces prolonged suppression of gastric acid secretion, as do other PPIs such as omeprazole and lansoprazole. The Applicant proposes Protonix be indicated for the treatment of short-term gastroesophageal reflux disease (GERD) in pediatric patients birth through 16 years of age.

Dosage Forms and Strengths
PROTONIX Delayed-Release Tablets:

- 40 mg, yellow oval biconvex tablets imprinted with PROTONIX (brown ink) on one side
- 20 mg, yellow oval biconvex tablets imprinted with P20 (brown ink) on one side

PROTONIX For Delayed-Release Oral Suspension:

- 40 mg, pale yellowish to dark brownish, enteric-coated granules in a unit dose packet
- 20 mg, white to dark brownish, enteric-coated granules in a unit dose packet (pediatric granules)

Each PROTONIX Delayed-Release Tablet contains 45.1 mg or 22.56 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg or 20 mg pantoprazole, respectively) with the following inactive ingredients: calcium stearate, crospovidone, hypromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. Pantoprazole Sodium Delayed-Release Tablets (40 mg and 20 mg) complies with USP dissolution test 2.

PROTONIX For Delayed-Release Oral Suspension, 40 mg contains the active ingredient pantoprazole sodium sesquihydrate in the form of enteric-coated granules in unit dose packets. Each unit dose packet contains enteric-coated granules containing 45.1 mg pantoprazole sodium sesquihydrate (equivalent to 40 mg of pantoprazole) with the following inactive ingredients: crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide.

PROTONIX For Delayed-Release Oral Suspension, 20 mg contains the active ingredient pantoprazole sodium sesquihydrate in the form of enteric-coated granules in unit dose packets.

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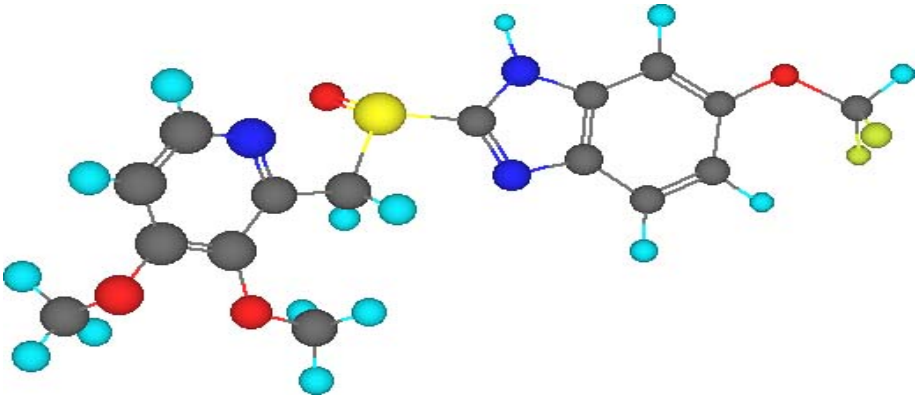


Figure 1: Pantoprazole molecular structure depicted

2.2 Currently Available Approved Treatments for Proposed Indications

Table 1: Available Approved Treatments for GERD in Pediatric Patients

Class	Example	Age range	Daily Dose (for 8 wks)
H2-Receptor blockers	ranitidine (Zantac)	1 month – 16 years	Up to 10 mg/kg
	famotidine (Pepcid)	neonate – 16 years	Up to 1 mg/kg
PPIs	lansoprazole (Prevacid)	1 yr -11 yrs 12 yrs - 17 yrs	15 mg 30 mg
	esomeprazole (Nexium)	1 yr -11 yrs 12 yrs - 17 yrs	10 or 20 mg 20 or 40 mg
	omeperazole (Prilosec)	1 yr - 16 years ▪ 5 to 10 kg ▪ 10 to 20 kg ▪ 20 kg +	 5 mg 10 mg 20mg

2.3 Availability of Proposed Active Ingredient in the United States

Pantoprazole is available in the United States as delayed-release tablet (20 mg or 40 mg) and delayed-release granules for oral suspension (40 mg). The adult granules on the market also suffice as a pediatric age appropriate formulation, but for historical reasons the two granule formulations took separate development tracks.

Oral and intravenous (IV) formulations of pantoprazole sodium have been marketed worldwide.
Feb 2, 2000: Short-term treatment (up to 8 weeks) in the healing and symptomatic relief of EE (NDA 20-987) was approved in the United States.
Mar 22, 2001: IV pantoprazole (NDA 20-988) for short-term treatment (7 to 10 days) of patients having GERD as an alternative to oral therapy in patients who are unable to continue taking oral pantoprazole, was approved.
Jun 12, 2001: Use for maintenance of healing of EE and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with GERD (NDA 20-987/S-001) was approved.
Oct 19, 2001: Use for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome (ZES) was approved (NDA 20-988/S-003).
Apr 19, 2002: Use for pathological hypersecretory conditions including ZES (NDA 20-987/S-007) was approved.
Dec 6. 2004: IV pantoprazole for short-term treatment (7 to 10 days) of GERD and a history of EE (NDA No. 20-988/S-027) were approved.
Nov 14, 2007: Pantoprazole sodium for delayed-release oral suspension (granules) for the short-term treatment of EE associated with GERD, maintenance of healing of EE, and pathological hypersecretory conditions including ZES (NDA 22-020) was approved in the United States.

2.4 Important Issues With Consideration to Related Drugs

Lansoprazole (Prevacid) is the first PPI that has completed a clinical trial 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.

There is class labeling for the *Warning and Precautions* section: "Symptomatic response to [specific PPI name] does not preclude the presence of gastric malignancy." For a number of the PPIs, there is also a warning stating that atrophic gastritis has been noted on biopsy from patients treated with long-term PPI. Also, there have been reports of false-positive urine screening tests for tetrahydrocannabinol in patients taking PPIs.

Pantoprazole is metabolized by the cytochrome P450 (CYP) isoenzymes. The major metabolic pathway of pantoprazole involves the enzyme CYP2C19, and the minor metabolic pathways involve the enzymes 3A4, 2C9, and 2D6. There have been postmarketing reports of INR and prothrombin time (PT) in subjects receiving PPIs, including pantoprazole, and warfarin concomitantly. Increases in INR and PT may lead to abnormal bleeding and even death. Patients treated with PPIs and warfarin concomitantly should be monitored for increases in INR and PT.

PPIs are thought to have a potential to interfere with the absorption of drugs where gastric pH is important for bioavailability. Lastly, it is recommended that Protonix is not administered with atazanavir, as decreased atazanavir levels are expected which would reduce its therapeutic effect.

2.5 Summary of Regulatory Activity Related to Submission

A Pediatric Written Request (PWR) letter was first issued by the FDA on Dec 31, 2001 for PROTONIX Delayed-Release Tablets (NDA 20-987) and PROTONIX I.V. for Injection (NDA 20-988). The pantoprazole PWR was amended on July 3, 2002; Dec 18, 2002; May 7, 2004; Mar 15, 2006; and subsequently revised on May 17, 2007. The deadline for reporting the full trial results from the requested trials is Dec 31, 2008.

This current submission is a response to the Protonix PWR and reflects trials evaluating the short-term use of pantoprazole sodium for the treatment of symptomatic GERD in pediatric patients from preterm infants and neonates through 16 years of age.

As reflected in official meeting minutes from FDA (Jun 23, 2005, t-con for Protonix Granules NDA), Wyeth understands that the pediatric data submitted in this sNDA is intended to satisfy all requirements of PREA and BPCA to provide important information for the safe and effective use of pantoprazole in pediatric patients by the due date of Dec 31, 2008. There was agreement made regarding endpoints for the PWR studies at this time.

During the current review cycle, consultation with Mike Jones to discuss user fee issues with the submission uncovered that at the time of submission, Wyeth should have paid two user fees as this sNDA submission consists of clinical data pertaining to two formulations: pediatric granules and adult tablets. Wyeth was notified that although the division would be agreeable to keeping the current PUDFA goal date for both portions of the review, the Applicant would need to pay the additional user fee as soon as possible to avoid an "Unfileable Action". Wyeth agreed to pay the second user fee and review of both formulations for the pediatric patients continued.

March 3, 2008: Type B pre-sNDA meeting held. The agency stated that it appeared to be acceptable for the sNDA to be submitted to NDA 22-020 with a letter of cross-reference to NDA 20-987 (tablets). Also, Wyeth stated that they plan to (b) (4)

Nov 21, 2008: sNDA was submitted containing the entire PWR trials and studies.
Feb 17, 2009: Pediatric exclusivity granted to Wyeth.
April 21, 2009: T-con was held with Wyeth to open a dialogue regarding the possibility of (b) (4).
June 30, 2009: (b) (4)

July 20, 2009: Wyeth agreed to proceed with the EE indication in the pediatric population via telephone communication.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the submission was organized and complete. All required information was readily available electronically.

3.2 Compliance with Good Clinical Practices

A DSI inspection was sent to two sites with the largest number of participants in this submission across age groups. Specifically, the sites of Dr. Bishop (University of Mississippi Medical Center Children's Hospital) and Dr. Tsou (Children's Hospital of the King's Daughter) were selected. Please refer to Dr. Roy Blay's review dated April 29, 2009. The inspection showed:

Dr. Bishop's Site Assessment of Data Integrity:
For study 3001A1-322-US:
Data appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data regarding subject 045 given the subject's use of a prohibited medication (Pepto-Bismol) on two separate occasions between Visits 4 and 5.

For study 3001B3-328-NA:
Data appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data regarding subject 004 given the subject's use of a prohibited medication (amoxicillin) from February 15 to March 18, 2007, and its relationship, if any to the CLOtest® screening procedure.

Dr. Tsou's Site Assessment of Data Integrity:
For study 3001A1-322-US:
Data appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data regarding subject 249 given the subject's use of a prohibited medication (Motrin).

For study 3001B3-328-NA:
Data appear acceptable in support of the respective application; however, the review division should consider the impact, if any, of the data regarding subject 151 given the subject's intake of the incorrect test article for a two week period. The above stated data were reviewed and I do not feel there is concern for significant impact.

The impact of the above mentioned data was assessed, and I do not feel they significantly impact the study results.

According to the Applicant, the clinical trial was conducted according to Good Clinical Practice

(GCP) guidelines, as documented in the International Conference on Harmonization (ICH) and the FDA.

3.3 Financial Disclosures

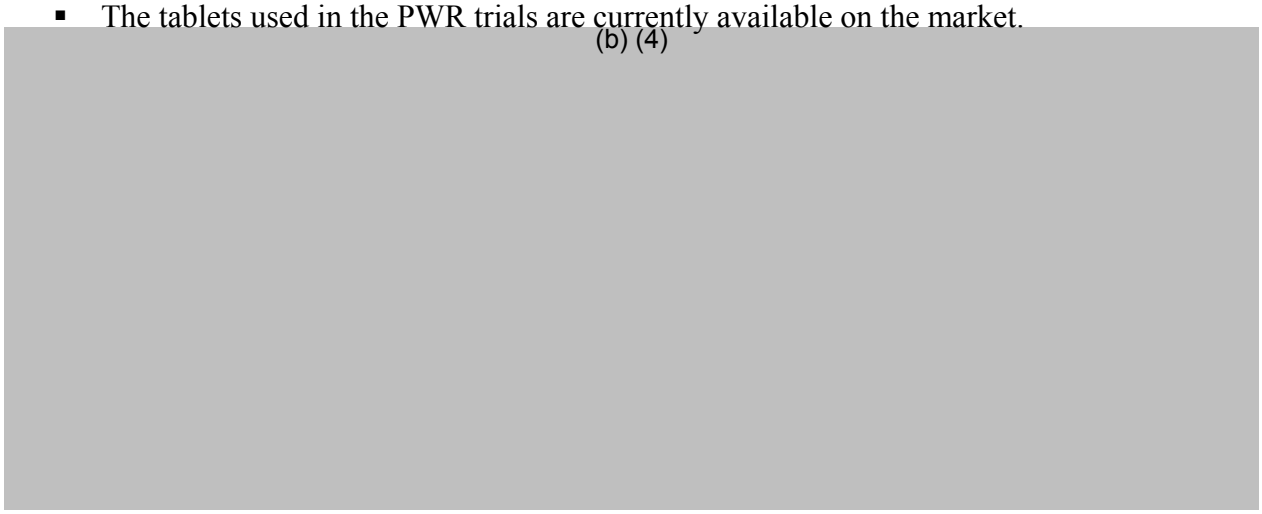
The Applicant has submitted form 3454, certifying that there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the trial, as defined in 21 CFR 54.2(a).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

- The tablets used in the PWR trials are currently available on the market.

(b) (4)



4.3 Preclinical Pharmacology/Toxicology

Please refer to the review dated May 22, 2009, by Dr. Yuk-Chow Ng for full details. Wyeth has submitted the following nonclinical toxicity studies in IND 35,441 and in this sNDA in response to the PWR:

- 25-day repeated oral (gavage) dose ranging study in juvenile rats
- 15-day repeated intravenous dose-ranging study in juvenile rats
- 15-day intravenous toxicity study in juvenile rats
- 2-month oral (gavage) toxicity study in juvenile rats
- 4-week oral (gavage) toxicity study with 3 month recovery in neonatal/juvenile rats
- 13-week oral (gavage) tolerability study in neonatal Beagle dogs
- 13-week oral (gavage) toxicity study in neonatal Beagle dogs with a 13-week recovery
- 1 week oral (gavage) toxicokinetic study in neonatal Beagle dogs

With the exception of the two dose-ranging studies and a supplementary histopathological study examining a complete set of tissues from the 13-week toxicity study in neonatal dogs, all the studies have been reviewed previously in IND 35,441.

- As in the adult studies, nonclinical data showed that the stomach is the common target organ of toxicity. Mucosal alterations in the stomach were observed in both juvenile/neonatal rats and dogs. Increased absolute and relative weights of the stomach were observed in both species.

- The effects of pantoprazole on neonatal dog stomach appear to be more severe than in adult animals.
- There were no apparent effects on the development of physical landmarks or overall growth in neonatal/juvenile rats or dogs.
- In general, results from the studies in neonatal/juvenile animals revealed a toxicology profile similar to that seen in adult animals.
- The submitted data are adequate to support the short-term use of pantoprazole in the pediatric population.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

This class of drugs is used in the treatment of gastric acid-related symptoms and pathology, such as GERD with or without EE. The primary advantage of treatment with PPIs is that they act directly on the final step in the acid-secretion pathway. An age-appropriate formulation of pantoprazole sodium for delayed-release granules has been developed for administration in patients who are unable to swallow tablets. Pantoprazole has shown therapeutic potential in the treatment of peptic ulcer disease, EE, and hypersecretory states in adults.

Like other benzimidazole derivatives such as omeprazole and lansoprazole, pantoprazole undergoes a molecular rearrangement in an acidic environment that is necessary for its activity. Although it is amphoteric, pantoprazole acts as a weak base (approximate pKa of 4.0) that is protonated in the low pH environment of the parietal cell secretory canaliculi. The protonated species forms a tetracyclic sulfenamide, which then becomes covalently bound to cysteine residues of the H+, K+-ATPase or gastric proton pump.

4.4.2 Pharmacodynamics

The effect of dose on pharmacodynamic (PD) parameters was evaluated for patients aged 1 through 11 months old. The dose of 1.2 mg/kg resulted in statistically significant increase in PD parameters which were (1) the mean intragastric pH and (2) the mean percentage of time for intragastric pH >3 and >4. The lower dose 0.6 mg/kg did not result in any statistically significant change in PD parameters. However, there was no statistically significant difference between dose groups for changes in any PD parameters, thus, no dose-response was observed for PD parameters. Based on these results, dose of 1.2 mg/kg was chosen for the efficacy trial for patients 1-11 months old of age.

4.4.3 Pharmacokinetics

The following are the main concepts from the preliminary clinical pharmacology review by Dr. Insook Kim:

- Plasma concentrations of pantoprazole in pediatric patients were highly variable. The coefficient of variation for PK parameter was about 90%. The systemic exposure of pantoprazole in pediatric patients after 1.2 mg/kg dose was comparable to that in healthy

adults after 40 mg pantoprazole. More specifically, systemic exposure of pantoprazole in pediatric patients 1 to 11 years old of age was lower than in healthy adults when the equivalent body-weight based dose was administered. For patients 12 to 16 years of age, the 40 mg dose resulted in similar AUC and Cmax to that in adults taking a 40 mg dose.

- The apparent oral clearance varied among age groups. Body weight is the key covariate affecting pantoprazole clearance in pediatrics patients >3 years of age. For children < 1 year old, clearance is reduced 20 to 80% of the adult value and at age 3, the age factor reduces clearance only 5%.
- The bioequivalence between pediatric granules and the marketed formulations i.e. tablet and adult granules (Delayed-Release Oral Suspension) was not demonstrated, however, there is sufficient bridging data to dose pediatric patients using either granule formulation.
  - Mean AUC and Cmax of pediatric granules was considerably lower than that of adult 40mg tablet. Furthermore, pediatric granules are not bioequivalent to the marketed delayed-release oral suspension for Cmax. The mean Cmax of the adult granules is approximately 18% higher compared with the pediatric granules. For Cmax, the 90% CI for the ratio of the geometric means between the adult and pediatric granules was from 108% to 129% and did not fall within the bioequivalence window of 80% to 125%.
  - The mean AUC of the adult granules was about 6% higher than the pediatric granules. For AUC, the 90% CI for the ratio of the geometric means between the adult and pediatric granules was from 100% to 113% and falls within the bioequivalence window of 80% to 125%.
  - Reviewing the values and confidence intervals for these various parameters, it appears that a 10% increased adjustment in the pediatric granule dosing would bring its PK parameters within bioequivalence specifications to the marketed adult granules.
- Six patients were identified as CYP2C19 poor metabolizers. The clearance of Protonix in these patients was decreased by 95% compared to extensive metabolizers and the dose-normalized AUC was approximately five fold increased. Although no major safety signal was reported in these patients, it is a small sample. Therefore, for known CYP2C19 poor metabolizers, a dose reduction should be considered.

5 Sources of Clinical Data

Clinical data consists of four safety and effectiveness trials, four PK/PD studies, and four supportive studies. Theses are described in more detail in the following tables.

5.1 Tables of Studies/Clinical Trials

Table 2: PWR Clinical Outcome and Safety Trials

Protocol	Location	Age	Population	Formulation	Design	No.
3001B3-329 PWR Trial 3	US, South Africa, Canada, and several other countries	1 to 11 months	Symptomatic GERD	Granules 1.2 mg/kg placebo	4-week, OL run-in, then 4-week, DB, PC, treatment withdrawal phase	129
3001B3-328 PWR Trial 4	North America	1 to 5 yrs	Endoscopic proven symptomatic GERD	Granules 0.3 mg/kg 0.6 mg/kg 1.2 mg/kg	R, DB, multiple-dose, parallel-treatment for 8 wks	60
3001A1-322 PWR Trial 4	US	5 to 11 yrs	Endoscopic proven symptomatic GERD	Tablets 10 mg 20 mg 40 mg	R, DB, multiple-dose, parallel-treatment for 8 wks	53
3001A1-326 PWR Trial 5	US	12 to 16 yrs	Symptomatic GERD	Tablets 20 mg 40 mg	R, DB, multiple-dose, parallel-treatment group for 8 wks	136

Table 3: PWR PK and Safety Trials

Protocol	Location	Age	Population	Formulation	Design	No.
3001B3-331 PWR Trial 1	Multiple Countries	Neonates and preterm infants	Clinical diagnosis of GERD	Granules 1.2 mg/kg 2.5 mg/kg	R, open-label, single-and multiple-dose PK trial with 2 arms for 5 days	59
3001B3-333 PWR Trial 2	Multiple Countries	1 to 11 months	Presumed GERD	Granules 0.6 mg/kg 1.2 mg/kg	R, open-label, single and multiple-dose, PK, safety and multiple-dose PD trial	67

Protocol	Location	Age	Population	Formulation	Design	No.
3001B3-334 PWR Trial 4	US	1 to 11 yrs	Endoscopic proven symptomatic GERD	Granules for ages < 6 yrs Tablets for ages ≥ 6 yrs 0.6 mg/kg 1.2 mg/kg	R, OL, single and multiple-dose, PK trial treated for at least 5 days	41
3001A3-337 PWR Trial 5	US	12 to 16 yrs	Suspected, symptomatic, or endoscopically proven GERD	Tablets 20 mg 40 mg	R, OL, single and multiple-dose, PK trial, treated for at least 5 days	22

Table 4: Supportive non-PWR Clinical Trials with Oral and IV formulations

Protocol	Location	Age	Population	Formulation	Design	No.
3001B3-335	Mutiple Countries	Infants < 12 mos	Presumed GERD	Granules 0.6 mg/kg 1.2 mg/kg	Open-label safety extension trial from 331 or 333	58
3001A1-109	US	5 to 16 yrs	Patients who could benefit from acid suppression therapy	Tablets 20 mg 40 mg	Open-label, single-dose, randomized, parallel group	24
3001K1-110	US	2 to 16 yrs	Inpatients who could benefit from acid suppression therapy	IV 0.8 mg/kg 1.6 mg/kg	Open-label, single-dose, randomized, parallel group trial	19
3001K1-117	US	1 to 2 yrs	Inpatients who could benefit from acid suppression therapy	IV 0.8 mg/kg 1.6 mg/kg	Open-label, randomized, single –dose trial	4

5.2 Review Strategy

The four clinical outcome protocols were reviewed in detail individually for effectiveness and safety. The four pharmacokinetic trials were reviewed in detail for safety evaluation only. The four supportive clinical trials (not part of the PWR requirement) were reviewed briefly for safety evaluation only. All eight protocols were reviewed for an integrated safety evaluation. Clinical outcome trials were not integrated across age groups, as there were slightly different trial designs and use of assessment tools between the trials.

5.3 Overview of Individual Studies/Clinical Trials for Clinical Outcomes

A brief overview of the effectiveness studies for pediatric patients birth through 16 years is presented in the following table. Please refer to the Appendix (Section 9.4) for detailed review of the eight individual clinical protocols for effectiveness and safety evaluation.

Table 5: Design Comparison of the Four Clinical Outcome Trials

	Infant <1 yr	**Age 1-5 years**	**Age 5-11 years**	**Age 12-16 years**
DB, Randomized	X	X	X	X
Placebo	X Random withdrawal			
Doses	1.2 mg/kg/day	0.3, 0.6 or 1.2 mg/kg/day	10, 20, or 40 mg per day	20 or 40 mg per day
Site #	31	26	12	24
Patient #	88	53	52	130
EE Patients		4	4	
Endoscopy		X	X	
Assessment Tool*	CAGS-I	eDiary GSS (GSQ-YC + I-GERQ)	GASP-Q	GASP-Q
Primary Endpoint	Weekly GSS (five items)	Weekly GSS	CSS (eight items)	CSS

*See section 6.1.4 for definitions of Assessment Tools

6 Review of Efficacy

For children ages 1 year through 16 years, efficacy of Protonix in the short-term treatment of EE associated with GERD is extrapolated from the adult data. The primary endpoint studied was the improvement of symptoms associated with GERD which is different than in the adult trials which primarily studied the healing of lesions due to erosive esophagitis associated with GERD. The trials for the pediatric patients in this age group did not have a placebo control or an active comparator, and there was no clear demonstration of dose response. Although the trials in patients ages 1 year through 16 years did not have negative outcomes, efficacy of Protonix in pediatric patients in the short-term treatment of symptomatic GERD can not be established independently.

In general, the inclusion criteria (other than age), exclusion criteria, concomitant medications, prohibited medications, treatment duration, and monitoring schedule were similar across all trials. One major difference in inclusion criteria involves the two trials with patients ages 1 year through 5 years and 5 years through 11 years. These patients were required to have endoscopically proven symptomatic GERD. For older patients 12 years through 16 years, endoscopy was not required prior to trial entry.

In the adult trials, no clear dose response could be demonstrated solely based on GERD symptom improvement. In adults, a dose-response and superiority of 40 mg could only be demonstrated when healing of EE or maintenance of healing was assessed. In a pivotal adult trial studying the healing rates of EE after eight weeks of treatment, pantoprazole 20 mg and 40 mg were superior to placebo by 45 and 55% respectively. In this trial, the secondary endpoint was overall absence of GERD symptoms. Unlike in the pediatric trials, the Applicant used a life-table approach to produce survival-type curves for each treatment group to represent time to absence of symptoms. The following was copied from Dr. Hugo Gallo-Torres' June 30, 1998, review of NDA 20-987:

Treatment Group	Median Time (days)
PL	65
PANTO 10 mg	54
PANTO 20 mg	49
PANTO 40 mg	28

Dr. Gallo-Torres concluded that, "the panto 40 mg dose was significantly more efficacious – beginning in the first week of therapy – than placebo in the persistent absence of any symptom, daytime heartburn, nighttime heartburn, and regurgitation associated with erosive esophagitis…approval of pantoprazole 40 mg once-a-day (4 to 8 weeks) for the healing of erosive esophagitis and the relief of symptoms associated with GERD is recommended." However, Protonix tablet and suspension currently are only labeled for the short-term treatment of EE associated with GERD and is not indicated for the relief of symptomatic GERD.

In trials with patients ages 1 year through 12 years old, there were eight patients with EE who were enrolled. None of the patients with EE was given the lowest dose, therefore we do not know for certain if a lower dose could be recommended for these patients even though GERD symptoms were reported to improve significantly with low dose treatment for patients age 1 year through 11 years old. Given the limitations of the number of EE patients studied, understanding dose response could have been improved had there been more EE patients studied at varied doses.

There are a number of statistical issues that are noted. First, the number of patients studied in the clinical trials for children ages 1 year through 16 years were based on regulatory and practical needs and was not set by statistical power. There was inadequate power to detect treatment difference with the number of patients studied. Second, due to the small number of patients enrolled, the baseline symptom scores were different between treatment groups.

For the clinical trials, comparison was done between treatment groups adjusting for weight and age subgroups. These analyses did not show large differences between treatment groups. Change in symptoms scores among treatment groups was more consistently correlated with baseline severity. That is, there was a tendency for the patients with higher baseline values (more severe symptoms) to show most improvement at end of trial.

The difference in age groups and trial designs precluded integration of the effectiveness results across the four clinical outcome trials. The trials are different in: dose regimens, symptom assessment tools, symptomatic versus endoscopically-proven symptomatic GERD. Because of different GERD manifestations due to age, they used different effectiveness endpoints. Thus the trials are individually described.

6.1 Indication

Short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease.

6.1.1 Methods

Other than the infant trial (Study 329), which was a placebo-controlled, randomized withdrawal design, all other clinical outcome trials were parallel group, multiple-dose, double-blind, randomized trial evaluating the safety and clinical outcomes of treatment with pantoprazole at variable doses given once daily for eight weeks. In general, improvement was evaluated using GERD symptom assessment questions developed by Wyeth targeted to each age group.

Infants 1 Through 11 Months

In a phase 3, multicenter, outpatient, randomized, double-blind, placebo-controlled, treatment-withdrawal trial, infants with symptomatic GERD from 1 through 11 months were treated with pantoprazole for delayed-release oral suspension once daily for up to eight weeks to evaluate the efficacy and safety of pantoprazole. The trial design encompassed two four-week treatment phases: an initial open-label phase and a double-blind placebo-controlled treatment-withdrawal phase.

Two strengths (5 and 10 mg) of pantoprazole were dispensed by weight group (<7 kg or ≥7 kg) to achieve an approximate daily dose of 1.2 mg/kg. The dose, 1.2 mg/kg pantoprazole sodium enteric-coated granules for suspension, was chosen on the basis of initial PK data from trial 3001B3-333-WW, which was conducted in a similar patient population (infants aged 1 through 11 months.

A total of 129 patients were screened with a mean corrected age of five months (48 females/81 males, 84 Caucasian, 26 African American, 12 Asian, 7 other). After screening procedures all patients received two weeks of standardized, non-pharmacologic, conservative treatment for GERD (hypoallergenic formula thickened with rice cereal and instructions on feeding and positioning). The run-in phase was placed to eliminate patients who would respond to environmental management and not require medical therapy. Also, inclusion of such patients could exaggerate the efficacy of the treatment effect. Then, 108 patients were randomized with 106 in the mITT population. These patients continued conservative treatment throughout the trial. Throughout the trial, an eDiary was used to collect data on GERD symptoms, respiratory symptoms, and rescue antacid use.

Patients whose symptoms resolved with conservative treatment were withdrawn from the trial. Patients whose symptoms failed to improve and who satisfied all the eligibility criteria entered a four-week treatment run-in phase and received open-label oral pantoprazole daily. Patients were stratified by body weight as of Visit 4 and randomly assigned to receive either pantoprazole or matching placebo daily for four weeks. During the double-blind phase, patients were monitored closely to allow for prompt discontinuation from the trial due to a lack of efficacy of their assigned test article or if otherwise clinically appropriate. The eDiary was also used to track patient compliance with test article.

Children 1 Year Through 5 Years

In an outpatient, multicenter, stratified and randomized, double-blind, parallel treatment group trial, children 1 through 5 years with endoscopically-proven symptomatic GERD were treated with three dose levels of pantoprazole delayed-release oral suspension (5, 10 or 15 mg for those < 2 years and 5, 10, or 20 mg for those ≥ 2 years) administered in applesauce or apple juice once daily for up to eight weeks to evaluate the exposure/response and safety.

Patients who met the inclusion and exclusion criteria were stratified by a diagnosis of either erosive esophagitis (EE) with Hetzel-Dent (HD) score ≥ 2 or non-erosive reflux disease (NERD, HD < grade 2). Three dose levels (low [0.3 mg/kg], medium [0.6 mg/kg], and high [1.2 mg/kg]) were selected to determine therapeutic effectiveness and safety. There were a total of 60 patients randomized (mean age 2.4 years, 23 females/37 males, 50 Caucasian, 4 African American, 3 Asian, 3 Others). The four patients with EE were randomly assigned to the medium-dose or high-dose groups. The remaining patients with NERD were randomly assigned to the low-dose, medium-dose, or high-dose group.

Children 5 Years Through 11 Years

In an outpatient, multicenter, randomized, double-blind, parallel treatment group trial, children 5 through 11 years with endoscopically-proven symptomatic GERD were treated with three dose levels of pantoprazole delayed-release tablets (10, 20, or 40 mg) for eight weeks. Of the 53 (mean age 8.1 years, 34 female/19 male, 31 Caucasian, 22 African American) randomized patients, 4 had EE, and 49 had NERD. Patients with EE were randomly assigned to the medium-dose or high-dose groups. Patients with NERD were randomly assigned to the low-dose, medium-dose, or high-dose group.

Adolescents 12 Years Through 16 Years

In an outpatient, multicenter, randomized, double-blind, multidose, parallel-treatment trial, adolescents 12 through 16 years with symptomatic GERD were randomized to receive 20 or 40 mg of pantoprazole delayed-release tablets daily for eight weeks. One hundred thirty-six (136) patients (mean age 14 years, 92 female/44 male, 105 Caucasian, 16 African American, 12 Hispanic, 1 Asian, 2 Other) were randomized.

6.1.2 Demographics

The following table summarizes the efficacy population demographics for the pediatric patients enrolled in the clinical outcome trials. Please refer to the Appendix for tables describing the efficacy population demographics for each of the individual trials.

Table 6: Demographics for Efficacy Population (Trials 329, 328, 322, and 326)

Characteristic	Low (n = 37)	Medium (n = 175)	High (n = 166)	Total (n = 378)
Postnatal Age (years)				
Mean	5.7	6.6	7.1	6.7
SD	3.4	6.4	6.3	6.1
Min – Max	1 - 11	0.08 – 16	0.13 - 16	0.08 - 16
Sex, N (%)				
Female	17 (45.9)	95 (54.3)	85 (51.2)	197 (52.1)
Male	20 (54.1)	80 (45.7)	81 (48.8)	181 (47.9)
Race, N (%)				
American Indian Or Alaska Native	0	1 (0.57)	2 (1.20)	3 (0.79)
Asian	0	9 (5.1)	7 (4.2)	16 (4.2)
Black or African American	9 (24.3)	30 (17.1)	29 (17.5)	68 (18.0)
Other	1 (2.7)	4 (2.3)	4 (2.4)	9 (2.4)
Caucasian	27 (73.0)	131 (74.9)	124 (74.7)	282 (74.6)
Ethnicity, N (%)				
Hispanic or Latino	2 (5.4)	13 (7.4)	11 (6.6)	26 (6.9)
Non-Hispanic	35 (94.6)	162 (92.6)	155 (93.4)	352 (93.1)

6.1.3 Subject Disposition

*Note for the Infant Study: The modified intent-to-treat population (mITT) was the primary analysis population and consisted of all patients who had a clinical diagnosis of GERD, completed the four-week open-label treatment period with a minimum of 21 days of test article, entered the double-blind treatment period, and received at least one dose of treatment. The Valid-for-Efficacy (VFE) population consists of patients from the mITT population who completed all eight weeks for treatment, took at least 80% of scheduled trial medication, had a completed assessment tool at week 8, and did not violate the protocol in a major way.

Infants 1 Through 11 Months

A total of 154 patients with symptomatic GERD were screened for the trial. Of those, 25 patients were screen failures (not meeting inclusion criteria, abnormal lab results, unable to comply with study procedures). A total of 129 patients of both sexes received at least one dose of the test article and composed the safety population. From the total, 21 (16%) patients were withdrawn from the trial during the open-label phase, the most common reason being parental noncompliance with maintaining the e-Diary.

Then, 108 patients were randomly assigned to the pantoprazole 1.2-mg/kg group or the placebo group in the double-blind phase. Two randomly assigned patients did not meet the mITT criteria and were withdrawn because of protocol violations, leaving 106 patients in the mITT population. Within the mITT population, 96 patients met the criteria for the VFE-1 population, and 77 patients met the criteria for the VFE-2 population. The VFE-2 population, is a subset of the VFE-1, was included only in those analyses involving the withdrawal endpoints. The VFE-2 subset were those patients who were at least 80% compliant with recording eDiary symptoms in the open-label phase.

*Note for older children: The mITT population consists of all randomized patients who received at least one dose of test drug. The VFE is a subset of the mITT population and have at least 80% test drug compliance, have completed the symptom diary for at least one week at baseline and at end of study, and patients who did not violate the protocol in any major way.

Children 1 Year Through 5 Years

A total of 101 patients were screened. Of these, 41 patients were screen failures (i.e., not meeting inclusion criteria, histology consistent with EE, abnormal lab results). The remaining 60 patients were randomly assigned to double-blind treatment groups and received at least one dose of test article; the safety population and the mITT population were the same. Within the mITT population in this trial, 47 patients were included in the VFE population.

Children 5 Years Through 11 Years

A total of 76 patients were enrolled to receive a daily dose of pantoprazole; 11 patients did not meet the initial entry criteria. A total of 65 patients underwent endoscopy; 5 did not meet entry criteria and 7 were excluded based on histology results (4 without GERD, and 3 with eosinophilic esophagitis). Overall, 23 patients did not meet all inclusion/exclusion criteria, including 3 patients with eosinophilic esophagitis, and were considered screen failures. Fifty-

three patients (ITT population) aged 5 to 11 years were randomly assigned to receive either pantoprazole 10 mg (n = 19), 20 mg (n = 18), or 40 mg (n = 16) once daily. Of the 53 randomly assigned patients, 4 had erosive esophagitis and 49 had non-erosive GERD. All 53 patients took at least one dose of trial drug (ITT/safety population) and 52 completed Visit 6 (end of treatment, Week 8). One patient in the 10 mg dose group withdrew after four weeks of treatment. Of the 53 ITT patients, 44 were in the VFE population: 15 in the 10 mg group, 15 in the 20 mg group, and 14 in the 40 mg pantoprazole group.

Adolescents 12 Years Through 16 Years

A total of 159 patients were screened for this trial. Of these, 23 patients were screen failures and were not randomized to treatment (mostly not meeting inclusion criteria). Of the remaining 136 patients, 68 patients were randomly assigned to the pantoprazole 20 mg group and 68 patients were randomly assigned to the pantoprazole 40 mg group. All 136 patients randomized to treatment received at least one dose of trial drug and completed at least one GASP-Q, and are included in the safety/ITT population. From the ITT population, 106 patients were VFE.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints are defined in terms of assessment tools. Thus, the assessment tools used for the trials are discussed first, followed by explanation of the primary endpoints.

Discussion of assessment tools used:

GSQ-I

The GSQ-I assessed five GERD symptoms in infants over the preceding seven days (vomiting/regurgitation, irritability/fussiness, refusal to feed, choking/gagging, arching back). An eDiary was distributed to the parents at the end of the screening visit to be completed daily, in the evening between six pm and midnight. The eDiary script assessed the five GERD symptoms using a 24-hour recall of the symptoms during the previous 24-hour period during screening and for eight weeks during treatment. The total mean weekly GERD symptom frequency was calculated each week. The eDiary also captured respiratory symptoms.

GSQ-YC

The GSQ-YC assessed five GERD symptoms in children ages 1 year through 5 years. The frequency of the GERD symptoms over the preceding seven days was assessed. The symptoms assessed for GERD were: vomiting/regurgitation, abdominal pain, refusal to eat, choking when eating, and difficulty swallowing.

GASP-Q

The GASP-Q was used in children 5 years through 16 years to measure the frequency and severity over the previous seven days for the eight symptoms presented: vomiting/regurgitation, abdominal pain, pain after eating, choking when eating, difficulty swallowing, burping/belching, nausea, and chest pain/heartburn. The ISS (Individual Symptom Score) is the product of the frequency and usual severity of each symptom. The sum of the ISS values made up the CSS.

The Applicant analyses suggest that an improvement of 40% to 50% in GERD total symptom frequency based on GASP-Q or eDiary and an improvement of 50% to 60% in the composite symptom score based on GASP-Q for an 8-week treatment is likely to be clinically meaningful with reasonable sensitivity and specificity using the PGA as a comparator.

SEALD (Endpoints and Labeling Team) was consulted to evaluate the assessment tools used to study Protonix in the pediatric population. There were prior agreements made between the Applicant and the Agency in 2005 to use the GERD Symptom Questionnaire for infants and the GSP-YC as endpoints to evaluate drug effectiveness. The review from SEALD does provide suggestions for consideration when evaluating these previously agreed upon endpoints. The following are comments copied from Dr. Paivi Miskala's review dated April 3, 2009.

- In the absence of empiric evidence for content validity of the proposed instruments in the target population, DGP should carefully evaluate the item content of these questionnaires from clinical perspective to make sure that we are not missing any key clinical symptoms. Furthermore, it needs to be ascertained if the caregivers understand the instructions, the concepts behind the items and the response options. Optimally, evidence should exist that each of the symptom-related behaviors contribute with equal importance to the summary score. If not, then the summary score is less interpretable as a measure of GERD symptom-related behaviors.
  DGP reviewer comment: Content seems appropriate.

- The Applicant's proposed description of the endpoints in the product labeling is not appropriate. The word (b) (4) " in the proposed label does not reflect what was actually measured by the instrument.
  - For infants and young children, the parents are observing frequency or duration of child's behavior, not symptoms per se. These behavior assessments should be clearly described as observer-based in the product label. Please note that parent report on the amount of time a young child complained of stomach/belly pain may not truly reflect the amount of pain child has. It is also noted herein that "amount of time" used as some of the instruments' item responses is a measure of duration, not frequency.
  - For older children, the composite score takes into consideration parent assessment of observable and non-observable symptoms, both their frequency and severity. It is this reviewer's impression that the child may not have been asked about the symptoms when parent was making the assessment. If the child was not asked for input on non-observable symptoms in particular then this questionnaire is problematic. Information should be requested from the Applicant to clarify this issue. It is noted that, generally, the Agency does not consider proxy-assessments adequate to support efficacy claims in medical product labeling.

  DGP reviewer comment: Agree with SEALD comments, Applicant replied that parents were interviewed and child participation was encouraged. Overall, the answers to questionnaires were observer based and not patient reported.

- It appears that the GASP-Q was interviewer (coordinator)-administered during some visits; however, the questionnaire is not in an interviewer format. Specific details related to this should be requested from the Applicant. It will be important to establish that the interview did not include additional filtering/interpretation of the responses by the interviewer.
  DGP reviewer comment: Standardized procedures were placed to limit subjective input.

- Usability/feasibility testing of the eDiary suggests that parents have difficulty differentiating wheezing from stridor. DGP should take this into consideration when evaluating these outcomes.
  DGP reviewer comment: Respiratory symptom evaluation is considered secondary and understandably difficult to interpret.

- Parent-reported data from open-label trials and treatment periods should be interpreted with caution because it is difficult to determine whether any observed differences in subjective assessments are real or due to bias.
  DGP reviewer comment: Agree.

- Exploratory evaluation of outcome data by fairly narrow age groups may be useful to determine that developmental differences do not influence efficacy findings.
  DGP reviewer comment: Agree that this is a possible consideration for further evaluation if necessary.

- Infant trial 3001B3-333-WW was conducted worldwide; however, the Applicant submission does not contain information on translation and cultural adaptation of the GERD Symptoms Questionnaire for infants. Therefore, we are uncertain whether the instrument is understood same way in different cultures and languages. SEALD recommends an exploratory analysis of the data by country in order to determine whether a treatment effect was demonstrated in all.
  DGP reviewer comment: As the infant trial did not meet its primary endpoint, further analysis of the data will not be conducted.

- Calculation of intrasubject (or intraobserver in this case) variability (day-to-day or week-to-week) may be useful to evaluate whether the changes observed in the scores are likely appreciable by the subjects. This could be calculated by the DGP statistician if the trial data is in house.
  DGP reviewer comment: Possible consideration for further analysis if necessary.

- SEALD also recommends evaluation of the cumulative distribution function of responses between treatment groups to characterize the treatment effect and examine the possibility that the mean improvement reflects different responses in subsets of patients.
  DGP reviewer comment: The trials were not powered to detect treatment difference.

Infants 1 Through 11 Months

The primary endpoint was the proportion who withdrew due to lack of efficacy during the treatment-withdrawal phase. Lack of efficacy was defined as one or more of the following conditions:

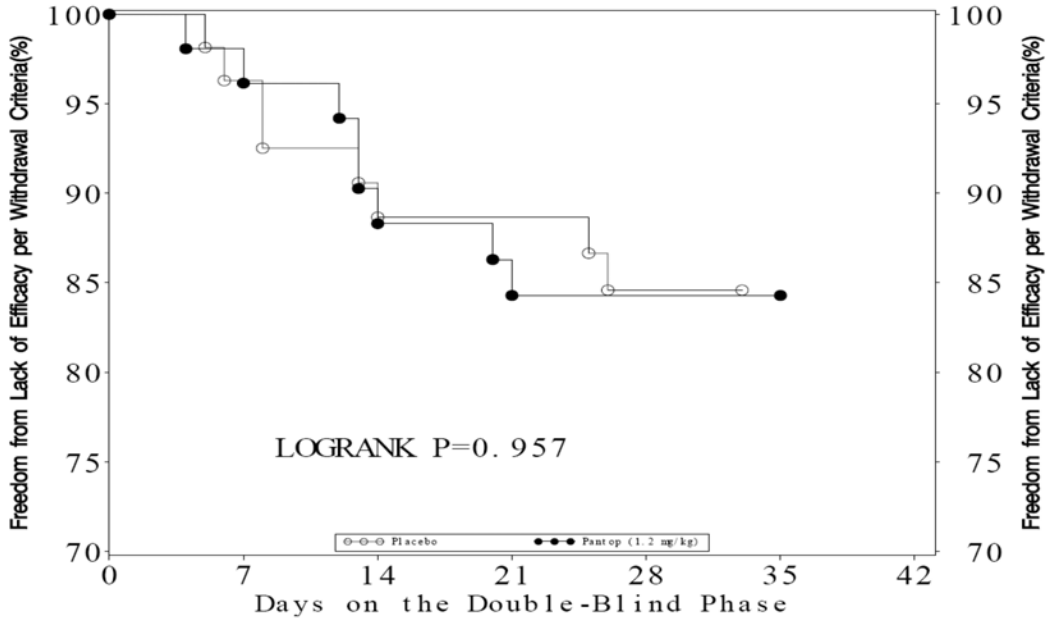
> Significant worsening of GERD symptom frequency (i.e., weekly GERD symptom score returned to baseline or above on two consecutive weekly evaluations not related to an intercurrent illness).
>
> OR
>
> A diagnostic test such as endoscopy demonstrates the worsening of esophagitis.
>
> OR
>
> Maximal antacid used for seven continuous days.
>
> OR
>
> Severe GERD symptoms based on physician's judgment, not related to intercurrent illness, as documented at an unscheduled or scheduled visit.
>
> OR
>
> Investigators determined if a patient should be withdrawn for lack of efficacy

The primary efficacy parameter of the trial was the difference in withdrawal proportion between the two treatment groups during the double-blind phase because of a lack of efficacy. A comparison of withdrawal proportion is shown in the following table for the mITT population. There was no difference in proportion. In all, 12 patients were withdrawn from the trial for this reason: 6 patients in the pantoprazole 1.2-mg/kg group and 6 patients in the placebo group. The Kaplan-Meier plot of time to lack of efficacy per withdrawal criteria for the double-blind phase also shows no differences between the treatment and placebo groups.

Table 7: Summary of withdrawal due to lack of efficacy (Trial 329 DB phase)

	Withdrawal/Total	Percent	P-Value
Placebo	6/54	11 %	1.000
Pantoprazole	6/52	12 %	

Figure 2: Kaplan-Meier Plot of Time to Lack of Efficacy per Withdrawal Criteria



Children 1 Year Through 5 Years

Erosive Esophagitis Endoscopy Findings

The number of patients with EE (HD ≥2 at baseline) and with a healing of EE (HD <2) at the end of trial were evaluated. There were four patients who had a diagnosis of EE: two in the medium-dose group and two in the high-dose group (patients with EE could not be randomized to the low-dose group). Repeat endoscopy demonstrated that all of the EE patients were healed at the final week of trial with HD scores of zero for all patients.

Table 8: Endoscopy Findings for EE Patients (Study 328)

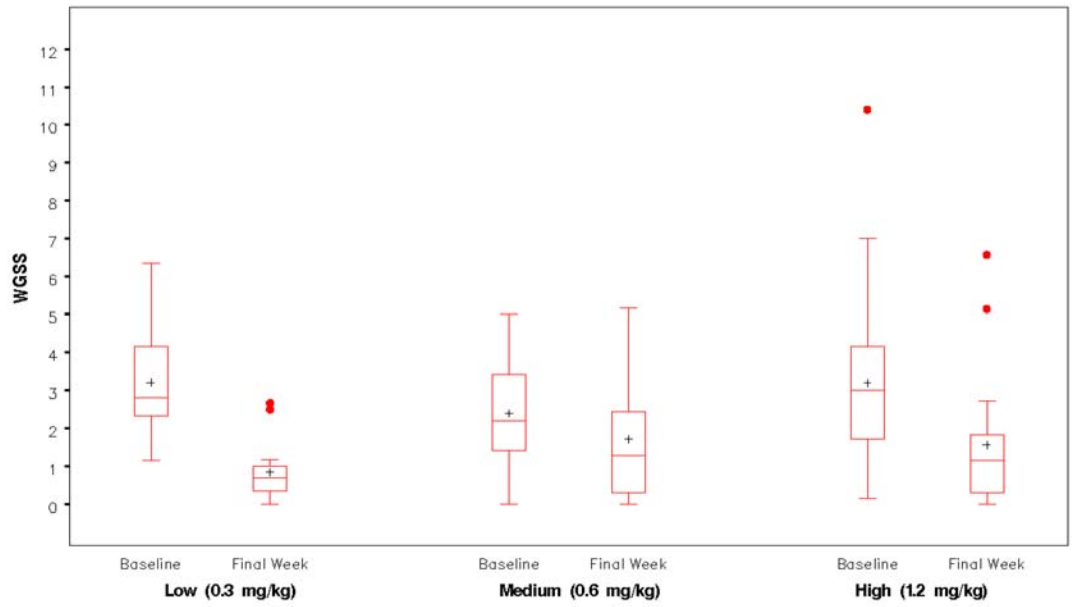
Patient	Age (Years)	Weight (kg)	Assigned Dose	Treatment	Study Week	HD Grade
009-0005	2	12	med	10 mg (0.8 mg/kg)	Baseline	2
					Final	0
045-0182	4	20	high	20 mg (1 mg/kg)	Baseline	2
					Final	1
076-1232	3	16	high	20 mg (0.8 mg/kg)	Baseline	2
					Final	0
083-1472	1	11	med	10 mg (0.9 mg/kg)	Baseline	2
					Final	0

Symptomatic GERD

The weekly GERD symptom score (WGSS), defined as the sum of the five selected individual weekly GERD mean frequency scores for vomiting/regurgitation (item 1c), chocking/gagging (item 2a), refusal to eat (item 3a), difficulty swallowing (max of 4a and 4b) and abdominal/belly pain (item 5a).

The primary effectiveness analysis was the change in mean WGSS from baseline week to final week for the mITT NERD population. A box plot of WGSS for the mITT population at baseline and final week for patients with NERD is presented in Figure 3 from the Applicant. The WGSS mean scores at baseline were 3.2, 2.4, and 3.4 for the low-dose, medium-dose, and high-dose groups, respectively. By the final week the mean scores had decreased to 0.8, 1.8, and 1.7 for the low-dose, medium-dose, and high-dose groups, respectively, indicating improvement in symptoms for all the dose groups. The low-dose, medium-dose, and high-dose groups included 0, 4, and 2 patients, respectively, who had baseline WGSS < 1. Interestingly, the low dose group has less variation in final week scores compared to the other treatment groups.

Figure 3: Box plot of WGSS Baseline and Final Week for mITT from Wyeth (Trial 328)



The boxes represent the lower to upper quartile range.

Descriptive statistics and within-treatment comparisons of WGSS for the mITT population (last observation carried forward, LOCF) for patients with NERD is presented below. For the mITT population, there were statistically significant within-group decreases in the mean WGSS from baseline to final week for the high-dose ($p < 0.001$) and the low-dose ($p < 0.001$) groups, but the decrease was not significant for the medium-dose group ($p = 0.06$).

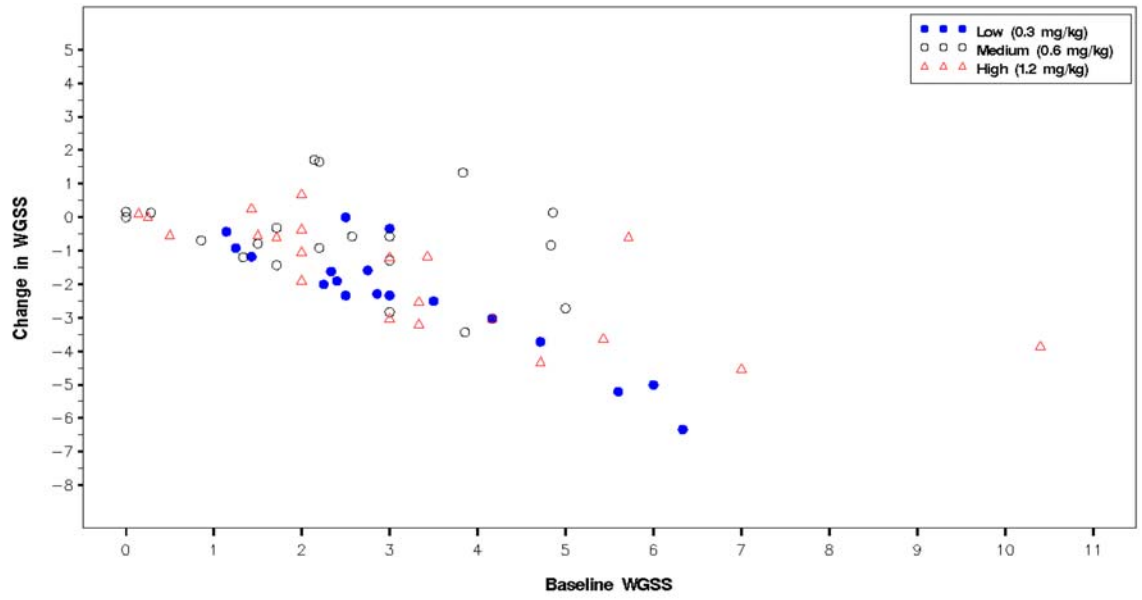
Table 9: Descriptive Statistics and Within Treatment Comparison of WGSS-mITT (Trial 328)

Characteristics		Pantoprazole treatment		
		Low (n=18)	Med (n=21)	High (n=21)
Week 1 Baseline	Mean [min, max]	3.2 [1.1, 6.3]	2.4 [0, 5]	3.4 [0.3, 10.4]
	Standard Dev	1.6	1.6	2.5
Final Week	Mean [min, max]	0.8 [0, 2.7]	1.8 [0, 5.2]	1.7 [0, 6.6]
	Standard Dev	0.7	1.8	1.7

Descriptive summary statistics and within-treatment comparisons by age and by baseline weight did not show significant differences between treatment groups. See section 9.4.2 for descriptive summary of CSS statistics and within-treatment comparison by age and weight.

Furthermore, Figure 4 shows the change in WGSS from baseline to the final week as compared to the baseline WGSS for each of the treatment groups. This figure suggests that the change in WGSS is more correlated to baseline WGSS than to the assigned treatment group. That is, the improvement after eight weeks of treatment was better in patients with higher baseline WGSS (more symptomatic).

Figure 4: Scatter Plot of Change in WGSS from Baseline to Final Week vs Baseline WGSS (Trial 328)



<u>Children 5 years through 11 years</u>:

Erosive Esophagitis Endoscopy Findings

Four patients, including three patients in the 20 mg group and one patient in the 40 mg group, had EE and Hetzel-Dent scores grade ≥2 at baseline. At the end of the trial, all of these patients had a score of 0 (normal) or 1 and were healed. Specifically, the patient in the 40 mg dose group had initial HD score of 3 and at the final visit the HD decreased to 0. All three EE patients in the

20 mg group entered with a HD score of 2. At the final evaluation, two of the patients had HD score of 1 and one patient had a score of 0.

Table 10: Endoscopy Findings from EE Patients (Trial 322)

Patient	Age (Years)	Weight (kg)	Assigned Dose	Treatment	Study Week	HD Grade
021-225	9	44	Med	20 mg (0.5 mg/kg)	Baseline	2
					Final	1
021-232	8	37	Med	20 mg (0.5 mg/kg)	Baseline	2
					Final	1
027-316	11	45	Med	20 mg (0.5 mg/kg)	Baseline	2
					Final	0
011-107	9	30	High	40 mg (0.8 mg/kg)	Baseline	3
					Final	0

Non-Erosive GERD Endoscopy Findings

Endoscopy and histologic assessment of esophageal biopsies were evaluated for patients with pathology at baseline and post treatment. Of the 53 patients randomized, 4 had EE and 49 had non-erosive GERD (NERD). Of the patients with NERD, 80% had endoscopic evidence of erythema and 65% had moderate or severe esophagitis on biopsy at baseline. After treatment, 70% of the endoscopy results were normal and 72% of the biopsy results were normal or showed mild esophagitis.

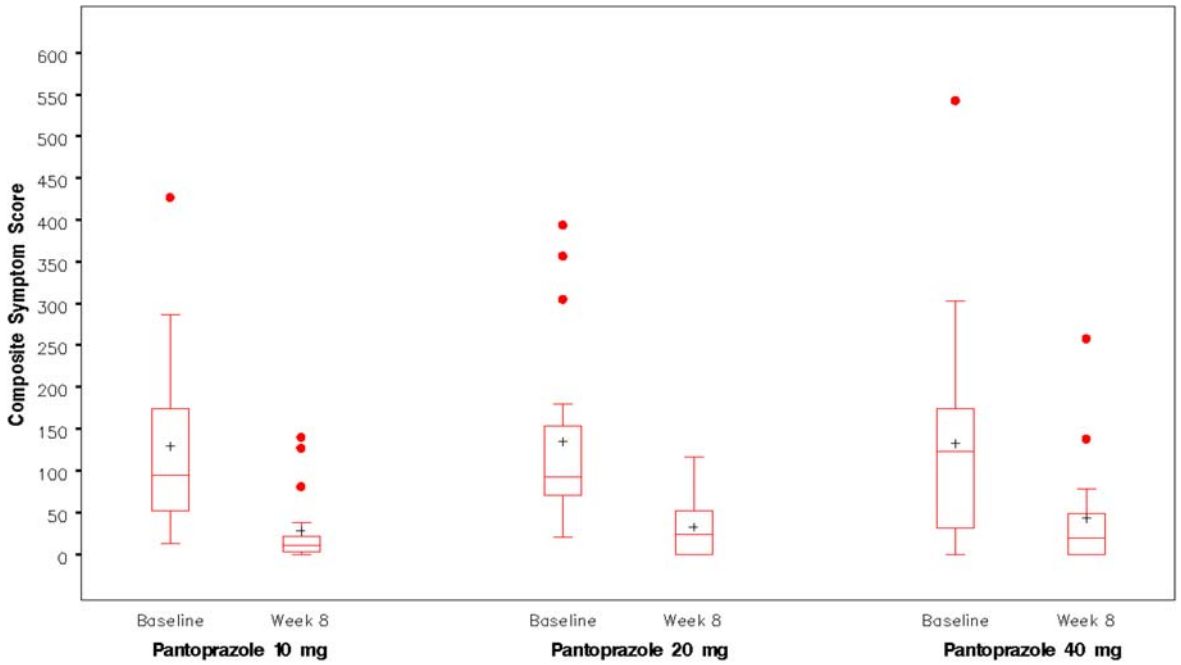
Symptomatic GERD

The primary endpoint was the change in the CSS as a measure of wellbeing from baseline to the final visit (week 8). Table 15 and Figure 4 summarize the mean CSS values at baseline and week 8, along with the changes in the mean from baseline to the final evaluation. The mean CSS values improved statistically significantly from baseline to the final visit both for the ITT ($p < 0.001$) and VFE ($p < 0.001$) populations in all three dose groups. No large differences were seen in the mean CSS change from baseline among the treatment groups at week 8 ($p > 0.05$). Of note, the standard deviations in the scores are large both at baseline and final week signifying a wide variability.

Table 11: Summary of CSS for the baseline and final evaluation for ITT (Trial 322)

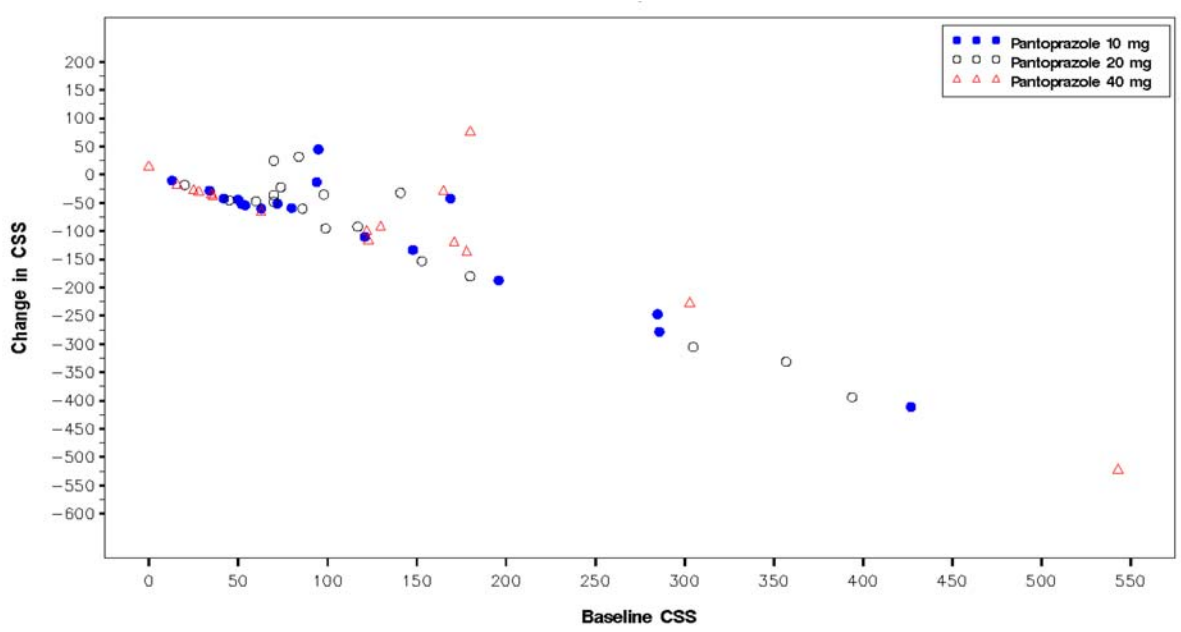
Characteristics		Pantoprazole treatment		
		10 mg (n=19)	20mg (n=18)	40 mg (n=16)
Week 1 Baseline	Mean [min, max]	129 [13, 427]	135 [20, 394]	132 [0, 543]
	Standard Dev	107.1	108.2	137
Final Week	Mean [min, max]	28 [0, 140]	33 [0, 116]	43 [0, 258]
	Standard Dev	43	39	68
p-value for difference		<0.001	<0.001	<0.001

Figure 5: Box plot of CSS at Baseline and Week 8 (Trial 322)



As in the younger 1 year to 5 years age group, the scatter plot below suggests that those patients with a higher baseline showed more improvement consistently across all three treatment groups. Subgroup analysis by age and weight did not show substantial differences between treatment groups. This suggests that improvement appears to be dependent on baseline severity more than age or weight subgroup.

Figure 6: Scatter plot of change in CSS from Baseline to Week 8 vs. Baseline (Trial 322)



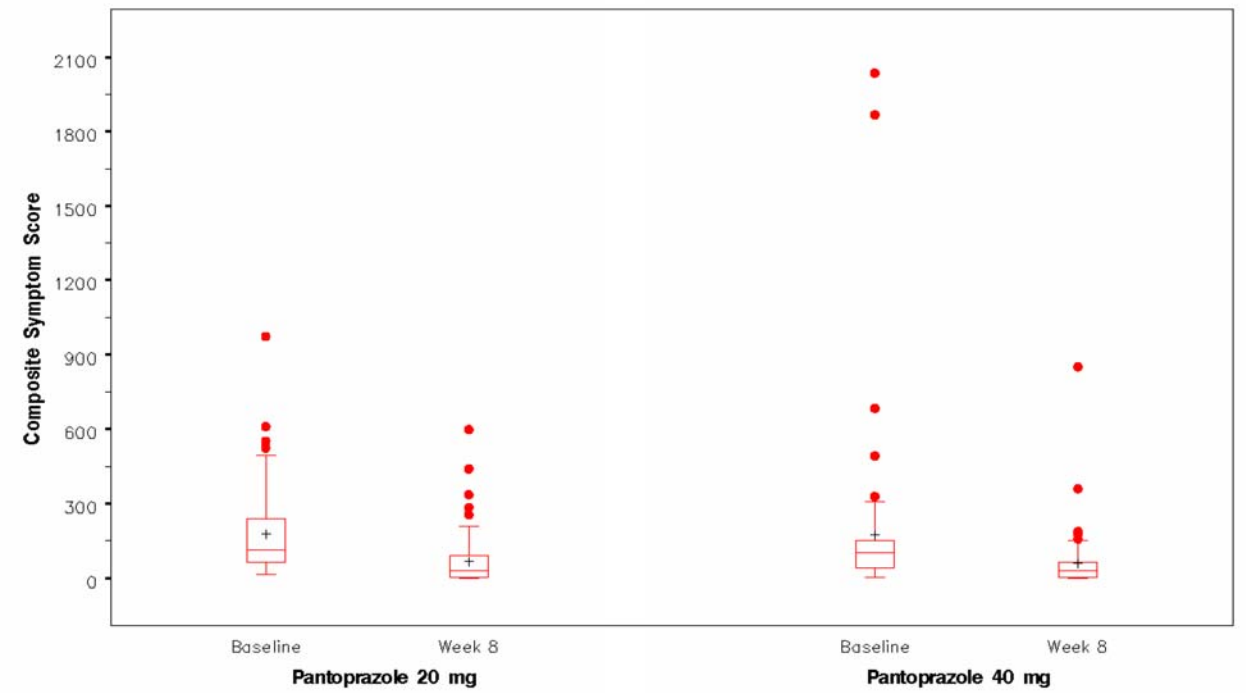
Children 12 years through 16 years:

There were no patients diagnosed with EE in this age group, however, as patients were not scoped as part of the inclusion criteria, it is possible that there were some individuals with EE enrolled in this trial. The primary endpoint was the change in the CSS from baseline to the last on-treatment evaluation at Week 8. For the ITT population, the CSS decreased approximately 100 points after eight weeks of treatment in both dose groups. This was a statistically significant change indicating improvement in symptoms ($p<0.001$). Results for the VFE population were comparable, with an even larger decline observed for the 40 mg VFE patients. The following Table and Figure depict the results in more detail.

Table 12: Summary of CSS for baseline and final evaluation for ITT (Trial 326)

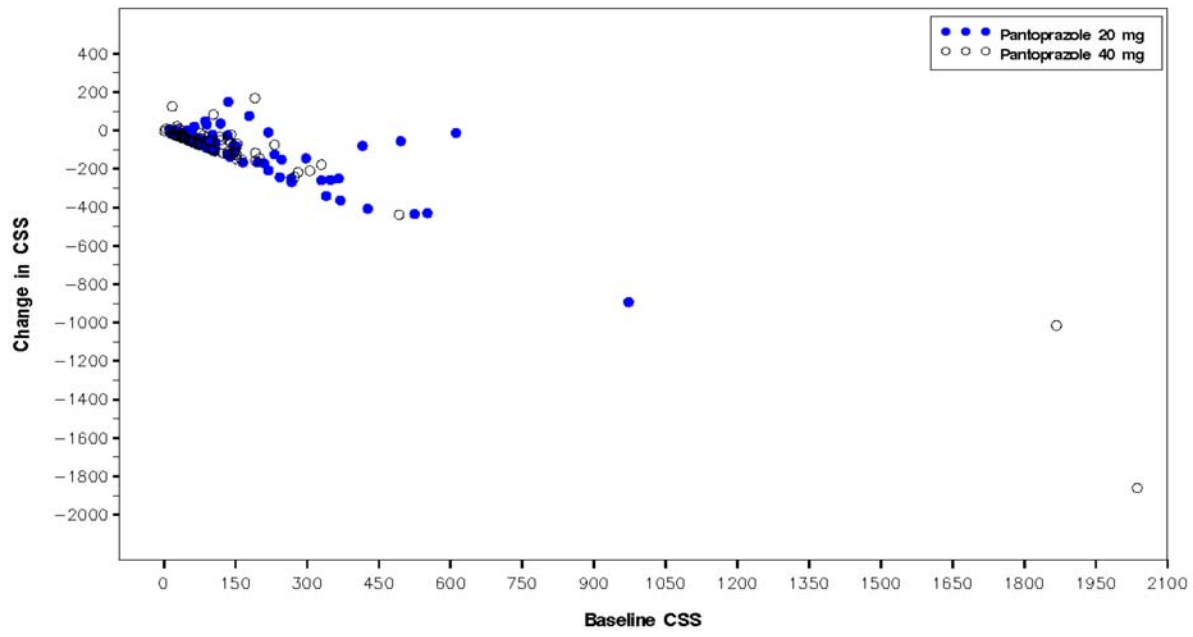
Characteristics		Pantoprazole treatment	
		20 mg (n=68)	40 mg (n=68)
Week 1 Baseline	Mean [min, max]	178 [12, 973]	174 [2, 2037]
	Standard Dev	172	332
Final Week	Mean [min, max]	67 [0, 600]	58 [0, 854]
	Standard Dev	108	119
p-value		<0.001	<0.001

Figure 7: Box Plot of CSS at Baseline and Week 8 (Trial 326)



Consistent with the patients with ages 1 year through 11 years, the scatter plot of change in CSS from baseline to week 8 compared to baseline CSS for the adolescent age group suggests that change in CSS is correlated linearly to severity of CSS at baseline.

Figure 8: Scatter Plot of Change in CSS from Baseline to Week 8 vs. Baseline CSS (Trial 326)



Integrated EE Healing Summary

There were a total of eight patients between the ages of 1 year and 11 years of age with endoscopically proven erosive esophagitis (defined as an endoscopic Hetzel-Dent score ≥2). All eight patients with EE had improved and were healed (with an endoscopic Hetzel-Dent score of 0 or 1) at eight weeks.

6.1.5 Analysis of Secondary Endpoints(s)

Infants 1 Through 11 Months

As the infant trial did not meet its primary endpoint, the secondary endpoints will not be discussed here (please see Appendix for details). In general, there were no notable differences between placebo and drug treatment.

Children 1 Through 5 Years

1. The individual mean frequency scores for each GERD symptom

   Both the individual symptom scores and the number of patients reporting symptoms decreased from baseline to the final week in all of the symptoms evaluated. However, only the improvement in abdominal pain from baseline to final week was statistically significant for all three dose groups.
2. The amount of antacid taken during each week, as well as the number of patients taking antacids.

   The mean amount of antacid (mL) taken weekly decreased from baseline week to Week 8 by 28.3 in the low-dose group ($p = 0.037$), 9.6 in the medium-dose group ($p = 0.069$), and 8.6 in the high-dose group ($p = 0.181$). For the mITT NERD population, there were no statistically significant between-group differences in the mean change from baseline week to Week 8 (or any other time point) in the amount of antacid taken weekly.
3. The individual mean score for respiratory symptoms

   The frequency of a cold or fever was fairly constant throughout the trial, with little difference between dose groups. The frequency of cough without a cold decreased from baseline to final visit but was only statistically significant in the low-dose group. Noisy breathing also decreased significantly in the low and high-dose groups. There was no significant change in the other respiratory symptoms between baseline and the final week of trial. The number of patients reporting respiratory symptoms (questionnaire items 6b through 6g) from baseline to final week decreased in all three dose groups.

There does not appear to be any secondary endpoints met which support additional labeling
.

Children 5 Through 11 Years and **Adolescents 12 Through 16 Years**

1. Change in ISS from baseline at each assessment and the change in CSS from baseline at each assessment (other than the final visit, which constituted the primary endpoint).

   Age 5 to 11: For each symptom, the ISS was defined as the product of the number of occurrences and the severity of that individual symptom (ranging from mild =1 to most severe = 7) in the previous seven days. Significant mean decreases from baseline to Week 8 were observed for abdominal pain/belly pain ($p < 0.001$), chest pain/heart burn ($p < 0.006$), difficulty swallowing ($p < 0.001$), nausea ($p < 0.001$), burping/belching ($p <$

0.001), and pain after eating ($p < 0.001$) for all three doses. No significant decrease was noted in vomiting/regurgitation and choking when eating for all three doses. Although there were some fluctuations from week to week, the mean symptom scores tended to decrease steadily over time.

Overall, improvements in the mean CSS of GERD symptoms were seen from baseline to all visits during and after treatment with pantoprazole 20 mg and 40 mg. Statistically significant decreases from baseline in the mean CSS of GERD symptoms were observed for all three treatment groups, starting at Week 3 and continuing to Week 10 ($p < 0.05$). These results indicate that symptoms improved faster in the 20 and 40 mg dose groups compared with the 10 mg dose group, which was also effective after two weeks of treatment

Age 12-16: The number of patients reporting each symptom decreased from baseline to Week 8 in the ITT population in both dose groups. The most common symptoms were abdominal pain/belly pain and burping/belching, reported by approximately 80% of patients in both treatment groups at baseline. At Week 8 these symptoms were reported by approximately 50% of patients. Difficulty swallowing showed the largest improvement, being reported by approximately 35% of patients at baseline and 10% of patients at Week 8. In addition to the number of patients with each symptom, the symptom frequency during each one-week period decreased from baseline to Week 8 in both dose groups. After eight weeks of treatment, the symptom frequency had decreased in most cases by half. However, the severity of symptoms did not change much after eight weeks of treatment.

A steady decline in mean CSS was observed in the ITT population throughout the course of the trial. A lower CSS was observed as early as Week 1. Results for the VFE population were comparable with the ITT population. The number of patients with a CSS below the entry criteria (less than 16) increased in both dose groups as the trial progressed. More patients in the 40 mg group achieved CSS below entry threshold at Week 1 ($p = 0.048$) and Week 6 ($p = 0.041$) but not at week 8 ($p = 1.00$).

2. Need for trial antacids

   Age 5 to 11: Patients in the 20 mg and 40 mg groups used slightly fewer Mylanta tablets at Weeks 7 to 8 than they had at baseline. However, there was no change in antacid use in the 10 mg group.

   Age 12 to 16: There was no difference between treatment groups in antacid use or the number of patients taking antacids in any two-week period. Antacid use decreased slightly at the end of the trial, but the change was not statistically significant in the ITT population.

3. Physician global assessment at the final visit (seven-point Likert scale)

   Age 5 to 11: A majority of patients in the pantoprazole 10 mg (58%) and 40 mg (56%) groups had improved greatly at the end of treatment. Eight (44%) patients in the 20 mg

group showed improvement in their GERD symptoms at the end of treatment. None of the patients worsened. Similar results were obtained for the VFE population. The patients had clinically significant disease improvement at the end of therapy within all three dose groups of pantoprazole ($p < 0.001$), although no statistical significant difference was seen among the dose groups ($p > 0.433$).

Age 12 to 16: Most patients (>75%) as moderately or greatly improved (Table 9.4.2.5-1). Both groups demonstrated significant improvement compared with baseline ($p<0.001$). No patient was rated as having moderately or greatly worsened. Results for the VFE population were comparable with the ITT population.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

None.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Based on the four clinical outcome trials, my recommendation for Protonix dosing regimen would be the following: children one to five years old should start at 10 mg and 20 mg can be considered if symptoms are not sufficiently improving. For the older age children six years old and up, 20 mg daily is recommended with dosage up to 40 mg if symptoms are not improving adequately.

Table 13: Initial Reviewer recommended Protonix Dosing Regimen

Pediatric Age Group	Dose
Children (1 to ≤ 5 years old) Pediatric Granules	10 mg or 20 mg
Children (5 years old to ≤ 16 years old) Tablets	20 mg or 40mg

Incorporating the analysis from the Pharmacometric and Clincal Pharmacology team members, the dosing regimen should be further refined as described below:

Table 14: Final Reviewer Recommended Protonix Dosing Regimen

Age	1 to ≤ 5 years Granules		5 to ≤ 16 years Tablets		Adults Tablets
Weight	< 15 kg	≥ 15 kg	< 40 kg	≥ 40 kg	
Dose	10 mg	20 mg	20 mg	40 mg	40 mg

Adult granules versus Pediatric granules

Review of the data suggests that the adult granules are approximately 15% higher in C_{max} as compared to the pediatric granules, whereas the AUCs are bioequivalent (BE). The upper bound

of the pediatric granule C_{max} missed the BE requirement by only 4%. There is sufficient PK data to suggest that a dosage adjustment would not be required when converting pediatric patients to using the adult granules, that is, the exposures in the pediatric patients would still fall comfortably within the range of exposure seen in adult patients during Protonix clinical trials. There do not appear to be safety concerns as: 1) there is a large margin of safety in general with this drug and 2) the division is recommending lower dosage than the Applicant.

7 Review of Safety

Safety Summary

Wyeth Research conducted eight clinical trials in pediatric patients to support the safety and tolerability request of the pantoprazole PWR:

- Trial 1 (Wyeth trial 3001B3-331-WW)
- Trial 2 (Wyeth trial 3001B3-333-WW)
- Trial 3 (Wyeth trial 3001B3-329-WW)
- Trial 4 (Wyeth trials 3001B3-334-US, 3001B3-328-NA, and 3001A1-322-US)
- Trial 5 (Wyeth trials 3001A3-337-US, and 3001A1-326-US).

In addition, four trials in children and adolescents with oral and IV pantoprazole sodium that are supportive of PWR requirements (3001B3-335-WW, 3001A1-109-US, 3001K1-110-US, and 3001K1-117-US) were also conducted. The safety data was reviewed; however, as there were no concerning safety signals a written review was not included. In accordance with the pantoprazole PWR, in each trial, as well as in this summary, routine safety and tolerability parameters were measured and pooled for adverse events (AEs), treatment-emergent adverse events (TEAEs), safety-related discontinuations, serious adverse events (SAEs), physical examination including growth parameters, vital sign measurements, laboratory evaluations, and 12-lead electrocardiograms (ECGs).

The safety population consisting of the eight trials in the PWR numbers 567 patients. There are 47 patients in the supportive trials not part of the PWR, 23 of whom received IV pantoprazole, most receiving only a single dose and none more than two days of treatment. No major safety signals were found.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

All four clinical outcome trials and four pharmacokinetic trials included in the PWR were analyzed individually and in an integrated manner to evaluate safety. The safety data from the supportive trials were reviewed but not summarized in this document as there were no new safety concerns.

7.1.2 Categorization of Adverse Events

Terminology from the Coding Symbols for the Thesaurus of Adverse Reaction Terms (COSTART) is used to describe the adverse events to be consistent with the terminology used in previous pantoprazole trial reports and to facilitate the integration of pantoprazole datasets.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Wyeth provided an Integrated Summary of Safety (ISS) in which data from all eight PWR trials were reviewed as a whole. The ISS presents data across the trials by dose, age group, formulation, and by intrinsic factors (sex, race, ethnicity).

7.2 Adequacy of Safety Assessments

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

A total of 614 pediatric patients (567 PWR) received at least one dose of pantoprazole: 333 received granules, 258 received tablets, and 23 received the IV formulation. Those in the tablet group received a mean of 41 doses over a mean of 44 days. The mean postnatal age of patients enrolled in these trials was 5.8 years with a range of birth to 16 years. The trial population included 57% male and 47% female patients; 75% Caucasian, 18% African American, and the remaining patients were Asian or other races. From the total approximately 8% were Hispanic or Latino.

Some demographic characteristics showed differences across the different dose groups because of trial design. Low-dose pantoprazole was used only in trial 328 (which involved patients 1 through 5 years of age) and trial 322 (which involved patients 5 through 11 years of age); therefore, all patients in the low dose group were in the 1 through 11 years age group. All 129 patients in trial 329, all of whom were infants 1 through 11 months, received high dose pantoprazole. Consequently, patients receiving high dose pantoprazole tended to be younger (4.7 years) than those receiving medium or low dose pantoprazole (7.8 years and 5.7 years, respectively), lighter (23 kg, 36 kg, and 26 kg, respectively), and shorter (95 cm, 120 cm, and 115 cm, respectively). Male and female patients were proportionately distributed across the three dose groups.

Table 15: Demographics for the Entire Safety Population

Characteristic	Low (n = 37)	Medium (n = 211)	High (n = 366)	Total (n = 614)
Postnatal Age (years)				
Mean	5.7	7.8	4.7	5.8
SD	3.4	6.0	5.8	5.9
Min – Max	1 – 11	0.02 – 16	0.02 - 16	0.02 – 16
Sex, N (%)				
Female	17 (45.9)	105 (50)	167 (45.6)	289 (47)
Male	20 (54.1)	106 (50)	199 (54.4)	325 (53)
Race, N (%)				
American Indian Or Alaska Native	0	1 (0.5)	2 (1)	3 (0.5)

Characteristic	Low (n = 37)	Medium (n = 211)	High (n = 366)	Total (n = 614)
Asian	0	2 (1)	18 (4.9)	20 (3.3)
Black or African American	9 (24.3)	37 (17.5)	65 (17.8)	111 (18.1)
Other	1 (2.7)	8 (3.8)	11 (3)	20 (3.3)
White	27 (73)	163 (77.3)	270 (73.8)	460 (75)
Ethnicity, N (%)				
Hispanic or Latino	2 (5.4)	18 (8.5)	30 (8.2)	50 (8.1)
Non-Hispanic and Non-Latino	35 (94.6)	193 (91.5)	336 (91.8)	564 (91.9)

7.2.2 Explorations for Dose Response

Oral doses ranging from approximately 0.3 mg/kg/day (low), 0.6 mg/kg/day (med), or 1.2 mg/kg/day (high=adult equivalent) were studied. Pantoprazole granules or tablets were dispensed as 1.25, 2.5. 5. 10. 15. 20 or 40 mg. In the supportive trials, IV pantoprazole was administered at doses of 0.8 mg/kg or 1.6 mg/kg. Adverse events were analyzed for possible dose-response relationship. No clear associations were identified between the observed rates of TEAE, PCI lab results, ECG, or vital sign abnormalities and the dose of pantoprazole administered. As an example, the table below copied from the sponsor submission summarizes the severity and drug relationship for TEAEs overall and by dose group.

Table 16: Number (%) Pts Reporting TEAEs by Dose from Wyeth

	Treatment			
Body System Severity / Drug Relationship[a]	Pantoprazole Low (n = 37)	Pantoprazole Medium (n = 211)	Pantoprazole High (n = 366)	Total (n = 614)
Any adverse event				
All severity / not related	28 (75.7)	109 (51.7)	200 (54.6)	337 (54.9)
All severity / related	7 (18.9)	26 (12.3)	42 (11.5)	75 (12.2)
Mild / not related	22 (59.5)	73 (34.6)	135 (36.9)	230 (37.5)
Mild / related	3 (8.1)	10 (4.7)	22 (6.0)	35 (5.7)
Moderate / not related	6 (16.2)	31 (14.7)	54 (14.8)	91 (14.8)
Moderate / related	4 (10.8)	10 (4.7)	18 (4.9)	32 (5.2)
Severe / not related	0	5 (2.4)	9 (2.5)	14 (2.3)
Severe / related	0	6 (2.8)	2 (0.5)	8 (1.3)
Life threatening / not related	0	0	2 (0.5)	2 (0.3)

7.2.3 Special Animal or In Vitro Testing

Please refer to section 4.3.

7.2.4 Routine Clinical Testing

Routine clinical testing of trial patients appears appropriate and the monitoring for adverse events followed the specifications as delineated in the PWR.

7.2.5 Metabolic, Clearance, and Interaction Workup

Summary of Pharmacometric and Genomics review
Review of the submitted data show that the proposed dosing regimen based on age produces exposures in the pediatric population with AUC values that exceed the mean AUC in the adult range by approximately 100%. As expected, increasing body weight appears to be correlated with a decrease in exposure within each dose group. Given that AUC shifts depending on body weight and that the AUC does not change with age lends itself to concluding that dosing by body weight more appropriately matches adult AUCs. Please see the figures below copied from Dr. Justin Earp's draft pharmacometric review for Protonix.

Figure 9: AUC vs. Weight and Age

AUC increases with decreasing weight in each dose group. Solid and dashed red lines represent the mean and limits (upper 90% and lower 10%) of the adult exposures. The symbols × and • indicate individual AUC estimates for the 20 and 40 mg dose groups (i.e. age < 6 yr receives 20 mg, age ≥ 6 yr receives 40 mg). Green, black and orange symbols indicate poor, extensive, or unknown CYP2C19 metabolizer status.

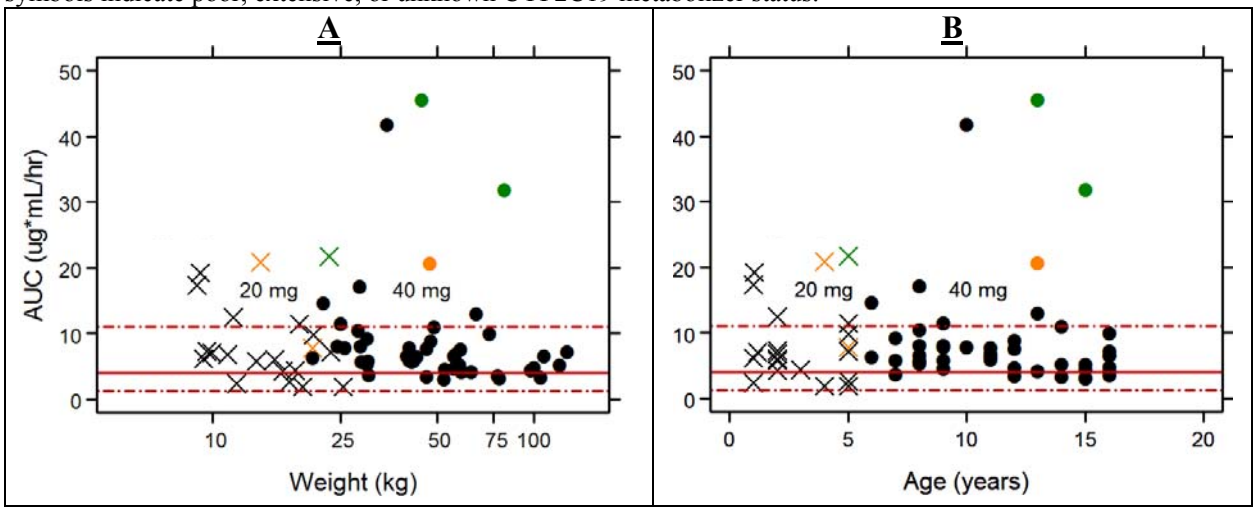


Table 17: Pharmacometrics proposed dosing regimen matches adult exposures*

(b) (4)

* Results are presented as mean and range (10 percentile – 90 percentile). Poor metabolizers are excluded from this analysis.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in the eight trials submitted as part of the PWR. One (0.2%) patient died after completing trial 110, which is a supportive trial that was included with the submission but not part of the WR. The patient was a seven-year-old white male patient who, prior to trial enrollment, was hospitalized for a closed head injury secondary to a fall. The patient received two doses of IV pantoprazole 1.6 mg/kg. Five days after completing the trial, the patient had progressive neurologic deterioration as a complication of the closed head injury and had respiratory failure requiring mechanical ventilation. The patient was subsequently withdrawn from life support. The AE was considered unrelated to pantoprazole (Trial 110: An Initial Trial of the PK, PD, Safety and Tolerability of Intravenous Doses of Pantoprazole in Hospitalized Pediatric Patients).

7.3.2 Nonfatal Serious Adverse Events

Overall, 23 (4%) patients reported at least one SAE. None of the SAEs was considered to be related to test article by the investigators. The event most commonly reported as an SAE was viral gastroenteritis which was reported in 3 (0.5%) infant patients. In two patients, seven events namely worsening of GERD, vomiting, dehydration, bronchiolitis, respiratory failure, stridor and otitis media were each reported as SAEs.

Infant trial: A total of eight patients had a total of 11 SAEs at some time during the trial, including screening and follow-up. The SAEs involved the following body systems: respiratory (4), digestive (3), metabolic and nutritional (2), cardiovascular (1), and special senses (1).

Age 1-5 years trial: Two (2, 3%) patients had a total of three SAEs at some time during treatment in this trial. None of these SAEs was considered to be related to the trial drug. Two

SAEs were of mild severity; one SAE was of moderate severity. The SAEs experienced by these two patients were abdominal pain, and anorexia and dehydration.

Age 5-11 years trial: No SAE reported.

Age 12-16 years trial: One SAE was reported in this trial. This patient was hospitalized at Week 5, for an inflamed gall bladder and a cholecystectomy was performed; the patient fully recovered and completed the trial.

Table 18: Listing of SAE during PWR trials

Age(y)/ Sex	Therapy Duration	Day of Event	Preferred Term – Verbatim
7/M	1	6	Accidental– respiratory failure due to closed head injury
9/M	1	5	Dyspnea – respiratory distress
14/F	1	5	Pancreas disorder – worsening of pancreatic pseudocyst
		20	Local reaction to procedure – post operative complications
1.08/F	1		Diarrhea – diarrhea
			Vomiting – vomiting
1.42/M	2		Stridor – stridor, worsened
12/F	55		Cholecystitis
3/M	7	7	Abdominal pain- abd pain
1/F	56	36	Anorexia – poor oral intake
		43	Dehydration – dehydration
0.31/F	28	17	FTT – failure to thrive
		44	FTT – poor weight gain
0.15/M	32	-5	Laryngitis – croup
		19	worsening of GERD
0.15/M	56	68	Bronchiolitis – bronchiolitis
		69	Otitis media – otitis media
0.42/M	56	10	Bronchiolitis – bronchiolitis
0.2/M	25	-7	Gastroesophageal reflux disease – GERD, worsening
0.75/F	29	2	Gastroenteritis – gastroenteritis
0.31/M	6	11	UTI – urinary tract infection
0.13/F	50	57	Resp d/o – choking in airway
0.04/M	6	33	GI hemorrhage – hematochezia
0.09/F	35	36	Respiratory failure – acute respiratory failure
0.83/F	58	5	Dehydration and vomiting

7.3.3 Dropouts and/or Discontinuations

Overall, 15 (2.4%) patients were withdrawn from the trial because of AEs. The AE resulting in the most withdrawals was headache (3 patients, 0.5%). Diarrhea, worsening of GERD, and sleep disorders each resulted in withdrawal of 2 (0.3%) patients. A listing of the patients who withdrew from pediatric trials because of AEs is presented:

Table 19: Listing of AEs Leading to Withdrawal from Wyeth

Age(y)/Sex	Therapy Duration	Day of Event	Preferred Term – Verbatim	Drug Relationship[b]
12/M	24		Headache – daily headache	Definitely
15/F	30		Headache – headache	Possibly
13/M	28		Headache – headaches	Definitely
2/M	23	16	Contact dermatitis – diaper contact dermatitis	No
		16	Diarrhea – diarrhea	Yes
3/M	25	24	Rectal hemorrhage – rectal bleeding	No
1/M	9	1	Sleep disorder – sleep disturbance	Yes
3/M	7	7	Abdominal pain – abdominal pain	No
0.65/M	42	33	Sleep disorder – sleep problems	Yes
0.21/F	5	2	Emotional lability – excessive crying	Yes
0.21/F	17	3	Gastroesophageal reflux disease – 'worsening of GERD'	No
0.47/M	14	1	Gastroesophageal reflux disease – 'worsening of GERD'	No
0.75/F	29	22	Diarrhea – diarrhea	Yes
0.16/F	39	38	Vomiting – excessive vomiting	Probably
0.09/F	35	36	Respiratory failure – acute respiratory failure	Definitely not
0.51/F	1	1	Gastroenteritis – acute gastroenteritis - rotaviral infection	Definitely not

Overall, 551 (89.7%) of the 614 patients in the ISS population completed the trial in which they participated; 63 (10.3%) patients discontinued. A total of 13.7% of patients in the high dose group discontinued compared with 5.4% and 5.2% in the low and medium dose groups, respectively. Of note, low dose therapy was only used in trials 322 and 328 where treatment was for eight weeks each. The medium and high doses were used in more trials and therapy duration ranged from single doses up to eight weeks.

Table 20: Summary of Primary Reason for Discontinuation by Dose

Conclusion Reason	Low (n = 37)	Medium (n = 211)	High (n = 366)	Total (n = 614)
Completed	35 (94.6)	200 (94.8)	316 (86.3)	551 (89.7)
Discontinued	2 (5.4)	11 (5.2)	50 (13.7)	63 (10.3)
Adverse event	1 (2.7)	2 (0.9)	11 (3.0)	14 (2.3)
Failed to return	0	1 (0.5)	2 (0.5)	3 (0.5)
Invest. request	0	0	2 (0.5)	2 (0.3)
Lost to f/u	0	0	1 (0.3)	1 (0.2)
Noncompliance	0	0	10 (2.7)	10 (1.6)
Other	1 (2.7)	2 (0.9)	2 (0.5)	5 (0.8)
Parent request	0	0	5 (1.4)	5 (0.8)
Patient request	0	4 (1.9)	2 (0.5)	6 (1.0)
Protocol violation	0	2 (0.9)	7 (1.9)	9 (1.5)
Unsatis. response	0	0	8 (2.2)	8 (1.3)

7.3.4 Significant Adverse Events

See above.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant reports that overall, 412 (67%) patients reported one or more TEAE. The most commonly reported TEAEs were headache (12%), URI (12%), rhinitis (10%), infection (9%), fever (8%), diarrhea (8%), accidental injury (7%), pharyngitis (7%) abdominal pain (6%), cough (6%), vomiting (6%), and otitis media (5%).

Comment: Reassignment of preferred terms for the adverse events reported for all submitted trials resulted in data as shown in Table 21.

Table 21: Comparison of AEs Analyzed by Various PWR Trial Groupings (numbers are %)

AE Preferred Term	Adult N=1473	All trials N=614	PWR Trials N=567	PWRs minus Infant trial N=438	Ages 1-16yrs (8 wk trials) N=249	Infant OL N=128	Infant DB only (TX-PBO) N=108
URI		21	23	19	29	23	
HA	12	13	14	18	30		
FEVER	1	11	11	9	8	12	
DIARRHEA	9	9	10	9	9	11	
ACCIDENT. INJURY		9	10	12	18	1	
PHARYNGITIS		9	9	11	18	2	
RHINITIS		7	8	8	8	5	4
COUGH INC		7	8	6	8	6	
VOMITING	4	7	7	7	8	5	
OTITIS MEDIA		7	7	5	3	10	
ABD PAIN	6	6	7	8	11	1	
NASAL CONGESTION		5	5	5	7	5	
RASH	2	5	5	4	4	5	
CONTACT DERM		4	5	4	2	6	
SINUSITIS		4	4	4	7	2	
Others	Nausea (7)				Nausea (5)	Thrush (5)	CPK inc (6), Otitis media (6) Laryngitis, (4%)

There is only placebo-controlled data from the infant study, however, it is useful to note that for most common adverse events seen in the older pediatric population there was not much difference seen between treatment and placebo. From the safety analysis, the labeling for Protonix should state that the most commonly reported (> 4%) adverse reactions in the pediatric population include: URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain. Accidental injury although common does not make physiologic sense and is likely more a reflection of the pediatric population. Pharyngitis, rhinitis, and cough are common symptoms of URI and I do not feel they need to be specifically described.

The following should be stated for the infant study: In the single pediatric trial which was placebo-controlled (involves infants < 1 year), the adverse reaction that was reported more commonly (difference of ≥ 4%) in the treated population compared to the placebo population was: elevated CPK, otitis media, rhinitis, and laryngitis.

In the spirit of the new PLR labeling, a detailed table specific for pediatric trials does not need to appear in the labeling as adverse reactions described in adults are relevant for the pediatric

patients. An exhaustive listing of adverse reactions reported in the trials less than 4% is not helpful to the prescribing practitioner, thus only those considered more meaningful should be described.

7.4.2 Laboratory Findings

The ISS dataset was reviewed for potentially clinically important (PCI) laboratory abnormalities that occurred during one or more of the trials for overall trend. In particular CPK, gastrin, triglyceride, Alk Phos, PTT, triglyceride, uric acid, and potassium were reviewed in detail as there were a number of patients with abnormal laboratory values in these parameters that warranted further evaluation as a potential safety signal. Further review of the submitted data does not show a dose response effect, nor is there a consistent trend seen across all age groups leading for concern.

7.4.3 Vital Signs

There was no pattern in the percentages of patients with a PCI vital sign assessment that suggests a dose relationship. Nor were there consistent abnormalities in the PCI vital signs.

7.4.4 Electrocardiograms (ECGs)

The ISS dataset was reviewed for ECG abnormalities see Appendix section 9.5 for details. On-treatment PCI prolonged QTc interval was recorded in 5 infants (3%). However, at the end of the double-blind period, equal numbers of infants on treatment and placebo had prolonged QTc intervals. No other age group had PCI QTc lab values. Therefore, it is unlikely that there is a safety concern for QTc prolongation with drug treatment. The longest QTc interval at the end of treatment was 588 msec. Of note, ECGs were collected as a screening procedure and routine safety measurement and were not designed to collect QT interval data, thus no attempts were made to standardize equipment across sites. Also, ECGs in infants are difficult to obtain reliably due to crying and the difficulty of keeping infants still during the measurement.

There was on-treatment PCI prolongation in the QRS interval in 10% of patients (30/314), however, there was an inverse dose response relationship between drug and frequency of QRS prolongation. Specifically, 44% of the affected patients were in the low dose compared to 6% in the high dose. No children in the 12 to 16 year age group had PCI QRS prolongation. The longest QRS interval at the end of treatment was 93 msec.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Overall, 452 (73.6%) patients reported one or more AEs, including 35 (94.6%) patients in the low dose group, 146 (69.2%) in the medium dose group, and 271 (74.0%) in the high dose group. One or more TEAEs were reported in 412 of 614 (67.1%) patients: 94.6% of patients who

received low dose pantoprazole, 64.0% of patients who received medium dose, and 66.1% of patients who received high dose. The higher rate of TEAEs in the low dose group may reflect the longer mean duration of therapy received by those patients (approximately 56 days) as compared to the shorter duration of therapy for patients in the medium and high dose groups (approximately 37 days each).

The frequency of TEAEs appeared to increase in dose-dependent fashion consistent with a dose response for only two events. These was otitis media, reported in 2.7%, 2.8%, and 6.6% of patients in the low, medium, and high dose groups, respectively; and contact dermatitis (mostly non-fungal diaper rash), reported in 0, 2.4%, and 3.8% of patients in the low, medium, and high dose groups, respectively. However, analyses by age group showed that the large majority of episodes of otitis media and contact dermatitis occurred among infants, 83% of whom received high dose pantoprazole. In infants, there was no evidence of a dose or treatment relationship for either otitis media or contact dermatitis. The apparent dose response observed for the overall analysis may represent an artifact of data pooling resulting from the relatively high incidence of otitis media and contact dermatitis in the infant population, and the disproportionate number of patients in this age group who received treatment with high dose pantoprazole.

In contrast to otitis media and contact dermatitis, the frequencies of other TEAEs were reported to decrease with increasing dose. Among these were headache (27%, 15.2%, 9.0%), infection (13.5%, 11.4%, 6.3%), accidental injury (18.9%, 9.5%, 4.4%), and pharyngitis (13.5%, 7.6%, 5.7%), all of which were reported more commonly in the two older groups, which included all of the patients receiving low dose and a larger proportion of those who received medium dose pantoprazole.

Overall, SAEs were reported for 23 (3.7%) patients: 7 (3.3%) in the medium dose group, and 16 (4.4%) in the high dose group. No SAEs were reported in the low dose group. No SAE was considered related to treatment with pantoprazole. The event most commonly reported as an SAE was gastroenteritis, which was reported in 3 patients: 2 (0.5%) in the high dose group and 1 (0.5%) in the medium dose group.

Table 22: Patients (>2%) Reporting TEAE by Dose Level

Body System AE	Low (n = 37)	Medium (n = 211)	High (n = 366)	Total (n = 614)
Any AE	35 (94.6)	135 (64.0)	242 (66.1)	412 (67.1)
Body as whole				
Headache	10 (27.0)	32 (15.2)	33 (9.0)	75 (12.2)
Infection	5 (13.5)	24 (11.4)	23 (6.3)	52 (8.5)
Fever	3 (8.1)	13 (6.2)	35 (9.6)	51 (8.3)
Accid. injury	7 (18.9)	20 (9.5)	16 (4.4)	43 (7.0)
Abd pain	3 (8.1)	16 (7.6)	19 (5.2)	38 (6.2)
Pain	3 (8.1)	5 (2.4)	6 (1.6)	14 (2.3)
Digestive system				
Diarrhea	6 (16.2)	8 (3.8)	33 (9.0)	47 (7.7)

Body System AE	Low (n = 37)	Medium (n = 211)	High (n = 366)	Total (n = 614)
Vomiting	3 (8.1)	9 (4.3)	22 (6.0)	34 (5.5)
Gastroenteritis	1 (2.7)	4 (1.9)	11 (3.0)	16 (2.6)
Constipation	1 (2.7)	1 (0.5)	13 (3.6)	15 (2.4)
Tooth disorder	1 (2.7)	3 (1.4)	11 (3.0)	15 (2.4)
Nausea	3 (8.1)	4 (1.9)	6 (1.6)	13 (2.1)
Respiratory system				
URI	8 (21.6)	16 (7.6)	47 (12.8)	71 (11.6)
Rhinitis	8 (21.6)	22 (10.4)	33 (9.0)	63 (10.3)
Pharyngitis	5 (13.5)	16 (7.6)	21 (5.7)	42 (6.8)
Cough inc	4 (10.8)	11 (5.2)	19 (5.2)	34 (5.5)
Sinusitis	2 (5.4)	6 (2.8)	8 (2.2)	16 (2.6)
Skin and appendages				
Contact dermatitis	0	5 (2.4)	14 (3.8)	19 (3.1)
Rash	1 (2.7)	5 (2.4)	11 (3.0)	17 (2.8)
Special senses				
Otitis media	1 (2.7)	6 (2.8)	24 (6.6)	31 (5.0)

7.5.2 Time Dependency for Adverse Events

None.

7.5.3 Drug-Demographic Interactions

An integrated analysis by age, sex, and race were presented. No specific safety signals were detected.

7.5.4 Drug-Disease Interactions

No specific studies were done.

7.5.5 Drug-Drug Interactions

Previously done in adult studies.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity trials have been performed.

7.6.2 Human Reproduction and Pregnancy Data

This was a pediatric trial involving patients infant to age 16 years. There were no reports of pregnancy during the trials.

7.6.3 Pediatrics and Assessment of Effects on Growth

Weight, height, BMI, and head circumference (age appropriate) studies were done. There do not appear to be any data showing that short term treatment of pantoprazole leads to negative impact on growth parameters.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In these trials, there were a few cases of accidental drug overdose, however, no adverse events were reported. There were no reports for drug abuse potential, withdrawal, or rebound with this treatment.

7.7 Additional Submissions

All trials were analyzed for safety by formulation (i.e., granule, tablet, or IV). As the age groups receiving the two different oral formulations were separate, analyses by formulation are confounded by age. Also, the IV formulation was used in hospitalized (sicker) patients as compared to the oral granules which were used mostly the outpatient setting. Therefore, I am unable to form any conclusion regarding effect of formulation by itself as contributing towards differences in safety events.

8 Postmarket Experience

Information is derived from post-marketing surveillance data for children and adolscents younger than 18 years from the Applicant's safety database (AEs from spontaneous reports, literature, solictited, as well as reports from observational trials for pantoprazole were derived from PSURs prepared by Nycomed). The period covered is from Aug 2005 through May 2008. Marketing data on the sales volume to children and adolescents is not available, thus exposure data for the patient population less than 18 years of age is not available.

A search for pediatric AEs identified 34 cases with 71 associated AEs terms. Of these 12 cases (35%) were regarded as serious. No deaths have been reported.

Table 23: Summary of Post-Market Pediatric SAE by Patient Sex and Age from Wyeth

Category		Serious Cases	Overall Total
Total case reports	n (%)	12 (35.3)	34 (100)
Total AE terms	n	34	71
Sex - n (%)	Male	5 (41.7)	12 (35.3)
	Female	7 (58.3)	18 (52.9)
	No data	0	4 (11.8)
Age group - n (%)			
	0-11 months	3 (25)	7 (20.6)
	1-5 years	1 (8.3)	3 (8.8)
	6-11 years	2 (16.7)	6 (17.6)
	12-14 years	1 (8.3)	5 (14.7)
	15-17 years	5 (41.7)	13 (38.2)

Table 24: AEs Reported for Pediatric Patients (≥3% of Total Terms) from Wyeth

MedDRA System Organ Class	MedDRA Preferred Term	N	% of AEs
Injury, poisoning and procedural complications	Drug exposure during pregnancy	4	5.6
	Medication error	3	4.2
Nervous system disorders	Headache	4	5.6
Gastrointestinal disorders	Nausea	3	4.2
Total		14	19.6

Of the 12 SAE cases, there were 32 SAE terms of which 19 were unlabeled. However, none of those was assessed as related to pantoprazole. Ten SAE terms were assessed as "not evaluable," these are summarized in a table from the Applicant.

Table 25: Unlabeled SAEs for Pediatric Patients Assessed by Wyeth as Unevaluable

Onset Date	Sex/Age	MedDRA Preferred Term
Jul-2003	F/14 years	Gastroesophageal reflux disease
Jul-2006	M/16 years	Chest pain
Jul-2003	F/14 years	Condition aggravated
Jul-2003	F/14 years	Drug effect decreased
Mar-2005	F/18 days	Drug exposure during pregnancy
Mar-2005	F/18 days	Drug screen positive
May-2007	F/10 months	Acute lymphocytic leukemia
Jul-2003	F/14 years	Dysuria
Jul-2006	M/16 years	Painful respiration
Jul-2003	F/14 years	Alopecia

The post-marketing safety information included in this submission does not reveal new safety concerns.

9 Appendices

9.1 Literature Review/References

The following three literature reviews were conducted by Wyeth in response to the PWR and summaries were submitted:

1. Use of Pantoprazole for the Maintenance of Healed Erosive Esophagitis in Pediatric Patients
2. Summary of Medical Literature on the Use of Pantoprazole in Pediatric Patients
3. Enterochromaffin-like Cell Hyperplasia, Proton Pump Inhibitors, and Pediatric Population Literature Search

1. The Applicant states that 200 articles in the literature were considered relevant and included in this review. The direct summary from Wyeth:

- *Clinically, the efficacy of pantoprazole and other PPIs in inducing healing of erosive esophagitis in children seems to mirror that seen in adults. In both adults and children, the efficacies of different PPIs in healing erosive esophagitis are comparable. However, it should be noted that the prevalence of erosive esophagitis in children under age 12 is uncommon and is rarely seen at all in infants (less than 12 months).*
- *In adults, the efficacy of pantoprazole and the other PPIs in maintaining healing of erosive esophagitis, mirrors that of their efficacy in inducing healing; again in this regard, the efficacies of different PPIs are comparable. PPIs, however, are superior to histamine-2 receptor antagonists (H2RAs) in maintenance of healing.*
- *For PPIs in general, and pantoprazole in particular, the drug effects in pediatric patients are similar as in adults. This is true in terms of the mode of action, the absorption and elimination pharmacokinetics of the pro-drug, and the "pharmacokinetics" of the inhibition of acid production by the activated drug. This reflects the common pathophysiology in children and adults, as well as the similar efficacy in healing erosive esophagitis and in the maintenance of healing.*
- *A retrospective review was conducted in children (ages 0.2 years through 17 years) with GERD with or without erosive esophagitis receiving PPI therapy, including pantoprazole, continuously for > 1 year (PPIs: 6 to 127 months; pantoprazole: 9 to 64 months) including baseline and follow-up esophageal and gastric biopsies to assess frequency, duration of PPI dosing, symptom relief, gastrin levels, histologic findings, and adverse events. This trial found no significant differences between the various PPIs, their dose, duration of treatment, or frequency of administration in any biochemical, endoscopic, or histologic changes. The results of this retrospective trial suggest that continuous long-term pantoprazole and PPI therapy in pediatric patients is safe.*
- *Similar to adults, in another retrospective review in children (9 months to 11 years) with GERD, PPIs (omeprazole and lansoprazole) were found to be safe and effective during*

continuous use for up to 11 years. Few adverse reactions to these drugs occurred, and discontinuation of the drug was seldom indicated.

2. Wyeth further summarizes the literature search on the effects of PPIs with specific attention to pantoprazole found the following:
   - *The results from the three short term trials with pantoprazole in children ages 5 through 17 years with symptomatic or symptomatic and endoscopically-proven GERD have shown that treatment with 10 to 40 mg pantoprazole is effective in reducing the clinical symptoms of GERD and is generally safe and well tolerated.*
   - *Pantoprazole was shown to be effective in improving clinical symptoms of GERD at different dosage in these age groups. Pantoprazole has shown to improve symptoms of endoscopically diagnosed GERD over 8 weeks of treatment compared with baseline, however, higher doses of 20 and 40 mg/day improved symptoms by one week of treatment.*
   - *The adverse effect profile of short-term treatment of up to eight weeks with pantoprazole in pediatric patients was similar to those described in the Protonix Package Insert for adults.*
   - *Additional trials up to eight weeks are either clinically complete or ongoing in children less than five years of age and in infants (< 12 months) to assess the safety and efficacy profile of appropriate formulations of pantoprazole in these age groups.*
   - *In a recent trial, long term continuous use of PPIs for up to 11 years showed to be safe and efficacious in children (mean age 7.8 years) with GERD.*
   - *The results of the long-term treatment (9 to 64 months) with pantoprazole (0.58 to 1.41 mg/kg) in children ages 6.1 through 15.9 years showed normal endoscopic and biopsy findings in 83% of children during and at the follow-up evaluations.*
   - *Finally, the results of this literature search showed that although the data on the long-term safety of pantoprazole in the management of pediatric patients is limited, short-term therapy of 8 to 12 weeks appears to be safe and an effective therapeutic modality in children and adolescents with GERD between 5 to 17 years of age with symptomatic or endoscopically-proven GERD.*

3. The Applicant states that on May 27, 2005, Wyeth submitted to IND 35,441 a critical summary of the clinical data (from the medical literature) that helped to determine if pediatric patients were at any increased risk with respect to proliferative changes in the gastric ECL cells. In addition, a complete report of a seven-day treatment in neonatal/juvenile dogs and an associated toxicokinetic report were submitted.

   A new literature search with a cutoff date of April 29, 2008, was performed to update the summary on the effect of PPIs on ECL cells hyperplasia and pediatric population as a part of a complete response to the PWR. In summary, 15 new relevant citations were identified based on the specified search criteria. The Applicant concludes that pantoprazole sodium, when used at approved doses for eight weeks in infants, children, and adolescents with symptomatic GERD, is not likely to be associated with clinically significant increases in serum gastrin levels or with ECL cell proliferative changes.

9.2 Labeling Recommendations

General labeling issues
The Protonix labeling will be converted to PLR format. The Pediatric and Maternal Health Staff were involved in the labeling review process.

Pediatric labeling issues

As discussed in Section 1 (Recommendations), there is a discrepancy in the indication originally sought between the adult and pediatric population. The adult indication is the short-term treatment of EE associated with GERD. (b) (4) Rather, the data submitted support the adult parallel indication of the short-term treatment of EE in pediatric patients ages 1 yr to 16 yrs.

(b) (4)

Adult labeling issues

The following materials were reviewed to evaluate the revisions in the current adult labeling:

- NDA review 20-987 by Dr. Hugo Gallo-Torres, June 30, 1998
- NDA 20-987 safety update review by Dr. Hugo Gallo-Torres, Feb 26, 1999
- NDA 22-020 review by Dr. Nancy Snow, March 15, 2007
- Lansoprazole labeling
- PSUR Module 5.3.6
- Annotated Labeling and Labeling History documents Module 1.14
- Clinical Safety Summary Module 2.7.4
- Post Marketing Experience 5.3.6
- Labeling roadmap with justifications for changes submitted by Wyeth electronically, April 17, 2009

In accordance with 21 CFR 201.56 (b)(iii), the proposed package insert is intended to conform to the new Physician Labeling Rule (PLR) format, which became effective June 30, 2006. Wyeth selected information for inclusion in the Adverse Reactions section of the labeling based on a comparison between the current US labeling and the cumulative safety data for Protonix. Other

adverse events that were considered by Wyeth to meet the definition of an Adverse Reaction following review (i.e., events as to which there is a "reasonable suspicion" of a causal relationship) were also included in the proposed Adverse Reactions section. The Applicant states taking into account factors including biologic plausibility, seriousness of the AE, medical condition for which pantoprazole is indicated, and frequency. Clinical trial data chosen as a reference included nine randomized controlled Phase 2 or 3 clinical studies with oral Protonix. The newly presented table of adverse reactions is an integrated listing of the frequencies of the adverse drug reactions from the nine studies, which may provide more meaningful information to the prescriber as compared to the three previous tables, by indication, in the current USPI. AEs not included in the newly proposed labeling include ambiguous terms such as abnormal ECG, skin disorder, and non-specified drug reaction.

Comment: The current extensive list of possible associated adverse reactions and post market reported events has been streamlined reasonably, and I agree with the method in which the Applicant has attempted to hone in on more relevant adverse reactions to help prescribing practitioners and patients.

9.4 Detailed Review of Individual Trial Reports

9.4.1 Trial 3001B3-329: Age 1 to 11 month - Efficacy and Safety Trial

A. General Design and Objective:

Trial 3001-B3-329 (Trial 329) is a Phase 3, multicenter, outpatient, randomized, double-blind, placebo-controlled, treatment-withdrawal trial of oral pantoprazole in approximately 130 infants aged 1 through 11 months who had symptomatic GERD. The trial was divided into an open-label run-in phase, in which all patients received pantoprazole treatment for four weeks, followed by a four-week double-blind phase, in which half of the patients were randomly assigned to continue on pantoprazole and the other half were withdrawn to placebo.

The duration of the open-label run-in treatment phase of four weeks exceeded by several weeks the time to reach steady-state for pantoprazole, which is five days. This trial design ensured that gastric acid suppression by pantoprazole was at steady-state, to meet the Pediatric Written Request (PWR) guidelines.

The primary objective of this trial was to assess the efficacy of treatment with pantoprazole granules administered as an oral suspension in patients aged 1 through 11 months with symptomatic GERD. The difference in treatment-withdrawal rates due to lack of effectiveness was compared between two groups of patients: those who continued treatment with pantoprazole and those who received placebo.

Other objectives were to assess the safety, tolerability, GERD symptoms, respiratory symptoms, antacid use, compliance, and growth parameters in patients aged 1 through 11 months with symptomatic GERD.

The trial was conducted at 31 sites, including 18 sites in the United States, 5 sites in South Africa, 3 sites in Canada, 2 sites in Poland, and 1 site each in Belgium, Latvia, and Spain. A total of 129 patients received at least one dose of pantoprazole, 108 patients received at least one dose of trial medication in the double-blind phase of the trial drug, and 88 patients completed the trial.

B. Background

Protocol Amendments
The protocol was amended after the original protocol was issued on Nov 15, 2005. Amendment 1 (Jun 14, 2006) was made before the start of the trial, and changed the trial design so that it complied with the revised PWR.

Amendment 2 (Apr 16, 2007) was requested by the WR medical monitor to make minor administrative changes to several sections. The changes did not affect the way the trial was conducted.

Amendment 3 (May 3, 2007) was a country-specific administrative amendment prepared for the Bundesinstitut für Arzneimittel und Medizinprodukte in Germany. However, the trial was not conducted in Germany.

C. Inclusion

The trial population consisted of preterm, term, or postterm infants aged 1 through 11 months with symptomatic GERD. Preterm infants were defined as infants who were born before 37 complete weeks of gestation. Term infants were defined as infants who completed 37 to 42 weeks of gestation, and postterm infants were defined as infants who completed more than 42 weeks of gestation. Patients who met all of the following criteria were eligible:

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

D. Exclusion

Patients who met any one of the following criteria were not eligible for trial participation:

1. Known history or presence of upper GI anatomic or motor disorders (endoscopy or other tests not required), including the following:
    a. Uncorrected esophageal atresia, esophageal strictures, webs, or diverticulae, tracheo-esophageal fistula, or choanal atresia.
    b. GI strictures of any kind.
    c. Esophageal or gastric motor disorders (e.g., scleroderma, achalasia).
    d. Barrett's esophagus.
    e. Peptic ulcer disease, erosive gastritis, and/or erosive duodenitis.
    f. Eosinophilic esophagitis clinically suspected or by histology (≥15 eosinophils per high powered field).
    g. GI malabsorption.
    h. Known active *Helicobacter pylori* infection.
    i. Uncorrected pyloric stenosis.
2. History of acute life-threatening events due to manifestations of GERD (e.g., respiratory arrest).
3. Clinically significant medical conditions during the pretrial screening physical examination, ECG recording, or laboratory testing, as assessed by the investigator without prior WR medical monitor approval. This included:

   a. Unstable cardiovascular, renal, hepatic, hematologic, or endocrine disease except with prior approval of WR medical monitor.
   b. Active childhood infectious diseases (e.g., measles, mumps, chickenpox).
   c. Known coagulation disorders (e.g., hemophilia).
4. Cystic fibrosis or any malignancy
5. Known history of human immunodeficiency virus (HIV) or clinical manifestations of acquired immune deficiency syndrome (AIDS) or other immunodeficiency disorder.
6. Any of the following abnormal test results:
   a. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2 times upper limit of normal (ULN).
   b. Total bilirubin ≥2 mg/dL (≥34.2 mcmol/L).
   c. Alkaline phosphatase (AP) ≥2 times ULN (age corrected).
7. Known positive serologic test for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody or an HCV RNA polymerase chain reaction (PCR) test.
8. Known hypersensitivity to PPIs, including pantoprazole.
9. Use of PPIs or H2 receptor blockers within 14 days before baseline questionnaire (start of open-label treatment run-in phase).
10. Use of nontrial antacids, bismuth subsalicylate containing products (Pepto-Bismol), sucralfate, misoprostol, anticholinergics, or prokinetic agents, prostaglandins, pH-dependent drugs, glucocorticoids, and any other medications used to treat a gastrointestinal condition within three days before baseline questionnaire.
11. Any disorder requiring chronic use of warfarin or other anticoagulants, carbamazepine, phenytoin, or anticholinergics.

E. Treatment

The dose, 1.2 mg/kg pantoprazole sodium enteric-coated granules for suspension, was chosen on the basis of initial PK data from trial 3001B3-333-WW (Section 9.4.6), which was conducted in a similar patient population (infants aged 1 through 11 months). In Trial 329, effectiveness was compared with that of placebo in patients who had responded to four weeks of open-label treatment with the pantoprazole granules for suspension formulation.

Two strengths (5 mg and 10 mg) of pantoprazole were dispensed by weight group according to Table 26 (from the Applicant) to achieve an approximate daily dose of 1.2 mg/kg.

Table 26: Dose Administration According to Wt Group (Trial 329)

Weight (kg)	Approximate Dose Strength: 1.2 mg/kg
≥2.5 kg to <7 kg	5.0 mg
≥7 kg to ≤15 kg	10.0 mg

Concomitant Medications:
Patients continued their usual medical therapies according to standard clinical practice. Continuous treatment with theophylline derivatives or digoxin was closely monitored throughout the trial to assure that proper serum levels of these drugs were maintained.

Medications used to treat non-GI conditions were allowed (with the exception of prohibited treatments listed), provided no dose adjustment was likely to be necessary during the trial.

Prohibited Medications:
Concurrent treatment with any of the following medications during the double-blind treatment phase of this trial was prohibited:

1. Other PPIs (omeprazole, esomeprazole, lansoprazole, or rabeprazole).
2. Prokinetic agents.
3. H_2RAs (e.g., cimetidine, famotidine, ranitidine, or nizatidine).
4. Antacids (other than trial-provided Mylanta Supreme liquid, Maalox Nighttime, Gaviscon Infant, or local equivalent) or other drugs that affect luminal pH.
5. Bismuth-containing agents (e.g., Pepto-Bismol).
6. Anticholinergics (scopalmine, belladonna, or donnatol).
7. Chronic (daily) use of glucocorticoids. Steroid inhalers and topical steroids may be used.
8. Chronic (daily) use of carbamazepine or phenytoin.
9. Prostaglandins (misoprostol).
10. Sucralfate (Carafate).
11. Warfarin (Coumadin), heparin, or other anticoagulants.
12. Any other medication used to treat a GI condition.
13. Use of special diets or herbal or alternative medications that might affect the metabolism of the test article.

F. Procedures/Safety Considerations/Monitoring

After screening, all patients received two weeks of standardized, nonpharmacologic, conservative treatment for GERD (hypoallergenic formula thickened with rice cereal, and instructions on feeding and positioning). Qualifying patients continued to receive this conservative treatment. An electronic diary (eDiary) was used to collect data on GERD symptoms, respiratory symptoms, and the use of rescue antacids.

After the two-week screening, the eDiary was also used to track patient compliance. Patients whose symptoms resolved with conservative treatment during screening were withdrawn from the trial. All patients whose symptoms failed to improve with the conservative treatment entered a four-week treatment run-in phase, and received open-label oral pantoprazole daily. (The terms "treatment run-in phase" and "open-label phase" refer to the same trial phase).

At the conclusion of the open-label phase, all patients who were at least 80% compliant with both the test article regimen and eDiary completion entered the four-week, double-blind, placebo-controlled, treatment-withdrawal phase. (The terms "treatment-withdrawal phase" and "double-blind phase" refer to the same trial phase). The investigator confirmed a clinical response to treatment (such as eDiary symptom improvement) before randomization. Patients were stratified by body weight as of Visit 4 and randomly assigned to receive either pantoprazole or matching placebo daily for four weeks.

At Visit 1 and all subsequent visits, patients were provided with two or three 355-cc bottles of the marketed product Mylanta Supreme for US sites, Maalox Nighttime for Canadian sites, or Gaviscon Infant liquid antacid or local equivalent in other countries (containing 300 to 400 mg $CaHCO_3$ per 5 mL), which was to be taken if needed after five or more minutes of severe GERD symptoms as rescue. The dose of antacid was not to exceed 35 mg/kg/day or 87.5 mg $CaHCO_3$/kg/day. Maximal antacid doses were to be given only to patients with low milk intakes.

Patients were brought to the investigative site for six trial visits (Weeks –2, 0, 2, 4, 6, and 8), and telephone contacts were conducted at Weeks 1, 3, 5, and 7. For all patients who entered the treatment–withdrawal phase, a post treatment follow-up telephone contact occurred approximately two weeks after the final trial visit (see Table 27).

A central computerized randomization/enrollment (CORE II) system was used to assign randomization numbers. Randomization was stratified by weight (see Table 26).

Table 27: Study schedule (Trial 329)

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

G. Endpoints

Efficacy Measurements
The eDiary included a symptoms script that prompted parents to assess the frequency of GERD symptoms during the previous 24-hour period. The script, called the Caregiver Assessment of GERD Symptoms in Infants (CAGS-I), was based on the modified GSQ-I, which was previously developed to assess GERD symptoms in infants aged 1 through 11 months. Questions on the

modified GSQ-I were adapted from the validated Infant Gastroesophageal Reflux Questionnaire (I-GERQ) by Orenstein and colleagues. The CAGS-I script included the following items:

1. Vomiting/regurgitation:
    - 1a: Since last evening, how many times did the baby spit up (anything coming into or out of the mouth)?
    - 1b: Since last evening, how much did the baby *usually* spit up (anything coming into or out of the mouth)?
    - 1c: Since last evening, did spitting up (anything coming into or out of the mouth) seem uncomfortable (i.e., crying, fussing, irritability) for the baby?
2. Irritability/fussiness:
    - 2a: Since last evening, did the baby cry or fuss during or after feedings?
    - 2b: Since last evening, how many times did the baby either cry a lot during or within1 hour after a feeding?
    - 2c: Since last evening, how much of the time did the baby cry or fuss?
3. Choking/gagging:
    - 3a: Since last evening, during how many feedings did the baby choke or gag?
4. Arching back/head retraction:
    - 4a: Since last evening, how many times did the baby have episodes of arching back?
5. Refusal to feed:
    - 5a: Since last evening, how many times did the baby refuse feedings even when hungry?
    - 5b: Since last evening, how many times did the baby stop eating even when hungry?

A Weekly GERD Symptom Score (WGSS) was calculated from five selected symptoms in the above list (items 1a, 2b, 3a, 4a, and the maximum of 5a/5b). WGSS was the sum of the weekly mean frequencies of these five symptoms.

In addition, the eDiary was used to assess the frequency of respiratory symptoms during the previous 24-hour period, based on the presence/absence of following items:

- 6a: Since last evening, did the baby have a cold or fever?
- 6b: Since last evening, did the baby have a cough *without* a cold?
- 6c: Since last evening, how much of the time did the baby have noisy breathing *without* a cold?
- 6d: Since last evening, did the baby have noisy breathing when breathing *out*?
- 6e: Since last evening, did the baby's breathing have a wheezy or whistling sound?
- 6f: Since last evening, did the baby have noisy breathing when breathing *in*?
- 6g: Since last evening, did the baby's breathing have a croupy or barky sound?
- 6h: Since last evening, did the baby stop breathing or turn blue or purple?

Primary Efficacy Variables

The primary endpoint was the **withdrawal** due to lack of efficacy during the treatment-withdrawal phase. Lack of efficacy was defined as one or more of the following conditions:

Significant worsening of GERD symptom frequency (i.e., WGSS returned to baseline or above on two consecutive weekly evaluations not related to an intercurrent illness).

OR
A diagnostic test such as endoscopy demonstrates the worsening of esophagitis.
OR
Maximal antacid used for seven continuous days.
OR
Severe GERD symptoms based on physician's judgment, not related to intercurrent illness, as documented at an unscheduled or scheduled visit.
OR
Investigators determined if a patient should be withdrawn for lack of efficacy.

Secondary Efficacy Variables

The secondary endpoints were as follows:

- Withdrawal for any reason.
- Time to withdrawal due to lack of efficacy, time to meeting the criteria for lack of efficacy, and time to withdrawal for any reason.
- WGSS and individual mean frequency for each GERD symptom.
- The amount of antacid taken during each week and biweekly (every 2 weeks).
- The number of patients taking antacids during each week and biweekly.
- Respiratory symptoms, e.g., frequency of cough, noisy breathing in or out, breathing with a wheezy sound, breathing with a croupy sound, and stopped breathing (apnea).

Throughout the trial, routine safety and tolerability were evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, height and weight measurements, 12-lead ECG recordings, clinical laboratory test results, and growth parameters, including z-scores for weight, height, and head circumference. Safety data were reviewed by the investigator and the WR medical monitor. The safety of pantoprazole was assessed on an ongoing basis by review of AEs and clinically laboratory test results.

Clinical Laboratory Evaluations

Laboratory evaluations were performed as outlined in the Trial Flowchart. A central Laboratory, (b) (4) coordinated and provided each trial site with shipping supplies and detailed instructions for the shipment and storage of blood samples. All laboratory tests with values that were considered to be abnormal to a clinically important degree after test article administration were repeated until the values returned to normal or baseline.

Vital Signs and Growth Parameters

Vital signs (tympanic or core temperature, supine blood pressure, supine pulse rate, and supine respiration rate) and growth parameters (height, weight, and head circumference) were measured and recorded during physical examinations.

Other Safety Evaluations

A standard 12-lead ECG recording was obtained during the pretrial screening at visit 1 and at the final visit of the treatment period (visit 6). Interpretations of the ECG recordings were provided by the investigator or a local cardiologist.

H. Data Analysis

Determination of Sample Size

In trial 3001A1-322-US, the dropout rate due to lack of efficacy among children aged 5 through 11 years treated with pantoprazole was 1 of 53 (1.9%). In a trial comparing famotidine to placebo in infants, reported by Orenstein and colleagues, the dropout rate for lack of efficacy in the placebo treatment group was 3 of 11 (27.3%). Assuming that the withdrawal rates in the pantoprazole 1.2 mg/kg and placebo groups in the current trial are 3% and 27%, respectively, it was determined that 38 patients per group entering the double-blind treatment-withdrawal phase would be needed to detect the assumed difference, using a 2-sided Fisher exact test at the 0.05 level with at least 80% power. It was further determined that approximately 136 patients total were to be screened to ensure that at least 38 patients per treatment group would enter the four-week treatment-withdrawal phase of the trial.

Analysis Populations

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

Two subsets of the mITT population were considered valid-for-efficacy (VFE).
The VFE-1 population was included in all efficacy analyses and had the following characteristics:

- The patients were at least 80% compliant with test article during the double-blind phase.
- The patients were at least 60% compliant with completing eDiary symptoms in the double-blind phase (completing approximately 4 out of 7 days of eDiary per week).
- The patients did not violate the protocol in a major way (i.e., have protocol violations that could affect trial analyses or results).
- The patients participated for at least 21 days in the open-label phase.

The VFE-2 population, a subset of the VFE-1 population, was included in only those analyses involving withdrawal endpoints and had one additional characteristic:

- Patients who were at least 80% compliant with recording eDiary symptoms in the open-label phase.

Efficacy Parameters

The primary efficacy endpoint was the withdrawal due to lack of efficacy during the double-blind treatment-withdrawal phase. The withdrawal rate for each treatment group was defined as

the ratio of the number of patients who were withdrawn from the trial due to lack of efficacy during the double-blind phase over the total number of patients who entered the double-blind phase. The withdrawal rates between treatment groups were compared using the Fisher exact test. The primary analysis population was the mITT population.

The same statistical methods used to analyze the primary efficacy endpoint were used to analyze the secondary endpoints of rate of lack of efficacy per withdrawal criteria and the rate of withdrawal for any reason. The rate of lack of efficacy per withdrawal criteria was the ratio of the number of patients who met the lack of efficacy withdrawal criteria during the double-blind phase over the number of patients who entered the double-blind phase. The withdrawal rate for any reason was the ratio of the number of patients who withdrew from the trial for any reason during the double-blind phase over the number of patients who entered the double-blind phase.

The other secondary efficacy parameters, such as time to withdrawal, WGSS, individual symptom frequency scores, and the amount of antacids used, were also analyzed. A paired t-test was used for within-group comparison of change from baseline to the end of the open-label phase (Week 4), baseline to the end of the double-blind phase (Week 8), and from the end of the open-label phase to the end of double-blind phase. The changes from baseline to the end of double-blind phase were analyzed by an analysis of covariance (ANCOVA) that included treatment and age group (≤6 months, >6 months) as factors and antacid use and the value of the endpoint at the end of the open-label phase as covariates. For time to event data, Kaplan-Meier estimates and p-values from the log-rank test were reported for treatment comparisons.

The change in amount of antacids used was analyzed in the same way as WGSS was analyzed. The selected respiratory symptoms (cough without a cold; noisy breathing when breathing in or out, wheezy breathing; croupy breathing; and apnea) were summarized by treatment group.

Safety Parameters

All patients who received at least one dose of test article in this trial made up the safety population and were included in summaries for safety evaluation. Summary results were presented by treatment group for all patients in the safety population as well as during open-label versus double-blind treatment phases.

The number of patients with AEs, TEAEs, and abnormal and/or potentially clinically important (PCI) laboratory test results and vital sign measurements were summarized for all patients, and compared by treatment group, as appropriate, using a Fisher exact test. Mean changes from baseline in safety (vital sign measurements and laboratory test results) and growth parameters (weight, height/length, head circumference, and z-scores) were summarized on days measured. Additional summaries and analyses were performed based on z-scores, as appropriate. Changes from baseline (before dose administration) were calculated and presented by treatment group using ANCOVA, as appropriate. The number of patients who were withdrawn prematurely from the trial for any reason was summarized by treatment group for all patients.

I. Results

Disposition of Patients
A total of 154 patients with symptomatic GERD were screened for the trial at 31 investigative sites. Of those, 25 patients were screen failures. Among those who were screen failures, 6 patients did not meet the trial inclusion criteria (5 had a GSQ-I ≤16, and 1 did not meet the age requirement), 3 patients had clinically significant abnormal laboratory test results, and the remaining patients were screen failures because parents or caregivers were unable to comply with trial procedures, parental request, or withdrawal of consent.

A total of 129 patients of both sexes received at least one dose of the test article, and comprised the safety population. This population included one patient (329-026-000760) who was inadvertently assigned to double-blind treatment before entering the open-label phase, which was not allowed per protocol. Owing to this protocol violation, the number of patients in the open-label population was 128. From the total, 21 (16%) patients were withdrawn from the trial during the open-label phase, the most common reason being parental noncompliance with maintaining the e-Diary.

Including patient 329-026-000760, 108 patients were randomly assigned to the pantoprazole 1.2-mg/kg group or the placebo group in the double-blind phase. Two randomly assigned patients (329-026-000760 and 329-064-001901) did not meet the mITT criteria and were withdrawn because of protocol violations, leaving 106 patients in the mITT population. Within the mITT population, 96 patients met the criteria for the VFE-1, and 77 patients met the criteria for VFE-2.

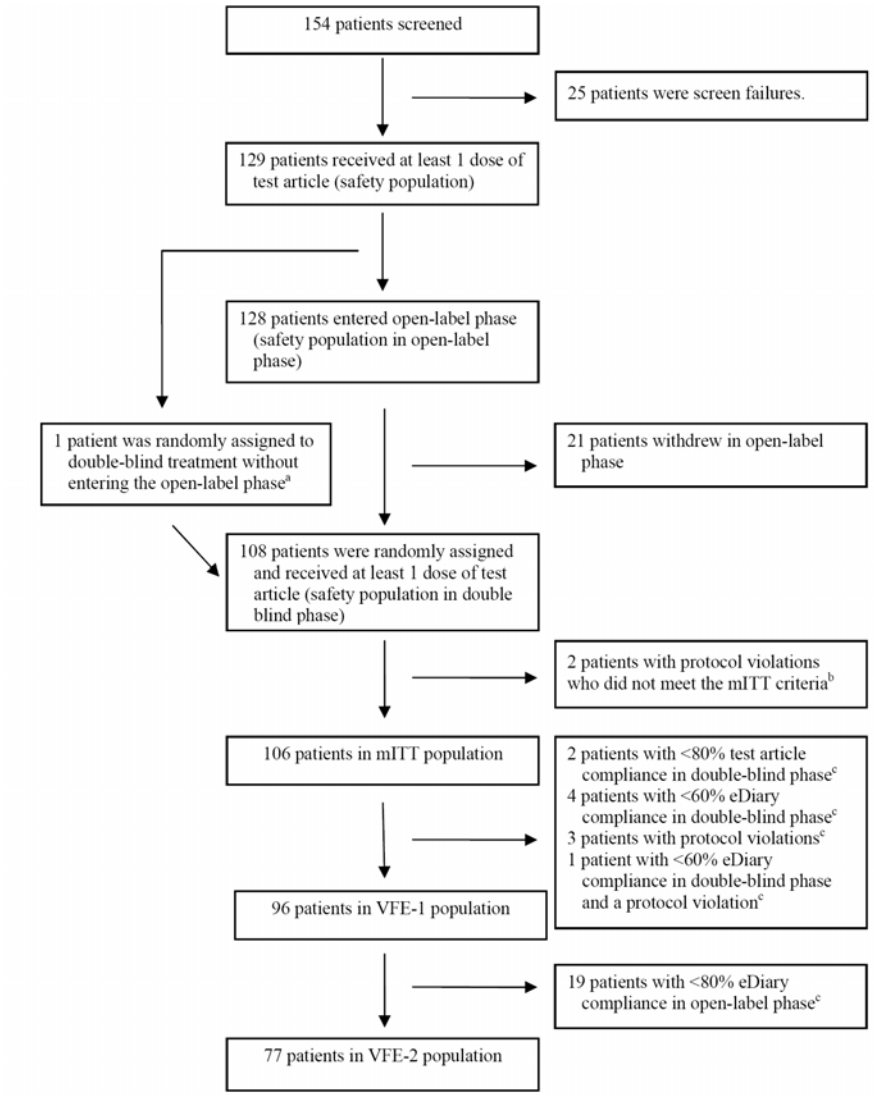


Figure 10: Patient Disposition (Trial 329)

Discontinuations

The most common reasons for discontinuation of patients from the trial during the open-label treatment phase are shown in the table below. Altogether, 21 of 128 (16%) patients were discontinued from the trial during the treatment run-in phase of the trial. The most common primary reason for discontinuation was noncompliance, which occurred with 9 (7%) patients (noncompliance included being <80% compliant with the eDiary or test article administration, or not completing trial visits). Other common reasons for discontinuation from the trial were as follows: 4 (3%) patients discontinued because of AEs and 4 (3%) patients had parental requests.

The most common reasons for discontinuation of patients during the double-blind treatment-withdrawal phase are poor efficacy followed by protocol violation as also shown in Table 28.

Table 28: Reason for Conclusion of Participation (Trial 329)

	Open Label	Double Blind Period	
	Panto 1.2 mg/kg N=128	Panto 1.2 mg/kg N=54	PBO N=54
Trial Completed		**43 (80)**	**45 (83)**
Discontinued	**21 (16)**	**11 (20)**	**9 (17)**
Investigator request	1 (0.8)		
Failed to return	1 (0.8)	1 (2)	0
Noncompliance	9 (7)	1 (2)	1 (2)
Parent request	4 (3)	0	1 (2)
Protocol Violation	1 (0.8)	3 (6)	1 (2)
Poor efficacy	1 (0.8)	6 (11)	6 (11)

Listed below are the patients with protocol violations or significant protocol deviations. Note that four patients in this trial had a total bilirubin test result at screening that exceeded the exclusion criterion ≥2 mg/dL, and were considered to be protocol deviations. The Investigators of all four patients considered the elevation in the total bilirubin result not to be clinically significant, and attributed to the benign condition of breast milk jaundice, which resolved as the patients matured. The medical monitor considered the values to be not clinically significant and approved the continued participation of all four patients.

Table 29: Patients with Protocol Deviations (Trial 329)

Patient Number	Age (months)/ Weight (kg)/ Sex	Dose in OL, DB Phases	Description
Protocol Violations			
329-026-000760	4.7/7.6/M	N/A, 5 mg pantop	Patient was randomly assigned in error to double-blind treatment at visit 2.
329-047-001383	6.0/9.2/M	10 mg pantop, 10 mg pantop	Patient received a daily maximal prescribed study antacid regardless of symptoms instead of receiving antacid as a rescue medication.
329-050-001474	1.8/5.38/M	5 mg pantop, 5 mg pantop	Patient was given prohibited medication (buscopan).
329-054-001591	3.2/4.8/M	5 mg pantop, placebo	Patient was assigned to double-blind treatment per incorrect weight/dose stratum at randomization.
329-060-001776	1.6/5.65/F	5 mg pantop, placebo	Patient was assigned to double-blind treatment per incorrect weight/dose stratum at randomization.
329-064-001892	3.9/6.7/M	5 mg pantop, N/A	Test article was administered incorrectly, ie, postprandially instead of before morning meal.
329-064-001901	8.1/7.4/F	10 mg pantop, 10 mg pantop	Patient received diagnosis of eosinophilic esophagitis; exclusion criterion #1.
Significant Protocol Deviations			
329-043-001261	1.4/4.3/M	5 mg pantop, placebo	Patient's total bilirubin was ≥2mg/dL; exclusion criterion #7 (breast milk jaundice).
329-043-001262	1.4/4.6/M	5 mg pantop, 5 mg pantop	Patient's total bilirubin was ≥2mg/dL; exclusion criterion #7 (breast milk jaundice).
329-045-001321	1.7/5.0/M	5 mg pantop, 5 mg pantop	Patient's total bilirubin was ≥2mg/dL; exclusion criterion #7 (breast milk jaundice).
329-049-001446	1.6/4.66/M	5 mg pantop, 5 mg pantop	Patient's total bilirubin was ≥2mg/dL; exclusion criterion #7 (breast milk jaundice).

Compliance

During the open-label phase, test article compliance was defined as the number of days taking the test article, divided by 25 or the number of days of duration in the open-label phase (whichever was greater), times 100. The mean compliance in the open-label phase was 95%. The mean compliance in the double-blind phase was 98% (equivalent across the two treatment groups).

Demographics

Baseline demographics of patients enrolled in the trial are described in the following table for the entire safety population. In general, most infants were full term and Caucasian. There was a slight imbalance in the male to female ratio in the higher weight infants compared to the lower weight infants.

Table 30: Safety Population Demographics (Trial 329)

Characteristics		Pantoprazole 1.2 mg treatment		
		Low weight N=70	High Weight N=59	Total N=129
Type of Birth	Full term	56 (80%)	49 (83%)	105 (81%)
	Preterm	14 (20)	10 (17)	24 (19)
Postnatal Age (months)	Mean	3.6	7.2	5.2
	Standard Dev.	1.8	2.6	2.9
Sex	Female	32 (46)	16 (27)	48 (37)
	Male	38 (54)	43 (73)	81 (63)
Race	Caucasian	44 (63)	40 (68)	84 (65)
	African American	16 (23)	10 (17)	26 (20)
	Asian	7 (10)	5 (8)	12 (9)
	Other	3 (4)	4 (5)	13 (10)
Baseline Wt (kg)	Mean	5.7	8.6	7
	Standard Dev.	0.7	1.3	1.7
Week 4 Wt	Mean	6.3	9.0	7.5
	Standard Dev.	0.7	1.2	1.7
Baseline Ht (cm)	Mean	60	68.9	64
	Standard Dev.	4.0	4.4	6.1
Open-label Duration (days)	Mean	28	29	28
	Standard Dev.	4.6	3.9	4.3
Double-Blind Duration	Mean	25	26	25
	Standard Dev.	7.5	5.2	6.6
Therapy Duration	Mean	49	50	49
	Standard Dev.	14	13	14

Note that in the double-blind portion, there were no significant differences in terms of demographic data between the patients randomized to pantoprazole versus placebo.

Table 31: Double-blind phase Demographics (Trial 329)

Characteristics		Double-Blind Phase		
		Pantoprazole N=52	Placebo N=54	Total N=106
Type of Birth	Full term	43 (83%)	44 (81%)	87 (82%)
	Preterm	9 (17)	10 (19)	19 (18)
Postnatal Age (months)	Mean	5.2	5.0	5.1
	Standard Dev.	2.8	2.8	2.8
Sex	Female	18 (35)	20 (37)	38 (36)
	Male	34 (65)	34 (63)	68 (64)
Race	Caucasian	35 (67)	35 (65)	70 (66)
	African American	10 (19)	10 (19)	20 (19)
	Asian	6 (11)	5 (9)	11 (10)
	Other	1 (2)	3 (6)	4 (4)
Baseline Wt (kg)	Mean	7.1	6.9	7.0
	Standard Dev.	1.9	1.7	1.8
Week 4 Wt	Mean	7.6	7.4	7.5
	Standard Dev.	1.8	1.6	1.7
Double-blind Duration	Mean	26	26	26
	Standard Dev.	5.8	6.9	6.3

GERD Indications at Screening

All patients entering the trial had to have a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Although the trial procedures did not include any diagnostic investigations, a number of patients had diagnostic tests for GERD as part of their routine medical care before enrolling in the trial. The patients who had a history of non-trial tests for GERD at screening are summarized in Table 32. A total of 43 (33%) patients entering the open-label phase had a history of non-trial diagnostic tests for GERD. Therefore, 100 (78%) of 129 patients who entered the trial did not have objective test results for GERD but had symptomatic GERD.

Table 32: % Pts with History of Nonstudy GERD Diagnostic Tests (Trial 329)

GERD Diagnosis Test	Total Patients (n=129)
Any Test	43 (33.3)[a]
Upper GI series	32 (24.8)
Esophagram	3 (2.3)
Video swallowing study	3 (2.3)
Direct laryngoscopy	1 (0.8)
Esophageal impedance monitoring	1 (0.8)
Esophageal pH-metry	16 (12.4)
Endoscopy	4 (3.1)
Biopsy	3 (2.3)

Concomitant Therapy/Medications

Review of non-trial medications taken by patients at any time during the trial show that over 90% of the patients received some type of non-trial medication. The most commonly used products were vaccines, with viral vaccines given to 46 (36%) patients, bacterial vaccines given to 42 (33%) patients, and combined bacterial and viral vaccines given to 29 (23%) patients. Analgesics and antipyretics (other) were also widely used and were given to 63 (49%) of the patients. Antibiotic use was often reported; beta-lactams and penicillins were given to 29 (23%) patients, and other beta-lactams were given to 19 (15%) patients.

During the open label phase, 93 (73%) took non-trial medications, and none of the patients received drugs for treatment of GERD. During the double-blind phase, 70 (65%) patients took non-trial medications. One patient took a prohibited medication, buscopan, to treat an adverse event of abdominal cramps. There were no outstanding differences between the treatment groups in the use of non-trial medications in the double-blind phase.

Efficacy Evaluation

The number and percentage of patients in each efficacy analysis population are summarized by treatment group in Table 33. The mITT population was the primary efficacy analysis population. This population consisted of all patients who had a clinical diagnosis of GERD, completed the four-week open-label treatment phase with a minimum 21 days taking test article, entered the double-blind phase, and received at least one dose of double-blind treatment.

Table 33: Summary of Analysis Population by Treatment Group (Trial 329)

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

Primary Efficacy Results in Double-Blind Phase

The primary efficacy parameter of the trial was the difference in withdrawal rates for lack of efficacy between the two treatment groups during the double-blind phase. The results show that there was no difference between treatment groups in withdrawal rates due to lack of efficacy. In all, 12 patients were withdrawn from the trial for lack of efficacy: 6 patients in the pantoprazole 1.2-mg/kg group and 6 patients in the placebo group. A comparison of withdrawal rates for lack of efficacy during the double-blind phase are shown in Table 34 (copied from the Applicant's submission) for the mITT population.

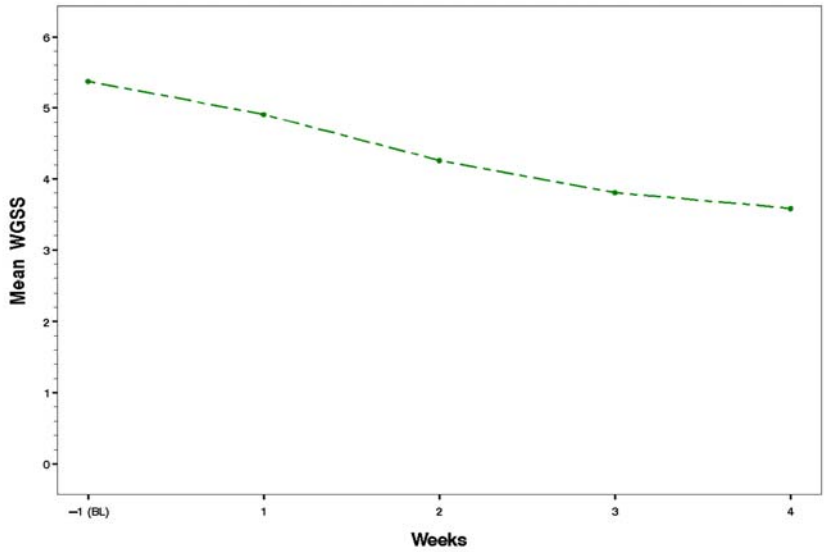
Table 34: Withdrawal Rate Due to Lack of Efficacy During DB Phase (Trial 329)

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

WGSS During Open-Label Phase

The WGSS was the sum of the weekly mean frequency scores for five symptoms of GERD: vomiting/ regurgitation, irritability/fussiness, choking/gagging, arching back, and refusal to feed. The daily eDiary was used to document each of the symptoms over the previous 24-hour period. The mean WGSS in the open-label population is shown by week in the following figure (copied from the Applicant's submission). The mean WGSS at baseline was 5.4 and decreased to 3.6 at week 4 ($p<0.001$): 3.55 and 3.44 in the pantoprazole 1.2-mg/kg group and the placebo group. The mean change from baseline was -1.9 with a standard deviation of 2.0 ($p=0.001$).

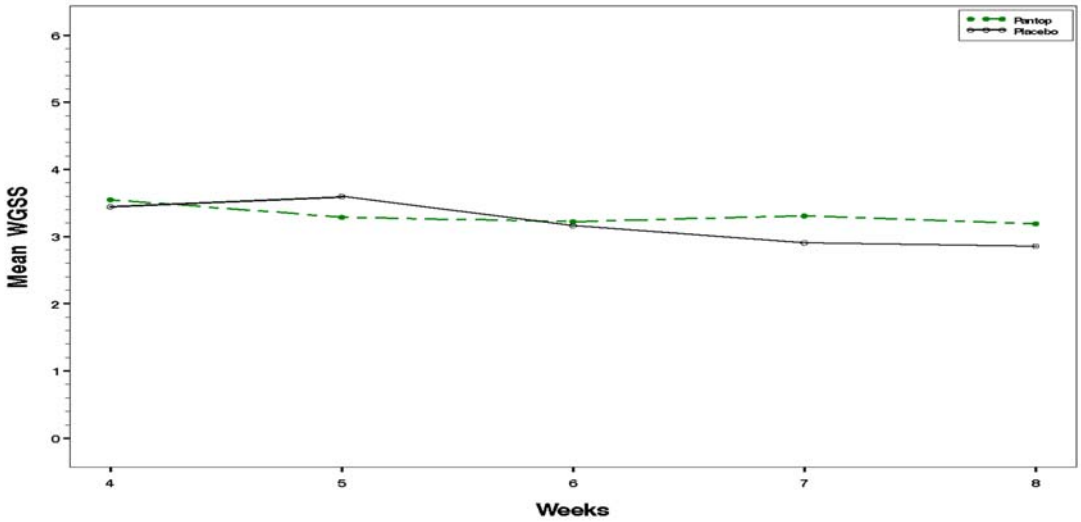
Figure 11: Mean WGSS During Open-Label Run-In Phase (Trial 329)



WGSS During the Double-Blind Phase

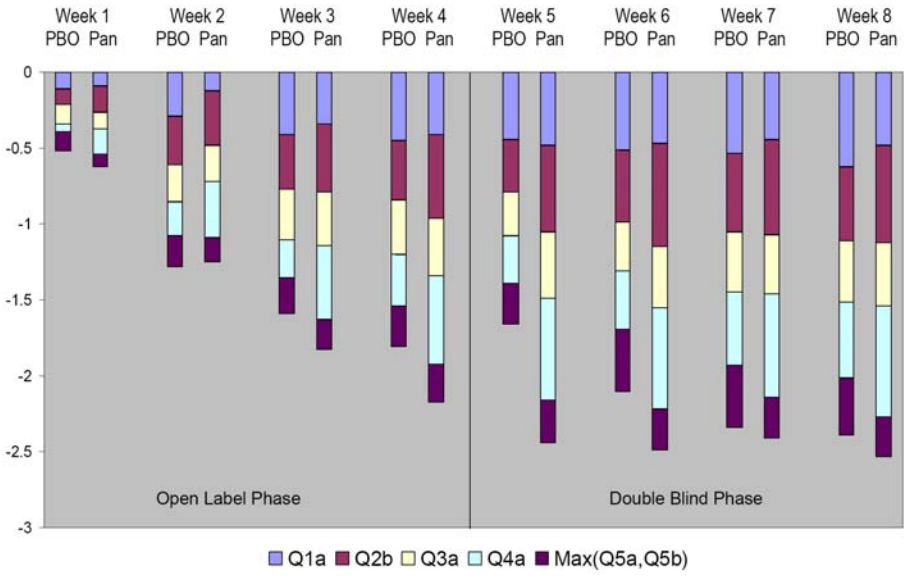
Looking at the change in mean WGSS from during the double-blind phase (Week 4 through Week 8) by treatment group, it is clear that there was no difference between treatment and placebo. The mean WGSS at week 4 is 3.4 (placebo) and 3.6 (pantoprazole). The mean WGSS at week 8 is 2.9 (placebo) and 3.2 (pantoprazole), the correlating mean change from Week 4 is -0.6 (placebo) and -0.4 (pantoprazole). See Figure 12 for a graphic description.

Figure 12: Mean WGSS During DB Phase by Treatment (Trial 329)



There were overall no meaningful differences observed between the two treatment groups. A bar chart from the Applicant showing the contribution of the five selected GERD symptom components to the mean WGSS is shown in Figure 13.

Figure 13: Changes from Baseline in WGSS by Individual Component (Trial 329)



Secondary Efficacy Results

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

1. Time to Actual Withdrawal Due to Lack of Efficacy/ Time to Lack of Efficacy per Withdrawal Criteria/Time to Withdrawal for Any Reason
   There was no difference between treatment groups in the above three parameters when Kaplan-Meier estimates and log-rank tests were used to compare the two treatment groups.

2. Amount of Antacid Taken Each Week
   The amount of antacid taken weekly decreased from a mean of 12mL at baseline to 7mL at Week 4 (7mL for patients randomized subsequently to placebo and 8mL for those enrolled into continued pantoprazole). At the end of the trial, the use of antacid decreased to 4 mL for those on placebo and 5mL for pantoprazole. The clinical meaningfulness of this small decrease in antacid use is questionable.

3. Number of Patients Taking Antacids
   At baseline 63% of patients used trial antacid at least once a week. At week 4, the number was reduced to 48% of patients. At the end of the trial 33% of patients on placebo compared to 39% of patients on pantoprazole were taking antacid weekly. There was no statistically significant difference between the treatment groups.

4. Presence of Respiratory Symptoms Associated with GERD
   The eDiary was used to document respiratory symptoms for the previous 24-hours. If the patient had a cold or fever, respiratory symptoms were not documented for that time period. Cold or fever occurred approximately 25% of the time in both treatment groups during the trial.

   Cough without a cold, noisy breathing without a cold, noisy breathing when breathing out, breathing with a wheezy or whistling sound, noisy breathing when breathing in, breathing with a croupy or barky sound, and apnea were the questions assessed. Many of these symptoms were infrequent at baseline, so improvement is difficult to assess without a more sensitive assessment tool. Overall, there appeared to be improvements in respiratory symptoms in both treatment groups, but no differences between the treatment groups.

J. Efficacy Conclusions

No statistically significant differences between treatment groups were observed for withdrawals due to lack of efficacy, meeting the criteria for lack of efficacy, or withdrawals for any reason in the mITT, VFE-1, and VFE-2 populations.

During the open-label phase, treatment with pantoprazole was associated with progressive improvements in WGSS over time. However, no relapse of symptoms was seen in the placebo group at the completion of the double-blind phase. As between-group comparisons during the double-blind phase showed no statistically significant differences, it questions the significance of the improvement in the WGSS symptoms seen during the open-label treatment phase.

The frequency of the five individual GERD symptoms decreased significantly from baseline to Week 4 during open-label treatment with pantoprazole, the caveat is that during this phase there was no comparator group. There was a significant decrease in vomiting/regurgitation, choking/gagging, and arching back in the pantoprazole 1.2 mg/kg compared with the placebo group at Week 5 but not at other weeks. Respiratory symptoms were not balanced between groups at baseline for noisy breathing and cough without a cold, there were more patients having these symptoms in the pantoprazole group compared to placebo, thus interpretation of data is challenging. General improvement in respiratory symptoms was seen, with greatest improvement during the first four weeks of treatment. There were no statistically significant differences between treatment groups in the final analysis. One difficulty observed was that parents did not differentiate well between different types of noisy breathing. Apnea was very uncommon and unchanged with treatment.

The Applicant states that the results of this trial suggest that extensive conservative treatment along with rescue antacids plus possibly a four to five week course of PPIs may be sufficient for the majority of infants with symptomatic GERD. Furthermore, the Applicant states that patients with more severe symptoms or failure of conservative treatment might benefit from objective testing to assess their disease and to exclude other disorders such as cow's milk allergy, eosinophilic esophagitis, and infantile colic, which are often confused with GERD. Infants with clinically significant GERD should be considered for longer term pharmacologic therapy.

However, any conclusion of understanding if antacid therapy ameliorates GERD in infants has been tenuous at best. At this time, there has been no convincing evidence that supports use of PPI in this age group.

Safety Evaluation

As this trial is the only placebo-controlled trial among the eight PWR, the all safety parameters were evaluated carefully between treatment groups for comparison.

Exposure

Days of trial-medication exposure are summarized in Table 35: Summary of Drug Exposure for all patients in the safety population. Most patients received at least one month worth of pantoprazole treatment, after week 4, half the patients were randomized to placebo, thus there is a drop in trial-medication exposure after day 25.

Table 35: Summary of Drug Exposure (Trial 329)

Cumulative Days Exposed[a]	Pantoprazole (1.2 mg/kg) n=129
≥1 day (%)	129 (100)
≥7 days (%)	128 (99.2)
≥14 days (%)	126 (97.7)
≥25 days (%)	114 (88.4)
≥35 days (%)	52 (40.3)
≥50 days (%)	46 (35.7)

Errors/Protocol Violations

Test article errors occurred in seven patients, including the patient who received double-blind treatment without entering the open-label phase. The other errors involved either receiving excess pantoprazole (n=4, two packets of medication instead of one) or receiving the incorrect test article for the patient's weight stratum (n=2). Two of the overdoses were with placebo. None of the overdoses were associated with any AE.

Serious Adverse Events

There were no deaths during this trial. A total of eight patients had a total of 11 SAEs at some time during the trial, including screening and follow-up. The SAEs involved the following body systems: respiratory (4), digestive (3), metabolic and nutritional (2), cardiovascular (1), and special senses (1). None of the SAEs were considered to be related to the test article.

Table 36: Listing of Pts with SAEs (Trial 329)

Patient Number	Body System	Adverse Event (Verbatim)	Treatment-related	Phase in Which Event Occurred
329-016-000455	Metabolic and Nutritional	Failure to thrive	No	Open-label
	Metabolic and Nutritional	Poor weight gain	No	Follow-up
329-017-000481	Respiratory System	Status asthmaticus	No	Double-blind
329-045-001332	Cardiovascular System	Syncope	No	Follow-up
329-050-001472	Respiratory System	Croup	No	Screening
	Digestive System	Worsening of GERD	No	Open-label
329-050-001474	Respiratory System	Bronchiolitis	No	Follow-up
	Special Senses	Otitis media	No	Follow-up
329-051-001503	Respiratory System	Bronchiolitis	No	Open-label
329-054-001592	Digestive System	Worsening of GERD	No	Screening
329-064-001908	Digestive System	Gastroenteritis viral	No	Open-label

Reviewer comment: Review of the individual narratives indicates that almost all of the SAEs were unlikely to be related to the trial drug. Patient 329-016-000455 had Failure to Thrive, which takes time to develop, and the feeding intolerance leading to this is unlikely secondary to the trial drug. Patient 329-017-000481 was an asthmatic patient on PBO at the time of the SAE.

Patient 329-045-001332 had been off trial drug almost two weeks when the syncopal event occurred. The two cases of GERD worsening occurred shortly after the open-label phase, when both patients were randomly assigned to placebo. The two cases of bronchiolitis also appear to be unrelated to trial drug as in Patient 329-050-001474, the patient had been off trial drug for five days due to a protocol violation when the SAE occurred. The second patient made full recovery from the infection while on trial drug.

However, for patient 329-064-001908 it is less clear that the trial drug did not potentially contributed to the SAE. Two days after starting treatment with open-label pantoprazole, the patient was admitted to the hospital with vomiting, diarrhea, and dehydration and was diagnosed with viral gastroenteritis. Treatment with pantoprazole was interrupted. The patient was discharged in stable condition two days later. The investigator considered the SAE of gastroenteritis to be resolved and not related to treatment with open-label pantoprazole. However, another episode of diarrhea began a day later. The following day, after four days of test article interruption, open-label pantoprazole was restarted. The AE resolved 12 days later, but the patient developed another episode of diarrhea four days later. Seven days after the onset of this AE, the patient was discontinued from open-label pantoprazole and withdrawn from the trial because of the AE of diarrhea. Given the pattern of diarrhea, to appears that there is a likely relationship between drug treatment and this adverse event for this patient.

Adverse Events

In total, 109 (85%) of 129 patients in the safety population had one or more AEs reported during the trial. Whereas, a total of 84 (66%) of 128 patients had one or more treatment emergent AE (TEAEs) during the open-label phase (these adverse events occurred after screening and medication had been dispensed). The most common TEAEs were upper respiratory infection (25; 20%), fever (13; 10%), and diarrhea (13; 10%). Other TEAEs were reported in at least 5% of patients were: otitis media (12; 9%), rhinitis (11; 9%), oral moniliasis (7; 6%), vomiting (7; 6%), and cough increased (7; 6%).

Altogether, 49 of 108 (45%) randomized patients had one or more TEAEs during the double-blind phase, including 25 (46%) of 54 patients from the pantoprazole 1.2-mg/kg group and 24 (44%) of 54 patients from the placebo group. There were no notable differences between the two treatment groups. The most common TEAE was upper respiratory infection, which was reported in 7 (13%) patients in each of the treatment groups. The TEAEs that were reported in at least 5% of patients in the pantoprazole 1.2-mg/kg group and $\geq$ 2% as compared to placebo were: fever, otitis media, vomiting, and creatine phosphokinase increased. Overall, the differences between the two treatment groups do not appear to be clinically meaningful as the number of patients affected were small (e.g. fever reported: 3 (6%) Panto vs. 1 (2%) PBO).

Table 37: Table of TEAEs (Trial 329)

Body System		Open-Label Phase Panto 1.2 mg/kg	Double- Blind Phase	
			Panto 1.2 mg/kg	Placebo
Any AE		84 (66)	25 (46)	24 (44)
Body as Whole	Total	19 (15)	5 (9)	6 (11)
	Abd pain	1 (1)		
	Injury	1 (1)	1 (2)	2 (4)
	Fever	13 (10)	3 (6)	1 (2)
	Flu syndrome	1 (1)	1 (2)	
	Hernia	1 (1)		
	Infection	4 (3)		1 (2)
	Injection rxn	1 (1)		
	Abn lab test	1 (1)		1 (2)
Digestive System	Total	36 (28)	7 (13)	7 (13)
	Anorexia	3 (2)	1 (2)	1 (2)
	Constipation	5 (4)	1 (2)	2 (4)
	Diarrhea	13 (10)	2 (4)	1 (2)
	Flatulence	1 (1)		
	Gastroenteritis	2 (2)		
	GERD	4 (3)		
	Oral candida	7 (6)	1 (2)	
	Tooth d/o	5 (4)		2 (4)
	Vomiting	7 (6)	3 (6)	2 (4)
Metabolic & Nutritional	Total	4 (3)	3 (6)	
	Alk Phos inc	1 (1)		
	CPK inc	1 (1)	3 (6)	
	Dehydration	1 (1)	1 (2)	
	Hyperlipidemia		1 (2)	
	FTT	1 (1)		
	SGOT inc	1 (1)		
	SGPT inc	1 (1)		
Musculo-Skeletal	Muscle Cramp	1 (1)	1 (2)	
Nervous System	Total	6 (5)	3 (6)	1 (2)
	Agitation	1 (1)		
	Anxiety	1 (1)		1 (2)
	Lability	2 (2)	1 (2)	
	Nervousness	1 (1)	1 (2)	
	Sleep d/o	1 (1)	1 (2)	
Respiratory System	Total	46 (36)	13 (24)	11 (20)
	Asthma	1 (1)		1 (2)
	Bronchiolitis	3 (2)	1 (2)	1 (2)
	Cough inc	7 (6)	2 (4)	4 (7)
	Dyspnea	1 (1)		
	Nasal Septum d/o	1 (1)		
	Laryngitis		2 (4)	
	Pharyngitis	2 (2)	1 (2)	
	Rhinitis	11 (9)	1 (2)	

Body System		Open-Label Phase Panto 1.2 mg/kg	Double- Blind Phase	
			Panto 1.2 mg/kg	Placebo
	Sinus Congestion	1 (1)		
	Sinusitis	3 (2)		
	Tachypnea		1 (2)	1 (2)
	URI	25 (20)	7 (13)	7 (13)
	Wheezing	1 (1)		1 (2)
Skin	Total	26 (20)	6 (11)	8 (15)
	Contact Dermatits	5 (4)	2 (4)	
	Cut. Moniliasis	5 (4)	1 (2)	1 (2)
	Eczema	5 (4)		1 (2)
	Erythema	2 (2)		1 (2)
	Fungal Dermatitis	5 (4)		
	Furunculosis			1 (2)
	Impetigo			1 (2)
	Miliaria	1 (1)		1 (2)
	Rash	5 (4)	2 (4)	2 (4)
	Seborrhea	1 (1)	1 (2)	
	Skin d/o	1 (1)		
Special Senses	Total	14 (11)	3 (6)	1 (2)
	Conjunctivitis	2 (2)		1 (2)
	Otitis Media	12 (9)	3 (6)	
Urogenital	Total	1 (1)		2 (4)
	Testis d/o	1 (1)		
	UTI			2 (4)

Discontinuations due to Adverse Events

A total of five patients withdrew from the trial because of AEs, four during the open-label phase and one during the double-blind phase. During the open-label phase, two safety-related discontinuations were considered to be related to the test article by the Investigator (diarrhea, emotional lability) and two were not (both worsening of GERD). During the double-blind phase, the one discontinuation was considered to be related to the test article, pantoprazole (sleep problems). The AEs resulting in withdrawal from the trial are summarized in Table 38: Pts Reporting AE Causing Withdrawal (Trial 329 (copied from the Applicant's submission).

Table 38: Pts Reporting AE Causing Withdrawal (Trial 329)

Patient Number	Body System	Adverse Event (verbatim)	Treatment-related	Phase in Which Event Occurred
329-017-000483	Nervous system	Sleep problems	Yes	Double-blind
329-058-001711	Nervous system	Emotional lability	Yes	Open-label
329-064-001896	Digestive system	Worsening of GERD	No	Open-label
329-064-001897	Digestive system	Worsening of GERD	No	Open-label
329-064-001908	Digestive system	Diarrhea	Yes	Open-label

As all of these discontinuations occurred on treatment and more than half are GI related adverse events. It is likely that there is some correlation between drug treatment and the adverse events,

however, during the open-label phase there is no placebo group for comparison, and in the double-blind phase there was only one withdrawal due to AE, which is too few to make any conclusion.

Other Clinically Important Adverse Events

Note that for the following lab values (Alk Phos, CPK, Gastrin, Triglyceride, PTT, Uric acid, and Potassium) a detailed analysis of potentially clinically important (PCI) lab values across all PWR trials is described in section 7.4.2.

There were nine patients with one or more laboratory test results that investigators reported as AEs; in six cases, the AEs were not test results that met predetermined PCI criteria. The patients with laboratory test results reported as AE were those with increased levels of Alk Phos (2 panto), AST and ALT (1 panto, 1 PBO), CPK (4 panto, 1 PBO), and triglycerides (1 panto, 1 PBO). Two parameters, CPK and gastrin levels, are notable as there were statistically significant changes that moved the means outside of the normal range. The investigator state that these were not clinically meaningful changes.

There were 30 (23%) of 129 patients who had PCI laboratory test results at screening, 22 (21%) of 104 patients who had PCI values during the open-label phase, and 12 patients who had PCI values during the double-blind phase: 6 (15%) of 40 patients in the pantoprazole 1.2-mg/kg group and 6 (14%) of 42 patients in the placebo group. No PCI laboratory test results were reported post-treatment. A total of 49 (38.0%) of 129 patients had PCI laboratory test results at some point during the trial. These results are summarized as follows:

Alkaline Phosphatase (AP): Two patients (329-038-001112 and 329-043-001269) had PCI elevations of AP during the trial. In both cases, the PCI AP levels occurred at the end of the double-blind phase in patients who had received continued treatment with pantoprazole 1.2 mg/kg.

Pt	Screen AP (mU/mL)	Wk 4	Wk 5	F/U
001112	229	972	3371	1493
001269	425	426		1458

Comment: This requires further evaluation for similar trends across the other trials in older patients on pantoprazole treatment. There were no associated adverse events reported with these elevations, however.

Alanine Aminotransferase (ALT): A PCI high ALT level was observed in one patient (329-049-001442). This patient had a non-PCI high ALT level at screening, which was unchanged at the end of four weeks of treatment with open label pantoprazole. The PCI high level of ALT occurred at the end of the double-blind phase, during which the patient received pantoprazole. The patient's AST level was also mildly elevated at the post-double-blind phase assessment.

Comment: As there was only one patient affected with this elevation, it is difficult to make any firm conclusion on the causality. Review of the other trials will be helpful to look for similar trends. For this patient the screen ALT- 92mU/mL, wk 4-92, wk 8-193, and post-trial-24. Given the resolution of the ALT, short term treatment with pantoprazole does not appear to cause sustained elevations in ALT.

Bilirubin: PCI elevations of total bilirubin were found in four patients (329-043-001261, 329-043-001262, 329-045-001321, and 329-049-001446). In each case, the elevated bilirubin was thought to be due to preexisting breast milk jaundice and was observed only at screening. Bilirubin levels returned to normal at all subsequent assessments. An elevated bilirubin >2mg/dL was an exclusion criterion to trial entry; however, each of these patients had a waiver from the trial's medical monitor to enter the trial.

Comment: The bilirubin levels, given their resolution during the trial, do not appear to be concerning and are likely unrelated to pantoprazole treatment. Highest bili was 18.8 mg/dL at wk 4.

Creatine Phosphokinase (CPK): PCI elevations of CPK levels at one or more laboratory evaluations occurred in five patients (329-016-000453, 329-032-000931, 329-041-001202, 329-049-001441, and 329-060-001775). All these patients had high CPK levels at screening, three of which were at PCI levels. In the three patients with PCI CPK levels at screening, the CPK levels remained elevated or declined to non–PCI levels after starting treatment with pantoprazole. In the two patients who had non-PCI CPK levels at screening, the PCI elevations occurred after the double-blind treatment-withdrawal phase; both patients had received placebo. Five additional patients had normal CPK levels at baseline and non-PCI elevations of CPK reported as AEs. The mean CPK level in the safety population increased from approximately 165 mU/mL at baseline to 200 mU/mL at week 4, the end of the open-label phase, and to 209 mU/mL at the end of the double-blind phase. The between-group analyses, however, show that in the double-blind phase there were no significant differences between the treatment groups, with the mean CPK level decreasing slightly in the patients continuing on pantoprazole and increasing moderately (from a lower base) in those treated with placebo.

Comment: These data appear to indicate that elevations in CPK levels are relatively common in this patient population. The highest CPK reported was for patient 000453 at screen with a value of 690 mU/mL which decreased to 587 at wk 8. Short term treatment with pantoprazole does not appear to be a major risk for elevation of CPK given the current data.

Gastrin: Two patients (329-038-001122 and 329-054-001591) had PCI elevated gastrin levels. In one patient, the gastrin level was PCI high at screening but dropped to a non-PCI high level at follow-up. In the other patient, the gastrin levels were non-PCI high at screening and at the end of the open-label phase but rose to a PCI high level at the end of the treatment withdrawal phase, during which time the patient received placebo.

Comment: This pattern of gastrin elevation for the above two patients does not appear consistent with drug effect.

Overall, the mean serum gastrin level was higher at the end of both the open-label and the double-blind phases compared with baseline. All of the increase from baseline was accumulated during the open-label phase. In the double-blind phase, the gain in gastrin level was maintained (but not increased) in the pantoprazole 1.2-mg/kg group, but in the placebo group the gain was virtually lost by Week 8. This is an expected result given the mechanism of PPI.

Triglycerides: PCI elevated fasting triglycerides were observed in four patients (329-043-001263, 329-051-1501, 329-058-001712, and 329-064-1908) at some point during the trial. Two of these patients participated in the open-label phase; one had a PCI high fasting triglyceride at screening and a normal, nonfasting triglyceride level at final evaluation after 31 days treatment with open-label pantoprazole; the other patient had a non-PCI high fasting triglyceride level at screening and a PCI high fasting triglyceride level at the end of 29 days of treatment with open-label pantoprazole. The other two patients both completed the double-blind phase of the trial during which they both received treatment with placebo. Both of these patients had non-PCI high triglyceride levels at screening (one fasting and one not); both had PCI high fasting levels at the end of the double-blind phase. Only one of these patients had a triglyceride level measured at the end of the open-label phase; it also was PCI high but not as high as the level at the final assessment (the triglyceride elevation in patient 329-058-001712 was reported as an AE, as discussed in section 10.3.4).

Comment: There are not sufficient data to indicate that treatment with pantoprazole causes a clinically significant increase in triglyceride levels. Highest reported triglyceride level was 6.5 mmol/L at wk 8 (no f/u information available).

Aspartate aminotransferase (AST): There was a significant (p=0.019) between-group difference in the changes in AST from baseline to Week 8, when an increase in AST was observed in the pantoprazole 1.2-mg/kg group but not in the placebo group.

Comment: Most of the increase had already accrued at week 4 before the patients were randomly assigned to treatment groups, and thus it is difficult to know if this elevation was caused by treatment with pantoprazole. A similar pattern is seen with ALT, although the differences between the groups did not achieve statistical significance. There were no adverse events that were associated with these elevations and do not appear to be clinically meaningful.

Vital Signs

There were 4 (3%) of 128 patients at screening who had PCI vital sign measurements. Nine (7%) of 127 patients had PCI values during the open-label phase. During the double-blind phase, none of the patients in the pantoprazole 1.2 mg/kg group and 3 of 50 (6%) patients in the placebo group had PCI vital sign measurements. Post-treatment, 1 of 32 (3%) patients had a PCI vital sign measurement. A total of 15 of 129 (12%) patients had PCI vital sign measurements at some point during the trial. The most common PCI vital sign measurements were high respiratory rates, which occurred in a total of 9 (7%) of 127 patients. The high rates were spread across the trial visits. Three events were concurrent with respiratory AEs, including asthma, an

upper respiratory tract infection, and bronchiolitis. Three patients had PCI high respiratory rates during the treatment-withdrawal phase; all these patients were receiving placebo.

The second most common PCI vital sign measurements were increases in systolic blood pressure (BP) readings, which occurred in three patients during the open-label treatment phase (1 patient at week 2 and 2 patients at week 4). Each patient had a single PCI high reading. None were associated with PCI increases in diastolic BP. There is no information if the increased respiratory rates and increased BP were associated with crying.

Table 39: % of Pts with VS Measurements of PCI (Trial 329)

Category	---------- Double-blind Treatment ----------		
Test+Units	Pantoprazole		
Data Analysis Interval	1.2 mg/kg	Placebo	Total
Total Vital Signs	4/ 54 (7.4)	9/ 54 (16.7)	13/108 (12.0)
Systolic Blood Pressure mm Hg	1/ 53 (1.9)	2/ 53 (3.8)	3/106 (2.8)
All	1/ 53 (1.9)	2/ 53 (3.8)	3/106 (2.8)
Week 2	1/ 51 (2.0)	0/ 51	1/102 (1.0)
Week 4	0/ 49	2/ 52 (3.8)	2/101 (2.0)
Diastolic Blood Pressure mm Hg	2/ 53 (3.8)	0/ 53	2/106 (1.9)
All	2/ 53 (3.8)	0/ 53	2/106 (1.9)
Screening	1/ 53 (1.9)	0/ 52	1/105 (1.0)
Week 4	1/ 49 (2.0)	0/ 52	1/101 (1.0)
Respiratory Rate Breaths/Min	1/ 53 (1.9)	7/ 53 (13.2)	8/106 (7.5)
All	1/ 53 (1.9)	7/ 53 (13.2)	8/106 (7.5)
Screening	0/ 53	1/ 52 (1.9)	1/105 (1.0)
Week 2	0/ 52	2/ 52 (3.8)	2/104 (1.9)
Week 4	1/ 51 (2.0)	2/ 51 (3.9)	3/102 (2.9)
Week 6	0/ 48	1/ 45 (2.2)	1/ 93 (1.1)
Week 8	0/ 36	1/ 39 (2.6)	1/ 75 (1.3)
DB Final Assessment	0/ 52	3/ 53 (5.7)	3/105 (2.9)

Comment: All of the PCI vital sign measurements appeared to be isolated events; none were associated with PCI measurements in other vital sign parameters and none were sustained through consecutive visits. Vital signs do appear to be negatively impacted with short term treatment of pantoprazole.

ECG

Two ECG recordings were to be conducted as part of the trial procedures, with the initial recording to occur during screening between Weeks -2 and 0 and the second to occur at Week 8, the end of the double-blind phase. A total of 20 (16%) of 128 patients had PCI ECG findings during screening. A total of 24 (22%) of 108 randomized patients had a PCI ECG measurement at some point during the trial, including 11 (20%) patients in the pantoprazole 1.2 mg/kg group and 13 (24%) patients in the placebo group. During the double-blind phase, 3 (8%) of 38 patients in the pantoprazole 1.2 mg/kg group and 6 (15%) of 41 patients in the placebo group had PCI ECG findings. In addition, 5 patients had ECG recordings during the open-label phase, 2 (40%) of whom had PCI findings, and 31 patients had ECG recordings post-treatment, 4 (12%) of whom had PCI findings. Altogether, 29 (23%) of 129 patients had a PCI ECG measurement at some point during the trial.

Table 40: % of Pts with ECG Results of PCI (Trial 329)

Category	---------- Double-blind Treatment ----------		
Test+Units	Pantoprazole		
Data Analysis Interval	1.2 mg/kg	Placebo	Total
Total ECGs	11/ 54 (20.4)	13/ 54 (24.1)	24/108 (22.2)
Heart Rate (beats/minute)	1/ 54 (1.9)	1/ 54 (1.9)	2/108 (1.9)
All	1/ 54 (1.9)	1/ 54 (1.9)	2/108 (1.9)
Screening	0/ 54	1/ 53 (1.9)	1/107 (0.9)
Week 8	1/ 36 (2.8)	0/ 37	1/ 73 (1.4)
DB Final Assessment	1/ 52 (1.9)	0/ 52	1/104 (1.0)
PR Interval (msec)	2/ 54 (3.7)	1/ 54 (1.9)	3/108 (2.8)
All	2/ 54 (3.7)	1/ 54 (1.9)	3/108 (2.8)
Screening	2/ 54 (3.7)	1/ 53 (1.9)	3/107 (2.8)
QRS Interval (msec)	3/ 54 (5.6)	5/ 54 (9.3)	8/108 (7.4)
All	3/ 54 (5.6)	5/ 54 (9.3)	8/108 (7.4)
Screening	2/ 54 (3.7)	4/ 53 (7.5)	6/107 (5.6)
Week 8	1/ 35 (2.9)	3/ 37 (8.1)	4/ 72 (5.6)
DB Final Assessment	2/ 51 (3.9)	3/ 52 (5.8)	5/103 (4.9)
QTc Interval, derived (msec)	6/ 54 (11.1)	7/ 54 (13.0)	13/108 (12.0)
All	6/ 54 (11.1)	7/ 54 (13.0)	13/108 (12.0)
Screening	4/ 54 (7.4)	5/ 53 (9.4)	9/107 (8.4)
Week 8	1/ 35 (2.9)	3/ 37 (8.1)	4/ 72 (5.6)
DB Final Assessment	3/ 51 (5.9)	3/ 52 (5.8)	6/103 (5.8)

The most common PCI findings were prolongations of the QT corrected (QTc) interval, which occurred in 16 (12%) of 129 patients, including 11 patients with PCI QTc intervals at screening. Of the 11 patients with PCI QTc intervals at screening, 4 patients had no subsequent ECG reading, 2 patients had QTc intervals that remained elevated throughout the trial, and 5 patients had QTc intervals that returned below the PCI threshold at subsequent readings (2 patients while on treatment with placebo and 3 patients while on treatment with pantoprazole). In addition, 5 patients who did not have PCI findings at screening did have prolonged QTc intervals during the trial: 1 patient while on open-label pantoprazole, 2 patients at the end of treatment with double-blind pantoprazole, and 2 patients at the end of treatment with double-blind placebo. These data show that prolonged QTc intervals were common in this patient population and provide no signal that treatment with pantoprazole leads to a prolongation of the QTc interval. Adult data do not show a concern for QT prolongation.

Ten (8%) of 129 patients had PCI abnormalities of the QRS interval, one having a PCI short QRS (at screening only) and nine having a PCI prolongation. Of the nine patients with a PCI prolonged QRS interval, five had the prolongation at screening—two of which resolved during the trial and three of which persisted. The remaining four patients developed PCI QRS prolongations during the trial, two during the open-label phase and two during the double-blind phase (one on pantoprazole and one on placebo).

Per protocol all ECGs were assessed overall by the ECG reader as "normal," showing a "non-clinically significant abnormality," or showing a "clinically significant abnormality." No ECG was reported as showing a clinically significant abnormality. It is known that mainly due to high heart rates, correct interpretation of the QT interval in infants is difficult. Overall, there does not

appear to be a signal for QT prolongation, and other trials in older pediatric patients will be reviewed for any notable trends in the reported ECG results.

Growth Parameter Analyses

The patients were monitored for changes in growth parameters.

Weight. Weight was measured at baseline, Week 2, Week 4, the final open-label assessment, Week 6, Week 8, and the final double-blind assessment. For patients in the safety population, mean weight increased from 7.0 kg at baseline to 7.5 kg at week 4 ($p<0.001$). Mean weight increased in both treatment groups from baseline to Week 4 and from Week 4 to Week 8 ($p<0.001$). At Week 8, the mean weight in both groups had increased by approximately 1 kg in both treatment groups. There were no statistically significant between-group differences in weight changes. In the safety population, the mean weight z-score was -0.38 at baseline and -0.32 at week 4 at the end of treatment with open-label pantoprazole, indicating that on average children in this trial were slightly below the norm for their peers and that their weight gains were in line with those expected without significant catch-up. Among patients completing the double-blind phase, the mean z-scores for weight at Week 8 showed small but statistically significant ($p=0.012$ and $p=0.017$) gains in both treatment groups.

Height. Height was measured at baseline, Week 4, the final open-label assessment, Week 8, or the final double-blind assessment. For patients in the safety population, mean height increased significantly ($p<0.001$) by approximately 2 cm from 64.0 cm at baseline to 66.3 cm at Week 4. In patients completing the double-blind phase of the trial, mean height increased ($p<0.001$) in both treatment groups by approximately 2 cm from baseline to trial Week 4 while on open-label pantoprazole and by a similar amount from Week 4 to Week 8 while on double-blind treatment. There were no statistically significant between-group differences in height changes. The height z-score for the safety population was -0.49, as with weight, these infants were on average slightly less tall than their peers. After four weeks of open-label treatment with pantoprazole, there was no change in the z-score in height, indicating that the rate of growth in height over the four weeks was in line with the norm for the patients' peers. Among patients completing the double-blind phase, the mean z-score for height at week 8 had increased from baseline by 0.42 ($p=0.015$) in the placebo group and 0.23 ($p=0.077$) in the pantoprazole 1.2-mg/kg group.

For patients in the safety population, mean head circumference increased ($p<0.001$) by approximately 1 cm from 42.4 cm at baseline to 43.3 cm at Week 4. In patients completing the double-blind phase of the trial, head circumference increased ($p<0.001$) from baseline to week 4 while on open-label pantoprazole in both treatment groups and increased ($p<0.001$) by approximately 1.7 cm in both groups by Week 8. There were no statistically significant between-group differences in head circumference changes. At baseline, the mean z-score was -0.15 (±1.4) overall. Head circumference increased from baseline to Week 4. The within-group analyses of head circumference z-scores showed that patients in pantoprazole 1.2-mg/kg group had statistically significant growth from baseline to Week 4 ($p<0.001$), and patients in both treatment groups had significant growth from baseline to Week 8 ($p=0.012$ in the pantoprazole 1.2-mg/kg group and $p=0.001$ in the placebo group). Between-group differences were not statistically significant.

Table 41: Growth Parameters - Comparisons to Baseline (Trial 329)

		Open Label 1.2 mg/kg		Double Blind Therapy Panto	PBO
		Baseline	Week 4	Final (post week 8)	
Weight (kg)	N	129	111	54	54
	Mean (SD) [min, max]	7.0 (1.7) [4.3,13.0]	7.5 (1.7) [4.6, 13.6]	7.9 (1.5) [5.0, 11.6]	8.1 (1.7) [5.2, 14.0]
	Mean change		0.5	1.0	1.0
Height (cm)	N	129	106	52	53
	Mean (SD) [min, max]	64.0 (6.1) [50.0, 78.7]	66.3 (5.6) [53.3, 81.5]	68.1 (5.9) [54.0, 82.5]	67.9 (5.5) [59.0, 82.0]
	Mean change From baseline		2.0	3.9	3.8
Head Circ. (cm)	N	129	110	51	53
	Mean (SD) [min, max]	42.4 (3.1) [35.5, 51.4]	43.3 (2.9) [36.0, 52.1]	44.1 (2.6) [38.1, 49.0]	44.0 (2.8) [37.5, 51.0]
	Mean change		0.9	1.6	1.9

Comment: Overall, growth in terms of weight, height, and head circumference do not appear to be impacted negatively by short-term treatment with pantoprazole.

Safety Conclusions

Daily 1.2 mg/kg doses of pantoprazole granules administered as an oral suspension were relatively safe and well-tolerated in these infants aged 1 through 11 months with symptomatic GERD. No deaths occurred, and there was no pattern of AEs indicative of a treatment related effect. Eight patients had 11 SAEs throughout the screening, treatment, and follow-up phases of the trial; of those one case of diarrhea is thought to be possibly related to treatment and required discontinuation from the trial. The most common TEAE was upper respiratory infection, which occurred with equal frequency in the two treatment groups. The most common TEAEs that occurred more frequently in the treated group during the double-blind period as compared to placebo were: otitis media, vomiting, fever, and CPK elevation. Five patients were withdrawn from the trial because of AEs, four during the open-label phase and one during the double-blind phase. Laboratory test results did not reveal any discernable treatment-related abnormalities. There are no major safety signals that have been identified in this trial.

CONCLUSIONS

The clinical outcome trial did not meet its primary endpoint. Assessment of symptoms was by parent observation and we may not be capturing the most relevant aspects to best detect effectiveness of treatment.

Sensitivity and specificity of the assessment tool used is questionable (Section 6.1.4) and further research is warranted to improve capture of data for studying GERD in this young patient population. Although there were no major safety signals detected from review of the safety data, use of pantoprazole treatment without supportive clinical outcome is unwarranted. 4

9.4.2 Trial 3001B3-328: Age 1 to 5 years - Clinical Outcome and Safety

A. General Design and Objective:

Trial 3001B3-328 (Trial 328) is a Phase 3, multicenter, outpatient, randomized, double-blind trial of the clinical outcomes, safety, and tolerability of multiple doses of pantoprazole sodium enteric-coated granules in children, ages 1 to 5 years, with endoscopically proven symptomatic GERD.

The primary objective of this trial was to evaluate the clinical outcomes of treatment with three doses of oral pantoprazole (low, medium, and high) in patient ages 1 to 5 years with endoscopically-proven GERD. The dosages of pantoprazole selected in this trial were selected as the dosages considered to be therapeutically effective and safe based on the results obtained from trial 3001B3-334-US (Section 9.4.7). Secondary objectives were to evaluate the safety, tolerability, and growth parameters of oral pantoprazole in these patients.

Trial period: May 11, 2006 to April 29, 2008

The trial was conducted at 26 sites in North America. A total of 53 patients of the 101 screened, completed the trial.

B. Background

Protocol Amendments
There were a total of three amendments that were made to the protocol, two of which were made prior to patient entry into the trials. Amendment 3 is described in detail:

Amendment 3 (Feb 22, 2007) reflected a change in the inclusion/exclusion criteria. "Neurologically impaired patients with endoscopically-confirmed EE" were removed from the inclusion criteria. "Severely neurologically impaired patients with NERD" was added to the exclusion criteria. In the exclusion criteria, "severely neurologically impaired patients with EE may be enrolled at lower weights with prior Wyeth medical monitor approval" was added. In the prohibited treatment, "except in severely neurologically impaired patients with EE" was added to "carbamazepine or phenytoin." Under efficacy, "For patients with EE" was added to the weekly GERD symptom score and the change from baseline was summarized in a separate analysis. Ability to take apple juice was added to the inclusion criteria and to the test article preparation and administration section. A history of treatment with PPIs within 14 days of endoscopy prior to randomization was added to the exclusion criteria and "administration of GSQ-YC" was removed. Previously failed adequately dosed and administered PPI with adequate duration of treatment was added to the exclusion criteria. The endoscopy prior to randomization was added.

The sample size was based on regulatory and practical needs not set by statistical power. That the sample size would be large enough to evaluate the safety, tolerability and relative

effectiveness of three doses of pantoprazole was also added to the rationale section for the number of patients and the trial sample size and power. The following note was added to the inclusion and exclusion criteria, "a decreased score, (exclusionary score <3) may be obtained from patients who have not been washed out of PPIs/H2RAs." If this occurs, the patient should be washed out of the PPI/H2RA therapy over a period of 14 days, and then the questionnaire should be re-administered. If the patient does not obtain a score of >3, the patient is considered a screen failure. The PPIs, H2RAs, prokinetic agents, and antacids prohibited periods were changed by removing the 14 days before screening questionnaire.

C. Inclusion

1. Male and female patients aged 1 through 5 years.
2. GERD endoscopically confirmed by one of the following:
    a. Positive endoscopic evidence of reflux-related EE within two weeks of enrollment (i.e., per modified HD ≥ grade 2); or
    b. Positive histologic evidence of esophagitis consistent with GERD within two weeks of enrollment.
    (Note: eosinophilic esophagitis must have been ruled out).
3. Pre-trial GERD symptom frequency score >3 on the GYQ-YC **(**Note: A decreased score, [i.e., exclusionary score < 3 was obtained from patients who had not been washed out of proton-pump inhibitors (PPI)/histamine2 receptor antagonists (H2RAs)]). If this occurred, the patient was washed out of the PPI/H2RA therapy over a period of 14 days and then the questionnaire was re-administered. If the patient did not obtain a score of >3, the patient was considered a screen failure).
4. Weight ≥ 7 kg for patients aged 1 through 5. (Note: Severely neurologically impaired patients with EE were allowed to enroll at lower weights with prior Wyeth medical monitor approval; although no severely neurologically impaired patients were randomly assigned to treatment in this trial).

D. Exclusion

Criteria are similar to infant trial (Section 9.4.1-D).

E. Treatment

Patients who met the inclusion and exclusion criteria were stratified by a diagnosis of either erosive esophagitis (EE) with Hetzel-Dent (HD) score ≥ 2 or non-erosive reflux disease (NERD, HD less than grade 2). Patients participated in the trial for approximately 14 weeks, which included screening (four weeks), active treatment (eight weeks), and follow up (two weeks after the last dose of test article). The test article was administered once daily for eight weeks.

Three dose levels (low [0.3 mg/kg], medium [0.6 mg/kg], and high [1.2 mg/kg]) were selected to determine therapeutic effectiveness and safety. Patients with EE were randomly assigned to the medium-dose or high-dose groups. Patients with NERD were randomly assigned to the low-dose, medium-dose, or high-dose group.

Capsules containing pantoprazole sodium enteric-coated spheroids in four strengths (5 mg, 10 mg, 15 mg and 20 mg) were dispensed in a blinded fashion. Patients randomized to the high-dose group were assigned to the 15-mg or 20-mg dose group based on their age to better approximate 1.2 mg/kg as shown in the following figure.

Figure 14: Pantoprazole Strength Based on Age Group

Pantoprazole Strength Based on Age Group

	Dose Groups		
Age[a]	Low	Medium	High
≥1 to <2 years	5 mg	10 mg	15 mg
≥2 to <6 years	5 mg	10 mg	20 mg

a. Age at randomization.

The pantoprazole sodium spheroids were sprinkled on a teaspoon of applesauce or in apple juice and orally administered within two hours after preparation, and at least a half hour before breakfast. The patient was allowed additional water or apple juice up to a maximum of four ounces (120 mL), which included the amount used for preparation and rinses. Patients who did not like the taste or texture of applesauce were permitted to sprinkle the spheroids into a teaspoon of apple juice. Only applesauce or apple juice was given to administer the pantoprazole spheroids.

Concomitant Medications

Patients were provided with two bottles of the marketed product Mylanta® Supreme liquid antacid (US) or the marketed product Maalox® Nighttime liquid antacid (Canada) (300 – 400 mg calcium bicarbonate [$Ca(HCO_3)_2$]/5 mL) for use after five or more minutes of GERD symptoms. The investigator provided dosage directions (e.g., ½ standard teaspoon, 4 to 6 times per day, not to exceed 35 mg/kg/day or 87.5 mg $CaHCO_3$/kg/day). Children weighing over 25 kg were permitted to receive a maximum of one teaspoon, four to six times per day. Maximal antacid doses were given only to children with low milk intakes.

Patients continued their usual medical therapies according to standard clinical practice. Continuous treatment with theophylline derivatives and digoxin were to be closely monitored throughout the trial to assure that proper serum levels of these drugs were maintained. Medications used to treat nongastrointestinal conditions were allowed, if not on the prohibited list, provided that no dose adjustments were necessary during the trial.

Prohibited Medications

Similar to infant trial (Section 9.4.1-E).

F. Safety Considerations/Monitoring

Visits occurred at -4, 0, 2, 4, 6, and 8 weeks, and telephone contacts were conducted at 1, 3, 5, and 7 weeks. The post-treatment telephone contact occurred approximately two weeks after the final visit. Safety evaluations were performed and assessed during all trial visits. The evaluation of safety included a complete medical history, physical examinations, use of concomitant

medications, and the assessment of vital signs, growth parameters (weight, height, weight/height and z-scores), ECG, clinical laboratory values. The assessment of AEs was conducted for each patient throughout the trial. Patients were followed until AEs were adequately resolved. Withdrawals from the trial due to SAEs or treatment failure were fully documented, as was the use of any rescue medications. All patients were followed via telephone contact at interim weeks 1, 3, 5, 7, and at two weeks following the final administration of the test article to obtain information regarding any new or persistent AEs which occurred during the course of the trial and the use of concomitant medication. Table 42 from the Applicant's submission summarizes the trial schedule.

Only one central laboratory, (b) (4) was used by each investigator for all laboratory determinations, unless a special test was required.

Table 42: Study Schedule (Trial 328)

Study period	Screening[a]		Treatment							Final Visit[b]	Post Treatment
Study week	-4	0	1	2	3	4	5	6	7	8	10
Study visit[c]	V1	V2		V3		V4		V5		V6	
Telephone contact[c]			T1		T2		T3		T4		T5
Informed consent	X										
Demography and medical history	X										
Inclusion and exclusion criteria	X	X									
Prior and current medications	X										
Complete physical examination[d]	X	X*								X	
Begin 14 day washout of PPIs / H_2RAs after informed consent is signed (if applicable)[e]	X										
Brief physical exam				X		X		X			
Symptom questionnaire (GSQ-YC)[e]	X										
Electronic diary, (GERD symptoms, test article and antacid use)	X	X	X	X	X	X	X	X	X	X	
Endoscopy and biopsies	X[f]									X[g]	
Routine laboratory evaluation[h]	X					X				X	
Fasting serum gastrin level[i]	X									X	
12-lead ECG[j]	X									X	
Vital signs	X	X		X		X		X		X	
Record adverse events[k]	----------X----------										
Record concomitant medications		----------X----------									
Dispense test article[k]		X		X		X		X			
Dispense study antacid, if needed[l]	X	X		X[l]		X[l]		X[l]			
Measure compliance of test article[m]				X		X		X		X	
Record study antacid usage[m]		X		X		X		X		X	

G. Endpoints

The primary effectiveness endpoint was the weekly GERD symptom score (WGSS), defined as the sum of the five selected individual weekly GERD mean frequency scores for vomiting/ regurgitation (item 1c), choking/gagging (item 2a), refusal to eat (item 3a), difficulty swallowing (maximum of 4a and 4b) and abdominal/belly pain (item 5a).

Secondary effectiveness endpoints were assessed from information recorded from the eDiary and from patient physical examination and endoscopy results:

1. The individual mean frequency scores for each GERD symptom.
2. The amount of antacid taken during each week, as well as the number of patients taking antacids.

3. The individual mean score for respiratory symptoms.
4. The change in endoscopy results at the end of the trial from baseline in patients with a second endoscopy.
5. The number of patients with EE (HD ≥2 at baseline) and with healing of EE (HD <2) at the end of trial.

Effectiveness Measurements

The Primary Effectiveness Endpoint

The weekly GERD symptom score (WGSS), defined as the sum of the five selected individual weekly GERD mean frequency scores for vomiting/regurgitation (item 1c), chocking/gagging (item 2a), refusal to eat (item 3a), difficulty swallowing (max of 4a and 4b) and abdominal/belly pain (item 5a).

Primary Effectiveness Variables

The eDiary included a symptoms script that prompted parents to assess the frequency of GERD symptoms during the previous 24 hours. The GSQ-YC was used in conjunction with Orenstein's I-GERQ questionnaire (Orenstein 1993, 1996) to develop a script for the eDiary. In addition, respiratory symptoms were added with questions also based upon the I-GERQ. The eDiary script included the following items:

1. Vomiting/regurgitation
    - 1a. Since last evening, did the child have vomiting, spitting up, or regurgitation (anything coming into or out of the mouth)?
    - 1b. When does most of the vomiting, spitting up, or regurgitation (anything coming out of the mouth) occur?
    - 1c. Since last evening, how many times did the child vomit or regurgitate (anything coming out of the mouth)?
2. Choking/gagging
    - 2a. Since last evening, during how many meals did the child choke or gag?
    - 2b Since last evening, how often did the child cough after choking while eating?
3. Refusal to eat
    - 3a. Since last evening, how many times did the child refuse to eat even when hungry?
4. Difficulty swallowing
    - 4a. Since last evening, how often did the child complain of food or liquids sticking?
    - 4b. Since last evening, how often did the child need to drink a lot to swallow his/her food?
5. Abdominal/belly pain
    - 5a. Since last evening, how often did the child complain of stomach/belly pain?
6. Respiratory symptoms
    - 6a. Since last evening, did the child have a cold or fever?
    - 6b. Since last evening, did the child have a cough without a cold?
    - 6c. Since last evening, how much of the time did the child have noisy breathing?
    - 6d. Since last evening, did the child have noisy breathing while breathing out?
    - 6e. Since last evening, did the child's breathing have a wheezy or whistling sound?
    - 6f. Since last evening, did the child have noisy breathing while breathing in?
    - 6g. Since last evening, did the child's breathing have a croupy or barky sound?

The Secondary Effectiveness Endpoints

1. The individual mean frequency scores for each GERD symptom
2. The amount of antacid taken during each week, as well as the number of patients taking antacids.
3. The individual mean score for respiratory symptoms
4. The change in endoscopy results at the end of the trial from baseline in patients with a second endoscopy.
5. The number of patients with EE (HD ≥2 at baseline) and with a healing of EE (HD <2) at the end of trial.

Safety Measurements

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

1. adverse events (AEs), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs)
2. laboratory test evaluations, including potentially clinically important (PCI) results, using predetermined PCI criteria
3. vital signs measurements, including PCI results, using predetermined PCI criteria
4. standard 12-lead ECG findings;
5. physical examination findings, including growth parameters.

Only one central laboratory, (b) (4) was used by each investigator for all laboratory determinations, unless a special test was required. In such cases, the investigator designated an additional local laboratory only for the special test.

H. Data Analysis

Statistical Analytical Plan

Analysis Populations

The mITT population consists of all randomized patients who received at least one dose of trial drug. The valid-for-efficacy (VFE) population is a subset of the mITT populations and is defined as:

1. Patients with at least 80% test article compliance
2. Patients with completed symptom diary for at least one week at baseline and for Week 8. This criterion was modified in the statistical analysis plan (SAP) to "patients who have completed the symptom diary for at least one week at baseline and at the trial week being analyzed."
3. Patients who did not violate the protocol in a major way.

The VFE population was determined and documented before the blind was broken. The primary population for the effectiveness analysis is the mITT population that includes all patients with

NERD. The safety population consists of all randomized patients who received at least one dose of trial drug.

Determination of Sample Size
Sample size was based on regulatory and practical needs, and was not set by statistical power. However, the Applicant states that the sample size was large enough to evaluate the safety, tolerability and relative effectiveness of three doses of pantoprazole based on the results of a similar trial, 3001A1-322-US. Approximately 100 NERD patients were enrolled in this trial to ensure at least 42 patients completing the trial. Once a sufficient number of patients (about 42) without EE completed the trial, only patients with EE were enrolled until at least four of these patients completed the trial. However, if after four months of time elapsed following the last NERD patient completed the trial, and no additional EE patients were randomized, the trial was closed.

Effectiveness Parameters - Statistical method for effectiveness endpoints
The changes in weekly GERD symptom score from baseline to Week 8 were analyzed for between-group comparison by an analysis of covariance (ANCOVA) that included treatment group and age cohort (<2 years old, ≥2 years old) as factors, and baseline GERD symptom frequency score and baseline antacid use as covariates. If the effect of the treatment group was significant, pairwise contrasts were used to further explore differences among the dose groups. The changes from baseline to other trial weeks were analyzed similarly. In addition, summary statistics for the weekly GERD symptom scores and the change from baseline were also reported by treatment group and trial week. Paired t-tests were was for the within-group comparison in changes from baseline.

For each individual GERD symptom frequency and respiratory symptom scores and the average daily amount of antacid used, similar analyses were performed and reported. The number of patients with healing of EE was compared among treatment groups by using Fisher's exact tests. For patients with EE, the weekly GERD symptom score and the change from baseline were summarized. To assess the consistency of the age-based dose strength assignment schedule with the randomized treatment groups, a weight-adjusted treatment group was assigned based on the actual dose level that was defined as the actual dose amount (mg) that a patient received divided by the patient baseline weight (kg). The change of WGSS from baseline to the final week was re-analyzed using an ANCOVA model with the weight-adjusted treatment group and baseline age group as fixed factors and baseline WGSS score and baseline antacid amount as covariates.

Safety Parameters

Safety parameters included adverse events AEs, TEAEs, abnormal and/or PCI laboratory test results and vital signs, and growth parameters (weight, height, weight/height and z-scores). Continuous safety parameters were analyzed using ANCOVA with treatment as a factor and baseline value as a covariate. Discrete safety parameters were analyzed by using either the Fisher exact test or the chi-square test. Growth parameters (weight, height/length, and their z- scores) were summarized. The changes in growth parameters from baseline were compared by an ANCOVA with the baseline as covariate and baseline age group and treatment as factors. For

patients with EE who were enrolled in the trial, descriptive statistics were provided to demonstrate changes from baseline. The number of patients who prematurely withdrew from the trial for any reason and by specific reason was summarized by treatment dose group for all patients.

I. Results

Number of patients

A total of 101 patients were screened at 26 investigational sites for the trial. Of these, 41 patients were screen failures. The remaining 60 patients (56 NERD and 4 EE patients) were randomly assigned to double-blind treatment groups and received at least one dose of test article; the safety population and the modified intent-to-treat (mITT) population were the same. Within the mITT population in this trial, 47 patients were included in the valid-for-evaluation (VFE) population. A summary of the patient disposition by analysis population and treatment groups is provided in Table 43 from the Applicant.

Table 43: Pt Disposition (Trial 328)

	Treatment			
Characteristic	Pantoprazole Low (0.3 mg/kg) n = 18	Pantoprazole Medium (0.6 mg/kg) n = 21	Pantoprazole High (1.2 mg/kg) n = 21	Total[a] n = 101
Screened	18 (100)	21 (100)	21 (100)	101 (100)
Screen Failures	0	0	0	41 (40.6)
Randomized and Treated	18 (100)	21 (100)	21 (100)	60 (59.4)
Safety	18 (100)	21 (100)	21 (100)	60 (59.4)
Modified Intent-to-Treatment	18 (100)	21 (100)	21 (100)	60 (59.4)
Valid for Efficacy	15 (83.3)	17 (81.0)	15 (71.4)	47 (46.5)

Discontinuations

Of the 60 patients included in the safety population, 53 (88%) patients completed all aspects of treatment during the trial. Of the 7 (12%) patients who discontinued from the trial, 4 (7%) patients withdrew due to AEs, which was the most common reason for discontinuation (328-036-000872 [contact dermatitis and diarrhea]; 328-042-000332 [rectal hemorrhage]; 328-046-000213 [sleep disorder]; and 328-057-000547 [abdominal pain]). Two (3%) patients withdrew due to parent request (328-005-000843 and 328-060-000962), and 1 (2%) patient (328-078-001321) was withdrawn from the trial at the request of the Applicant due to protocol violation (medication error).

Table 44: Discontinuation Reasons (Trial 328)

		Treatment			
Conclusion Status Reason[a]	Overall p-value	Pantoprazole Low (0.3 mg/kg) (n = 18)	Pantoprazole Medium (0.6 mg/kg) (n = 21)	Pantoprazole High (1.2 mg/kg) (n = 21)	Total (n = 60)
Total		18 (100)	21 (100)	21 (100)	60 (100)
Study completed	0.485	17 (94.4)	17 (81.0)	19 (90.5)	53 (88.3)
Discontinued	0.485	1 (5.6)	4 (19.0)	2 (9.5)	7 (11.7)
Adverse event	1.000	1 (5.6)	2 (9.5)	1 (4.8)	4 (6.7)
Parent request	0.324	0	2 (9.5)	0	2 (3.3)
Protocol violation	1.000	0	0	1 (4.8)	1 (1.7)

Protocol Deviations and Compliance

There were seven patients, half of which belong in the high dose group, with protocol deviations as described in the following table from the Applicant's submission.

Table 45: Protocol Deviations (Trial 328)

Patient Number	Dose Group (mg/kg)	Description
328-078-001321	1.2	Major protocol violation: patient received incorrect assignment number and dose.
328-009-000005	0.6	Significant protocol deviation: patient took Prevacid® after ICF was signed.
328-031-000151	1.2	Significant protocol deviation: patient took Zantac® 3 days before randomization and received incorrect assignment and dose at visit 5.
328-077-001261	1.2	Significant protocol deviation: patient received IV pantoprazole 16 mg for 3 days during hospitalization for SAE (anorexia).
328-009-000002	0.3	Significant protocol deviation: patient did not have the 14-day washout before endoscopy because patient took Prevacid up to the day of endoscopy.
328-043-000423	1.2	Significant protocol deviation: patient did not have the 14-day washout before endoscopy because patient took amoxicillin up to the 6 days before endoscopy.
328-009-000004	0.3	Significant protocol deviation: patient did not have the 14-day washout before endoscopy because patient took amoxicillin on the day of endoscopy.

There were no statistically significant differences among the dose groups in mean compliance during treatment.

Table 46: Summary of Compliance Data (Trial 328)

Characteristics		Pantoprazole treatment Low (n=18)	Med (n=21)	High (n=21)	Total (n=60)
# Trial Med Exposure Days	Mean [min, max]	53 [17, 61]	48 [5, 61]	52 [23, 64]	51 [5, 64]
	Standard Dev	9.4	17.7	9.9	13.0
Compliance w/ drug (%)	Mean [min, max]	94 [32, 98]	85 [9, 100]	92 [43,100]	90 [9, 100]
	Standard Dev	15.7	30.4	15.9	22.0
Compliance w/ eDiary (%)	Mean [min, max]	82 [55, 98]	89 [69,100]	87 [66,100]	86 [55, 100]
	Standard Dev	12.0	10.3	9.5	10.8

Demographics

The table below details the demographic information. The medium-dose group had more patients in the younger age group, more male patients, and lower mean GSQ-YC scores at screening.

Table 47: Summary of Demographic Data (Trial 328)

Characteristics		Pantoprazole treatment			
		Low (n=18)	Med (n=21)	High (n=21)	Total (n=60)
Age (years)	Mean [min, max]	2.7 [1, 5]	1.9 [1, 5]	2.8 [1, 5]	2.4 [1, 5]
	Standard Dev	1.6	1.2	1.3	1.4
Age group	≥ 1 to < 2 yrs	7 (39%)	10 (48%)	5 (24%)	22 (36%)
	≥ 2 to < 6 yrs	11 (61)	11 (52)	16 (76)	38 (63)
Sex	Female	6 (33)	4 (19)	13 (62)	23 (38)
	Male	12 (67)	17 (81)	8 (38)	37 (62)
Race	Caucasian	16 (89)	16 (76)	18 (86)	50 (83)
	African American	1 (6)	1 (5)	2 (10)	4 (7)
	Asian		2 (10)	1 (5)	3 (5)
	Other	1 (6)	2 (10)		3 (5)
Baseline Wt (kg)	Mean	16.7 [9, 34]	13.4 [9, 26]	14.8 [8, 24]	14.9 [8, 34]
	Standard Dev.	7.4	3.8	4.2	5.3
Baseline Ht (cm)	Mean	95.7 [76, 121]	88.7 [73,118]	95.1 [75,119]	93.0 [73, 121]
	Standard Dev.	14.4	11.4	12.2	12.8
Diagnosis of GERD	NERD	18 (100)	19 (90)	19 (90)	56 (93)
	EE		2 (10)	2 (10)	4 (7)
Grade of Esophagitis	Grade 0	11 (61)	11 (52)	10 (47)	32 (53)
	Grade 1	7 (39)	8 (38)	9 (43)	24 (40)
	Grade 2		2 (10)	2 (10)	4 (7)
Therapy Duration (days)	Mean	54 [23, 62]	49 [6, 62]	54 [25, 64]	52 [6, 64]
	Standard Dev.	8.2	17.9	9.5	12.8

Concomitant Medications

Non-trial concomitant medications usage was reported by 95% of the safety population and this was equally distributed in each of the trial treatment groups. The usage of non-trial concomitant medications by >10% of the safety population, excluding the antacids classification, is presented in Table 8-5. The most common non-trial concomitant medications reported by >10% of the safety population were: paracetamol (n = 24, 40%), ibuprofen, and amoxicillin (n = 11, 18%, each), multivitamins (n = 10, 17%), and cetirizine (n = 9, 15%). Statistically significant (p = 0.041) differences between treatment groups was noted for the usage of Miralax in the safety population.

Comment: There appears to be a dose dependent correlation between treatment and Miralax use. Constipation is not a known adverse reaction to PPIs. This may need to be further evaluated if there are similar patterns across other trials.

Table 48: Nonstudy Concomitant Medication Usage (Trial 328)

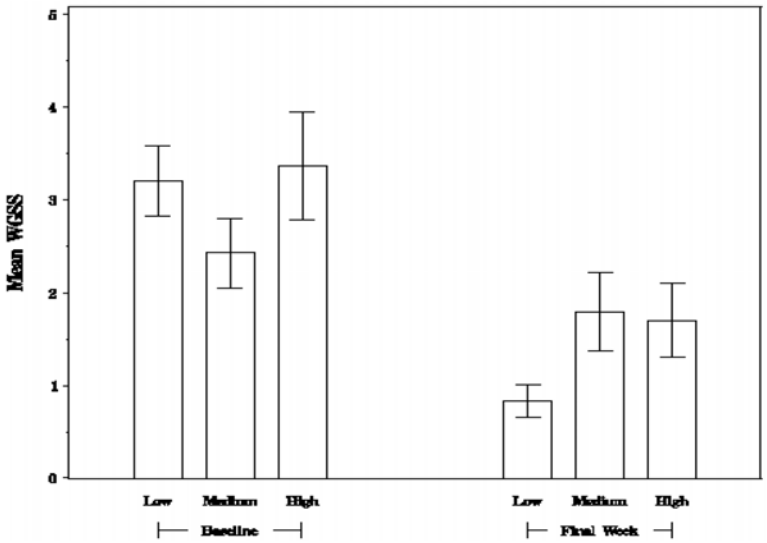
		Treatment			
Generic Term	Overall p-value	Pantoprazole Low (0.3 mg/kg) (n = 18)	Pantoprazole Medium (0.6 mg/kg) (n = 21)	Pantoprazole High (1.2 mg/kg) (n = 21)	Total (n = 60)
Any Nonstudy Medication	1.000	17 (94.4)	20 (95.2)	20 (95.2)	57 (95.0)
Amoxicillin	0.535	5 (27.8)	3 (14.3)	3 (14.3)	11 (18.3)
Budesonide	0.894	3 (16.7)	3 (14.3)	2 (9.5)	8 (13.3)
Cetirizine	0.208	3 (16.7)	5 (23.8)	1 (4.8)	9 (15.0)
Dextromethorphan	0.855	2 (11.1)	1 (4.8)	2 (9.5)	5 (8.3)
Diphenhydramine	1.000	2 (11.1)	3 (14.3)	2 (9.5)	7 (11.7)
Ibuprofen	0.083	1 (5.6)	3 (14.3)	7 (33.3)	11 (18.3)
Levosalbutamol	0.603	3 (16.7)	3 (14.3)	1 (4.8)	7 (11.7)
Lidocaine	0.086	2 (11.1)	0	0	2 (3.3)
Magnesium hydroxide	0.446	2 (11.1)	0	2 (9.5)	4 (6.7)
Miralax	0.041*	0	1 (4.8)	5 (23.8)	6 (10.0)
Montelukast sodium	1.000	2 (11.1)	2 (9.5)	2 (9.5)	6 (10.0)
Multivitamins	0.828	2 (11.1)	4 (19.0)	4 (19.0)	10 (16.7)
Paracetamol	0.507	5 (27.8)	9 (42.9)	10 (47.6)	24 (40.0)
Salbutamol	0.197	0	2 (9.5)	4 (19.0)	6 (10.0)

Effectiveness Evaluation

Primary Effectiveness

The primary effectiveness analysis was the change in mean WGSS from baseline week to final week for the mITT NERD population. A bar graph of the mean (with ±1 standard error) WGSS for the mITT population at baseline and final week for patients with NERD is presented in Figure 15 from the Applicant. The WGSS mean scores at baseline were 3.2, 2.4, and 3.4 for the low-dose, medium-dose, and high-dose groups, respectively. By the final week the mean scores had decreased to 0.8, 1.8, and 1.7 for the low-dose, medium-dose, and high-dose groups, respectively, indicating improvement in symptoms for all the dose groups. The low-dose, medium-dose, and high-dose groups included 0, 4, and 2 patients, respectively, who had baseline WGSS < 1.

Figure 15: WGSS at Baseline and Final Week for All Doses (Trial 328)



Descriptive statistics and within-treatment comparisons of WGSS for the mITT population (last observation carried forward, LOCF) for patients with NERD is presented below. For the mITT population, there were statistically significant within-group decreases in the mean WGSS from baseline to final week for the high-dose ($p < 0.001$) and the low-dose ($p < 0.001$) groups, but the decrease was not significant for the medium-dose group ($p = 0.06$).

Table 49: WGSS in mITT Population with NERD (Trial 328)

		Pantoprazole treatment		
		Low (n=18)	Med (n=21)	High (n=21)
Week 1 Baseline	Mean [min, max]	3.2 [1.1, 6.3]	2.4 [0, 5]	3.4 [0.3, 10.4]
	Standard Dev	1.6	1.6	2.5
Final Week	Mean [min, max]	0.8 [0, 2.7]	1.8 [0, 5.2]	1.7 [0, 6.6]
	Standard Dev	0.7	1.8	1.7

Table 50: CSS and Comparison by Age Subgroup for mITT with NERD (Trial 328)

		Age ≤ 1 to < 2 years			Age ≤ 2 to ≤ 6 years		
		Low N=7	Med N=9	High N=5	Low N=11	Med N=10	High N=14
Baseline	Mean [min, max]	3.3 [1.3, 6.3]	3.2 [0.9, 5]	3.7 [2, 5.7]	3.2 [1.1, 5.6]	1.8 [0, 4.8]	3.3 [0.3,10.4]
	SD	2.1	1.4	1.8	1.3	1.5	2.7
Final	Mean [min, max]	0.6 [0, 1.2]	2.3 [0.2, 5.2]	2.0 [0.2, 5.1]	1.0 [0.2, 2.7]	1.4 [0, 4]	1.6 [0, 6.6]
	SD	0.4	2.0	1.9	0.9	1.5	1.7

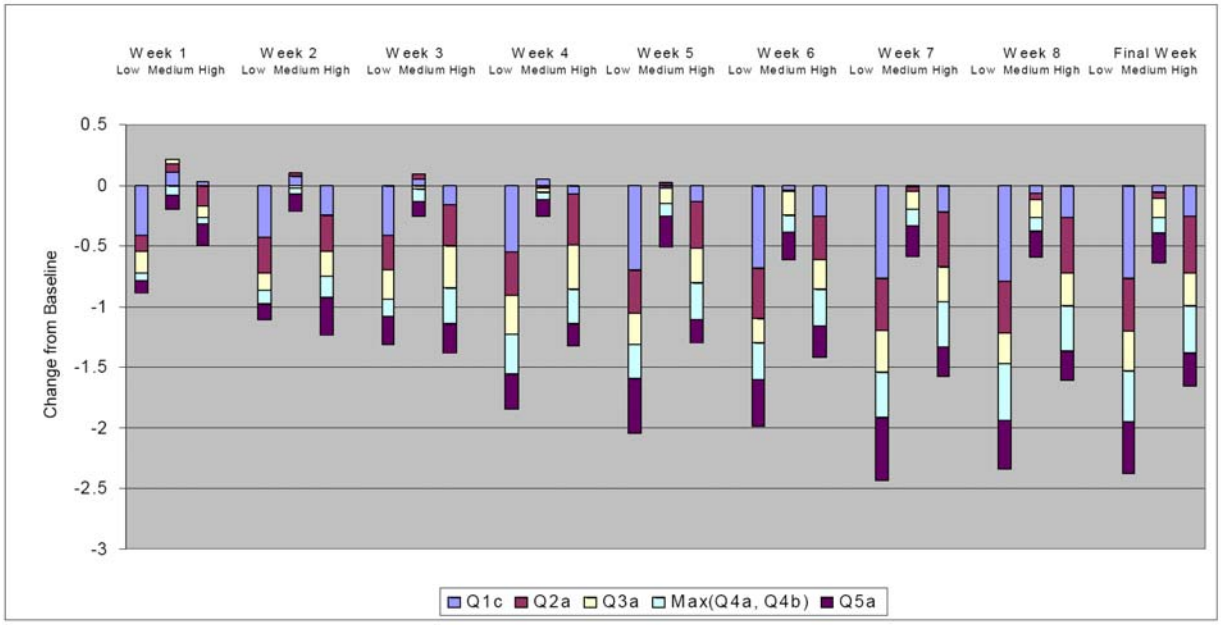
Table 51: CSS and Comparison by Wt Subgroup for the mITT with NERD (Trial 328)

Weight	Dose	Baseline N Mean (SD)	Week 8 N Mean (SD)	Change from baseline N Mean (SD)
< 15 kg	5 mg	9 3.18 (1.81)	9 0.79 (0.93)	9 -2.38 (2.03)
	10 mg	17 2.61 (1.56)	18 1.93 (1.88)	17 -0.59 (1.56)
	15/20 mg	11 3.45 (1.98)	11 1.86 (1.39)	11 -1.60 (1.51)
≥ 15 kg	5 mg	9 3.24 (1.39)	9 0.94 (0.89)	10 -2.29 (1.70)
	10 mg	3 1.17 (0.77)	3 0.61 (0.34)	3 -0.56 (0.73)
	15/20 mg	10 2.91 (2.97)	10 1.32 (1.92)	10 -1.58 (1.81)

A bar chart depicting the contribution of the five individual component scores to the mean WGSS is shown in Figure 16 from the Applicant's submission. The components appear in separate bar segments for questionnaire items (Q) 1c, 2a, 3a, Max (4a and 4b), and 5a. Changes to the WGSS are shown for Weeks 1 through 8 and final week for the low, medium, and high dose groups. All GERD symptoms decreased from baseline to the final week. The largest mean change from baseline to final week was a reduction in vomiting/regurgitation (-0.77) in the low-dose group. Both the individual symptom scores and the number of patients reporting symptoms decreased from baseline to the final week. The improvement in abdominal pain from baseline to

final week was nominally statistically significant for all three dose groups. The largest decreases from baseline to final week in the numbers of patients reporting symptoms were observed for choking/gagging, refusal to eat, and difficulty swallowing; the decreases were observed in all three dose groups.

Figure 16: WGSS Changes from Baseline by Individual Components (Trial 328)



Secondary Effectiveness Endpoint

EE Patients

There were four patients who had a diagnosis of EE: two in the medium-dose group and two in the high-dose group (patients with EE could not be randomized to the low-dose group). Repeat endoscopy demonstrated that all of the EE patients were healed at the final week of trial.

Table 52: Listing of Patients with EE (Trial 328)

Patient	Age (Years)	Weight (kg)	Assigned Dose	Treatment	Study Week	HD Grade
009-0005	2	12	med	10 mg (0.8 mg/kg)	Baseline	2
					Final	0
045-0182	4	20	high	20 mg (1 mg/kg)	Baseline	2
					Final	1
076-1232	3	16	high	20 mg (0.8 mg/kg)	Baseline	2
					Final	0
083-1472	1	11	med	10 mg (0.9 mg/kg)	Baseline	2
					Final	0

From Figure 14, the weight based dosing was calculated showing that all patients with EE received a dose that is approximately 1 mg/kg pantoprazole regardless of the dosing group to which they were assigned.

Effects on Antacid Use

The mean amount of antacid (mL) taken weekly decreased from baseline week to week 8 by 28.3 in the low-dose group (p = 0.037), 9.6 in the medium-dose group (p = 0.069), and 8.60 in the high-dose group (p = 0.181). The changes from baseline in the amount of antacid taken weekly are summarized for the mITT NERD population from the baseline week through trial week 8 are presented in Table 53: Comparison of Study Antacid Used in mL(Trial 328) from the Applicant. For the mITT NERD population, there were no statistically significant between-group differences in the mean change from baseline week to Week 8 (or any other time point) in the amount of antacid taken weekly as shown below.

Comment: There is a difference in mean amount of antacid used in the low dose group as compared to the medium and high dose groups. It also appears that there is a much larger SD and range for the low dose group. Therefore, it is most likely that one patient is off-setting the values for this group and that overall there is no significant decrease in the use of antacid taken weekly. However, there does appear to be a trend towards decreased usage of antacid by Week 8. The clinical meaningfulness of this decrease from approximately 4 tablespoons of antacid to 2 tablespoons per week is unknown.

Table 53: Comparison of Study Antacid Used in mL(Trial 328)

Study Week		Pantoprazole Low (0.3 mg/kg)	Pantoprazole Medium (0.6 mg/kg)	Pantoprazole High (1.2 mg/kg)
Week -1 (Baseline)	N	18	19	19
	Mean, SD	34.31 (53.95)	18.55 (28.62)	18.95 (21.62)
	Median	8.75	10.00	10.00
	Min, Max	0.00, 180.00	0.00, 110.00	0.00, 85.00
Week 8	N	18	19	19
	Mean, SD	6.00 (19.15)	8.96 (22.19)	10.35 (22.72)
	Median	0.00	0.00	0.00
	Min, Max	0.00, 80.77	0.00, 70.00	0.00, 95.00
	Change from Baseline			
	N	18	19	19
	Mean, SD	-28.31 (53.05)	-9.59 (21.62)	-8.60 (26.90)
	Median	-1.25	-5.00	-2.50
	Min, Max	-180.00, 10.77	-75.00, 35.00	-75.00, 60.00
	95% CI	(-54.69, -1.92)	(-20.01, 0.83)	(-21.56, 4.37)
	p-Value	0.037	0.069	0.181

Summary of Respiratory Symptom Improvement

The frequency of a cold or fever was fairly constant throughout the trial, with little difference between dose groups. The frequency of cough without a cold decreased from baseline to final visit but was only statistically significant in the low-dose group. Noisy breathing also decreased significantly in the low and high-dose groups. There was no significant change in the other respiratory symptoms between baseline and the final week of trial. The number of patients

reporting respiratory symptoms (questionnaire items 6b through 6g) from baseline to final week decreased in all three dose groups.

Effectiveness Conclusions

For the mITT NERD population, the mean WGSS decreased from baseline to the final week in the low-dose and high-dose treatment groups. The medium-dose group had more patients in the younger age group, more male patients, and lower mean GSQ-YC scores at screening. An additional ad hoc analysis showed that the weight-adjusted treatment groups were consistent with the randomized treatment groups for most of the patients. However, there was some shift between the dose groups when the doses were adjusted for weight. This was evident in the low-dose and medium-dose groups.

Weekly mean frequency scores for individual symptoms decreased from baseline to the final week in all the dose groups. The decreases in the medium-dose group were less than in the low-dose and high-dose groups. The between-group comparisons showed no statistically significant differences. The frequency of a cold or fever was fairly constant throughout the trial, with little difference between dose groups. Decreases in other individual respiratory symptoms from baseline to the final week were observed in all dose groups, although the decreases were not statistically significant. The between-group comparisons showed no statistically significant differences.

All four patients with EE, who were treated with either medium (0.6 mg/kg) or high (1.2 mg/kg) doses of pantoprazole, were healed at eight weeks. In this trial, only patients with EE had a repeat endoscopy at the end of treatment.

Safety Evaluation

Exposure

More than 88% of patients received 43-49 days of treatment with pantoprazole and >78% of patients received ≥ 50 days of treatment.

Serious Adverse Events

No deaths were reported.

Two (2, 3%) patients had a total of three SAEs at some time during treatment in this trial. None of these SAEs was considered to be related to the trial drug. Two SAEs were of mild severity; one SAE was of moderate severity. The SAEs experienced by these two patients were abdominal pain (328-057-000547), and anorexia and dehydration (328-077-001261).

Patient 328-057-000547 was a three-year old white male with GERD whose medical history included, left ear infection, abdominal pain, thrush, yeast infection, asthma and mild cerebral palsy all of which were continuing at the time of trial entry. Prior to trial entry the patient was receiving ranitidine for the treatment of GERD which was stopped on Jan 15, 2008. At trial entry the patient was receiving Tylenol, levalbuterol, phenylephrine/chlorpheniramine, amoxicillin/clavulanate, xopenex and nystatin. Amoxicillin was stopped on Jan 16, 2008, 21

days prior to endoscopy. The patient was randomized on Feb 15, 2008 [pantoprazole 10mg] and received the first dose on this date. On (b) (4) 2008, (b) (4) days after starting trial medication, the patient experienced abdominal pain. The test article was discontinued that day. The principal investigator referred the child to the hospital with abdominal pain, diarrhea and dehydration the next day. An abdominal x-ray was normal. No additional tests were performed and the patient was sent home. On (b) (4) 2008, the patient was admitted to a different hospital. A CT scan of the abdomen and pelvis, CBC, BMP, amylase, CRP, ESR, urinalysis were all negative. The patient was treated with IV fluids and was discharged (b) (4), 2008. The investigator reported the cause of the abdominal pain and diarrhea was unknown and considered the events to be not related to trial medication. On March 13, 2008, the patient was started on Prevacid 15 mg daily. Abdominal pain remains on going and the patient was continuing to be followed by the principal investigator.

Comment: Given the timing of the abdominal pain, it is possible that the test drug could have had a contributory role in the patient's abdominal pain. However, as the patient has a baseline history of abdominal pain and continued to have abdominal pain more than seven weeks after the test drug was discontinued despite extensive medical evaluation, it is less likely that the patient's SAE was a direct effect of pantoprazole.

Patient 328-077-001261 was a 1-year-old-white female with GERD, whose medical history included cortical dysplasia, chronic constipation, diarrhea, vomiting, and enlarged tonsils, all of which were ongoing at trial entry. On trial Day 36, the patient underwent an elective adenoidectomy and tonsillectomy, which was planned prior to trial entry, and partial removal of an ingrown toenail. The patient's postoperative oral intake was inadequate, and required IV fluids which prolonged her hospitalization. By postoperative day 4, the patient's oral intake increased and the patient was discharged. The investigator considered that the poor postoperative oral intake was not related to treatment with the trial medication. Two days after discharge, the patient developed a temperature of 101.7°F, irritability, and refused food and liquids. The following day (trial day 43), the patient was readmitted to the hospital because of dehydration. The patient was treated with IV fluids and antibiotics for a toenail infection at the operative site. The patient's oral intake improved over a 24 hour period, and she was discharged the next day (trial day 44). The investigator considered the event of dehydration to be not related to treatment with the test article. The patient completed the trial.

Comment: I agree with the investigator that in this situation, the test drug is unlikely to be related to the SAE of anorexia and dehydration, but rather that these events were secondary to the elective surgeries performed.

Adverse Events

AEs were reported by 57 (95%) of 60 patients in the safety population. The most common AEs reported by body system were as follows: respiratory system (43; 72%), body as a whole (32; 53%), and digestive system (29; 48%). TEAEs were reported in 55 (92%) of 60 patients in the safety population, 18 of 18 (100%), 19 of 21 (91%), and 18 of 21 (86%) of patients receiving low-dose, medium-dose and high-dose pantoprazole, respectively. Specific TEAEs reported in three or more patients (≥5%) by body system and event were as follows: body as a whole - fever

(11, 18%), accidental injury and headache (8, 13%, each), and abdominal pain (5, 8%); digestive system - diarrhea and vomiting, (9, 15%, each), and gastroenteritis (4, 7%); heme and lymphatic system – lymphadenopathy (5, 8%) and ecchymosis (4, 7%); respiratory system - URI (23, 38%), rhinitis (9, 15%), cough increased (7, 12%), pharyngitis (5, 8%), and sinusitis (3, 5%). None of these TEAES showed any increasing incidence with increased trial drug dose.

In three patients with TEAEs of ecchymosis (328-008-000907, 328-009-000007, and 328-029-000121), the bruising was isolated to one site (i.e., two forehead, one thumb); in the fourth case, the bruising was reported as being on the anterior lower legs. In addition, this patient (328-029-000123) had a TEAE of accidental injury (fell and hit head and abrasions on cheek), and also had low normal platelet counts at all evaluations, including screening (187 x 109/L), Week 4 (150 x 109/L), and week 8 (184 x109/L). Fifty-five (92%) of 60 patients in the safety population had at least one TEAE. Overall, 11 (18%) patients had 14 TEAEs that were considered related to trial drug by investigators.

TEAEs considered by investigators to be related to trial medication were: headache (3 patients), diarrhea (2), and gastroenteritis, hyperlipidemia, sleep disorder, hyperkinesia, epistaxis, URI, maculopapular rash, lab test abnormal (elevated gastrin), and urticaria (1 patient, each). TEAEs were assessed by the investigator as being of mild severity in 46 patients, and moderate severity in 9 patients. No TEAEs were categorized by investigators as severe.

Table 54: Number (%) of Pts Reporting TEAE-Safety Population (Trial 328)

Body System		Pantoprazole Treatment			
		Low 0.3 mg/kg N=18	Medium 0.6 mg/kg N=21	High 1.2 mg/kg N=21	Total N=60
Any AE		18 (100)	19 (91)	18 (86)	55 (92)
Body as Whole	Total	7 (39)	10 (48)	11 (52)	28 (47)
	Abd pain	1 (6)	1 (5)	3 (14)	5 (8)
	Injury	3 (17)	3 (14)	2 (10)	8 (13)
	Fever	2 (11)	5 (24)	4 (19)	11 (18)
	Flu syndrome	0	1 (5)	1 (5)	2 (3)
	Headache	3 (17)	1 (5)	4 (19)	8 (13)
	Infection	1 (6)	0	1 (5)	2 (3)
	Injection rxn	0	1 (5)	0	1 (2)
	Abn lab test	0	0	1 (5)	1 (2)
CV System	Hemorrage	1 (6)	0	0	1 (2)
Digestive System	Total	9 (50)	6 (29)	10 (48)	25 (42)
	Anorexia	0	0	1 (5)	1 (2)
	Constipation	1 (6)	0	1 (5)	2 (3)
	Diarrhea	4 (22)	2 (10)	3 (14)	9 (15)
	Gastroenteritis	1 (6)	1 (5)	2 (10)	4 (7)
	GERD	0	0	1 (5)	1 (2)
	Gingivitis	0	0	1 (5)	1 (2)
	Nausea	0	0	1 (5)	1 (2)
	Rectal hemorrhage	0	0	1 (5)	1 (2)

Body System		Pantoprazole Treatment			
		Low 0.3 mg/kg N=18	Medium 0.6 mg/kg N=21	High 1.2 mg/kg N=21	Total N=60
	Tooth disorder	2 (11)	1 (5)	0	3 (5)
	Vomitting	2 (11)	4 (19)	3 (14)	9 (15)
Hemic and Lymphatic	Total	2 (11)	2 (10)	3 (14)	7 (12)
	Echhymosis	2 (11)	1 (5)	1 (5)	4 (7)
	Lymphadenopathy	1 (6)	1 (5)	3 (14)	5 (8)
Metabolic & Nutritional	Total	1 (6)	2 (10)	3 (14)	6 (10)
	Dehydration	0	1 (5)	1 (5)	2 (3)
	FTT	0	1 (5)	0	1 (2)
	Hyerlipidemia	0	0	1 (5)	1 (2)
	Peripheral edema	1 (6)	0	1 (5)	2 (3)
Nervous System	Total	0	1 (5)	2 (10)	3 (5)
	Ataxia	0	0	1 (5)	1 (2)
	Hyperkinesia	0	0	1 (5)	1 (2)
	Sleep disorder	0	1 (5)	0	1 (2)
Respiratory System	Total	12 (67)	12(57)	12 (57)	36 (60)
	Asthma	0	0	1 (5)	1 (2)
	Bronchitis	0	0	1 (5)	1 (2)
	Cough inc	3 (17)	3 (14)	1 (5)	7 (12)
	Epistaxis	0	1 (5)	1 (5)	2 (3)
	Laryngitis	0	1 (5)	1 (5)	2 (3)
	Pharyngitis	3 (17)	2 (10)	0	5 (8)
	Rhinitis	3 (17)	1 (5)	5 (24)	9 (15)
	Sinusitis	1 (6)	0	2 (10)	3 (5)
	URI	8 (44)	7 (33)	8 (38)	23 (38)
	Wheezing	1 (6)	0	0	1 (2)
Skin	Total	1 (6)	3 (14)	3 (14)	7 (12)
	Contact Dermatits	0	1 (5)	1 (5)	2 (3)
	Exfoliative Derm.	0	0	1 (5)	1 (2)
	Rash	1 (6)	1 (5)	1 (5)	3 (5)
	Urticaria	0	1 (5)	0	1 (2)
Special Senses	Total	3 (17)	0	1 (5)	4 (7)
	Ear pain	1 (6)	0	0	1 (2)
	Eye pain	1 (6)	0	0	1 (2)
	Otitis Media	1 (6)	0	1 (5)	2 (3)
Urogenital	Total	1 (6)	0	1 (5)	2 (3)
	UTI	0	0	1 (5)	1 (2)
	Vulvovaginal d/o	1 (6)	0	0	1 (2)

Safety Related Discontinuations

A total of 4 (7%) patients withdrew from the trial due to AEs as seen in Table 55 from the sponsor. Of the five AEs experienced by these four patients, two AEs were related to the trial drug (diarrhea, sleep disturbance) and three AEs (contact dermatitis, rectal bleeding, dehydration=SAE pt 328-057-000547) were not related to treatment.

Table 55: % of Pts Reporting AEs Causing Withdrawal (Trial 328)

Body System[a] Adverse Event	Overall p-Value	Treatment: Pantoprazole Low (0.3 mg/kg) (n = 18)	Pantoprazole Medium (0.6 mg/kg) (n = 21)	Pantoprazole High (1.2 mg/kg) (n = 21)	Total (n = 60)
Any adverse event	1.000	1 (5.6)	2 (9.5)	1 (4.8)	4 (6.7)
Body as a whole	1.000	0	1 (4.8)	0	1 (1.7)
Abdominal pain	1.000	0	1 (4.8)	0	1 (1.7)
Digestive system	0.751	1 (5.6)	0	1 (4.8)	2 (3.3)
Diarrhea	0.300	1 (5.6)	0	0	1 (1.7)
Rectal hemorrhage	1.000	0	0	1 (4.8)	1 (1.7)
Nervous system	1.000	0	1 (4.8)	0	1 (1.7)
Sleep disorder	1.000	0	1 (4.8)	0	1 (1.7)
Skin and appendages	0.300	1 (5.6)	0	0	1 (1.7)
Contact dermatitis	0.300	1 (5.6)	0	0	1 (1.7)

Patient 328-036-000872 was a two year old white male whose medical history, in addition to GERD, included penicillin allergy and diarrhea. On trial day 16, the patient, who received pantoprazole 5 mg daily, developed diarrhea and contact diaper dermatitis. Treatment with the trial drug was discontinued seven days later (23 days after initiation), and trial participation concluded on trial Day 48 due to these AEs. The investigator considered that the diarrhea was related to the trial drug, and the contact diaper dermatitis was not related to trial treatment.

Comment: Diarrhea is a possible side effect of treatment and diaper dermatitis is likely secondary to the diarrhea.

Patient 328-042-000332 was a three year old white male who received pantoprazole 20 mg. On trial day 24, the patient developed rectal bleeding. Treatment with the trial drug was withdrawn on trial day 25, and the trial participation was concluded on Oct 2, 2006 (trial Day 33) due to the AE of rectal bleeding. The rectal bleeding was considered not related to the trial drug by the investigator.

Comment: Given the timing of the AE and lack of further description on the potential other cause for rectal bleeding by the investigator in the CRF, I am unable to evaluate the relationship of the AE to the trial drug. There remains a possibility that there is a correlation.

Patient 328-046-000213 was a one year old white male whose medical history, in addition to GERD, included chronic congestion, penile adhesions, otitis media, and eczema. Twelve days prior to initiation of therapy with pantoprazole 10 mg daily, treatment with nasal triamcinolone, which the patient received for the treatment of snoring, was discontinued. On trial Day 1, the patient developed a sleep disturbance (not further specified). The AE of sleep disturbance was considered related to trial drug by the investigator. Trial treatment was withdrawn on trial Day 9, and the trial participation concluded on 27 Oct 27, 2006 (trial day 32) due to this AE.

Comment: Insufficient information available to understand exact relationship of sleep disturbance and drug treatment.

For Patient 328-057-000547, see the description of this event under SAE.

ECG

Potentially clinically important ECG measurements were reported in 14 (23%) of 60 patients during the trial. All 14 of these patients had a PCI prolonged QRS interval (>84 ms) (reference range <40 to >84 ms). One patient also had a PCI short PR interval (<64 ms). Of the 14 patients who had a PCI prolonged QRS interval, 13 had a PCI prolonged QRS interval at screening. Only one patient (328-009-000001) developed the PCI prolonged QRS interval while on treatment. The investigator's overall evaluation of the ECG showing this PCI prolongation was assessed as normal. Of all the patients with a PCI prolonged QRS interval at screening, the PCI QRS prolongation resolved during treatment in 3 patients and persisted in 10 patients.

The patient with the PCI short PR interval (328-057-000543) had the abnormality both at screening and on treatment.

Per protocol, all ECGs were read and were assessed overall by the investigator or a consultant as "normal", showing a "nonclinically significant abnormality" or showing a "clinically significant abnormality." Only one patient's (328-008-000902) ECGs were assessed as showing a clinically significant abnormality. At both the screening and final evaluations, this patient's ECG showed a primary RSR pattern of the QRS complex in leads V1, V2 and V3. On the posttrial follow-up evaluation for this abnormality, the patient was found to have a bicuspid aortic valve.

There were no significant within-group or between-group differences in ECG parameters during the trial for the safety population. There were no abnormal QTc changes reported in this trial.

Comment: Overall, there is no notable concern for changes in ECG due to pantoprazole treatment.

Vital Signs

A total of 6 (10%) patients had PCI vital sign readings. One patient (328-009-000007) had a PCI high systolic blood pressure measurement (>140 mm Hg) at screening and also at Week 2 of treatment, but non-PCI measurements at all subsequent visits. Two patients (328-045-000184 and 328-043-000423) had a PCI low systolic blood pressure measurement at screening. No other PCI systolic blood pressure measurements were noted at subsequent visits for these patients. One (2%) patient (328-045-000181) had a single PCI low diastolic blood pressure measurement (<40 mmHg) at screening; a second measurement at screening and all other measurements at subsequent visits were non-PCI. Three (5%) patients had PCI abnormal respiratory rates (< 14 breaths per minute or > 40 breaths per minute), all at post screening visits. Two of the patients (328-102-000692 and 328-005-000841) had only one PCI measurement. The other patient (328-045-000184) had PCI high respiratory rates at 3 of 5 assessments; at both the other assessments, including screening, the respiratory rate was borderline PCI at 40 breaths per minute. This patient had no significant medical history. This patient had two AE episodes of upper respiratory infection, one of these coincided with a PCI high respiratory rate measurement. No patients were reported as having abnormalities in vital signs of actual clinical importance.

Comment: The abnormal vital signs are mostly reported at screening and non-sustained. Respiratory rates can be difficult to measure consistently in young children and can vary wildly based on confounding factors such as respiratory illness or emotional state. Overall, there does not appear to be any reason for concern for vital sign disturbances due to treatment with pantoprazole.

Laboratory Results

A total of 15 (25%) of 60 patients had PCI laboratory test results at some point during the trial; four of these patients had PCI blood chemistry test results, three patients had PCI endocrinology test results, four patients had PCI hematology test results, and five patients had PCI urinalysis test results.

Table 56: On-treatment Significant Changes in Lab Value from Baseline (Trial 328)

Low	Med	High
Creatinine Phosphorus Triglycerides CPK Urine LE +	Gastrin inc	Phosphorus Triglycerides Gastrin inc Urine LE +

The most common PCI laboratory test abnormalities occurring during the trial were urinary leukocyte esterase levels, which occurred in 4 of 59 (7%) patients, serum gastrin levels in 3 of 60 (5%) patients, serum triglyceride levels in 2 of 59 (3%) patients, serum phosphorous levels in 2 of 60 (3%) patients, white blood cell (WBC) count in 2 of 60 (3%) patients, and platelet count 2 of 60 (3%) patients.

Patient (328-042-000331) had a PCI elevated creatinine level. This patient was a 4-year-old male with asthma on concomitant medications of mometasone, fluticasone, and salmeterol. The patient was randomly assigned to the low-dose treatment group (0.3 mg/kg). At screening, he had a high-normal serum creatinine of 44 μmol/L (reference range: 18-44 μmol/L) with a normal blood urea nitrogen (BUN) of 11.0 mg/dL (reference range: 4-24 mg/dL). At the trial Week 4 visit (trial day 31), the serum creatinine value was PCI high (>88.4 μmol/L) at 318 μmol/L, with a non-PCI high BUN of 37 mg/dL. On repeat evaluation at a different laboratory two days later, the serum creatinine had returned to the baseline level of 44 μmol/L (reference range: 18.0-88.0 μmol/L) other blood chemistry parameters were not assessed at that time. At Week 8, the serum creatinine level, assessed by the original laboratory, was slightly elevated at 53 μmol/L (reference range: 18.0-44.0 μmol/L) and the BUN was normal at 13 mg/dL (reference range: 4.0-24.0 mg/dL); the phosphorous, magnesium, calcium, and uric acid levels had all returned to normal. The patient had no associated clinical AEs, no renal-pertinent medical history, and completed his allocated course of trial medication.

Comment: There appears to be a real event underlying the change in BUN and Cr values, however, the relationship with drug treatment is uncertain.

A patient (328-046-000214) had a PCI elevated CPK level. This 1-year-old female was in the low-dose treatment group (0.3 mg/kg) and had an extensive medical history including low weight and intermittent abnormal liver function tests (LFTs). The patient had a normal CPK level of 99 mU/mL (reference range: 18-134 mU/mL) at screening. At the Week 6 visit (trial day 39), the CPK level was PCI high (>402 mU/mL) at 1589 mU/mL. On repeat testing at a different laboratory five days later, the CPK level had decreased substantially to a non-PCI elevated level of 153 mU/mL (reference range: 0-100.0 mU/mL). Apart from some swelling of the fingers which was noted on the day the repeat blood work was obtained, and which resolved the following day, the patient had no temporally associated AEs. At the final evaluation on trial day 67, the patient's CPK level, measured by the original lab, was normal at 113 mU/mL (reference range: 18.0-134.0 mU/mL).

Two patients had PCI phosphorus levels. Patient 328-045- 000182, who had Albright's hereditary osteodystrophy (pseudohypoparathyroidism) and hypothyroidism, had PCI high phosphorus levels at screening and Week 8, and a non-PCI high phosphorus at Week 4. This patient also had non-PCI high magnesium levels at all evaluations, and non-PCI low or low-normal calcium levels at all evaluations. Hyperphosphatemia and hypocalcemia are features of Albright's osteodystrophy. This patient also had PCI high (>3.39) fasting triglyceride levels of 3.41 mmol/L at Week 8; at screening the fasting triglyceride levels had been non-PCI elevated at 1.31 (0.4-1.24mmol/L); the blood sample at Week 4 was nonfasting. The other patient (328-042-000331) with PCI high phosphorus levels also had a PCI elevated creatinine level and is described above.

Two patients had PCI high fasting triglyceride levels. Patient 328-045-000182, who also had a PCI phosphorus level, is described above. Patient 328-057-000542, who had no screening blood chemistry results, had a PCI high (> 3.39mmol/L) fasting triglyceride level of 4.30 mmol/L at the Week 4 evaluation. The fasting triglyceride levels were non-PCI elevated at 2.20 mmol/L (reference range: 0.4-1.24 mmol/L) at Week 6, and normal at 0.9 mmol/L at week 8. The patient's fasting cholesterol levels were normal at all assessments. This patient was noted to have unexplained hepatosplenomegaly at trial entry.

Three patients had PCI high fasting gastrin levels at Week 8, all having had normal levels at screening. One patient (328-009-000005) had discontinued treatment with lansoprazole 16 days prior to the start of trial medication and one patient (328-008-000906) had discontinued treatment with ranitidine 18 days prior to the start of trial medication. The other patient (328-102-000692) was not receiving any PPI or H2RA prior to trial entry. Statistically significant increases in fasting gastrin levels, from baseline to Week 8, were seen in the two higher dose groups.

All four patients who had PCI hematology test results (1 patient with a PCI-low WBC count, 1 patient with a PCI-elevated WBC and a PC-elevated lymphocyte count, and 2 patients with elevated platelet counts) had the PCI abnormalities only at screening, and had normal or improved hematology test values at subsequent assessments.

All five patients who had PCI urinalysis results (4 patients with positive leukocyte esterase, and 1 patient with 2+ hemoglobin and protein) had the PCI result at screening. In one patient, the leukocyte esterase remained positive at Week 4, but was negative at Week 8. In all the other patients, the PCI abnormality was seen only at screening.

Comment: Review of the CRFs for the above cases indicate that it is likely that only the elevated gastrin and triglyceride levels are associated with trial drug administration. For the other PCI laboratory results, these returned to within normal range by end of trial while on treatment, therefore making it less likely that the treatment was the cause for the abnormalities.

Growth

Patients were monitored for changes in growth parameters (weight, height, weight z-score, and height z-score) by trial week. Changes in actual weight (kg) at baseline and the final trial visit assessment for the treatment groups in the safety/mITT population are summarized in Table 57 from the sponsor. For patients in the safety population, mean weight significantly increased from baseline through the final visit assessment for all trial treatment groups. There were no significant between-group differences in mean changes from baseline in actual weight for patients in the safety population. In the safety population with NERD and EE patients combined, mean weight z-score at final visit increased by 0.1 in the low-dose group, by 0.12 in the medium-dose group, and by 0.03 in the high-dose group. Between-group differences in weight z-score were not statistically significant.

Table 57: Comparisons to Baseline for Wt in kg (Trial 328)

Study Week		Pantoprazole Low (0.3 mg/kg)	Pantoprazole Medium (0.6 mg/kg)	Pantoprazole High (1.2 mg/kg)
Baseline	N	18	21	21
	Mean, SD	16.68 (7.37)	13.35 (3.77)	14.79 (4.21)
	Median	14.90	12.50	14.70
	Min, Max	8.63, 34.30	9.38, 26.10	7.90, 23.80
Final Assessment[a]	N	18	21	21
	Mean, SD	17.32 (7.38)	13.85 (3.88)	15.15 (4.17)
	Median	15.00	13.10	14.70
	Min, Max	9.08, 35.00	9.54, 26.40	7.75, 23.36
	Change from baseline			
	N	18	21	21
	Mean, SD	0.64 (0.82)	0.50 (0.36)	0.36 (0.49)
	Median	0.40	0.37	0.30
	Min, Max	-0.20, 3.00	0.00, 1.30	-0.44, 1.70
	95% CI	(0.23, 1.05)	(0.33, 0.66)	(0.14, 0.59)
	p-value[b]	0.004	< 0.001	0.003

Height was measured at baseline, Week 8, and during the final visit assessment. For patients in the safety population, the mean actual height increased significantly from baseline to Week 8, and also to the final trial visit assessment for all treatment groups. Changes in actual height (cm) from baseline to the final assessment for the safety population are summarized in Table 10-9. No significant between-group differences in height were shown in the safety population. See Table 58 from the Applicant's submission for details.

Table 58: Comparison to Baseline for Ht in cm (Trial 328)

Study Week		Pantoprazole Low (0.3 mg/kg)	Pantoprazole Medium (0.6 mg/kg)	Pantoprazole High (1.2 mg/kg)
Baseline	N	18	21	21
	Mean, SD	95.74 (14.43)	88.66 (11.41)	95.09 (12.15)
	Median	95.10	85.00	95.00
	Min, Max	76.40, 120.90	73.40, 118.10	75.30, 119.00
Final Assessment[a]	N	18	21	20
	Mean, SD	97.79 (14.30)	90.84 (11.32)	96.54 (11.60)
	Median	95.95	87.00	96.65
	Min, Max	78.00, 122.10	78.00, 121.00	77.00, 119.00
	Change from baseline			
	N	18	21	20
	Mean, SD	2.05 (2.30)	2.18 (1.98)	1.61 (1.94)
	Median	1.80	1.40	0.70
	Min, Max	0.00, 10.10	0.00, 6.80	-0.50, 5.80
	95% CI	(0.91, 3.19)	(1.27, 3.08)	(0.70, 2.51)
	p-value[b]	0.001	< 0.001	0.002

Comment: Overall, short term treatment with the trial drug does not appear to hinder growth in these pediatric patients.

Safety Conclusions

In this trial, daily treatment with pantoprazole at doses of 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg was tolerated in patients aged 1 through 5 years with endoscopically-proven symptomatic GERD. No major safety issues were identified. There were no deaths. Two patients had SAEs, neither of which was considered by the investigator to be related to treatment with the trial medication, this conclusion seems reasonable given the case histories. Four patients were withdrawn from the trial because of AEs. Two of which were considered related to trial drug: diarrhea in one patient and an unspecified sleep disorder in the other patient.

While TEAEs were reported in most patients, they were events commonly occurring in this age group: respiratory infections, minor accidental injuries, and gastrointestinal effects. None showed a dose-related pattern suggestive of a drug effect. No TEAEs were assessed as severe by the investigators.

The changes from baseline to Week 8 in the PCIs for lab, ECG, and vitals signs do not appear to be clinically significant. There were small, but significant increases in mean weight and mean height in all dose groups during the treatment period of the trial; the z-scores indicated that there was no significant change in the rate of growth.

CONCLUSIONS

The data supports use of pantoprazole for the short-term treatment of EE in pediatric patients age 1 to 5 years old based on the clinical outcome trial and safety data reported. (b) (4)

9.4.3 Trial 3001A1-322-US: Ages 5 to 11 year – Clinical Outcome and Safety

A. General Design and Objective

Trial 3001A1-322-US (Trial 322) is a Phase 3, multi-center, out-patient, randomized, double-blind trial of the safety, tolerability, and clinical outcomes of multiple doses (10, 20, and 40 mg) of oral pantoprazole in children (5 to 11 yrs old) with endoscopically proven GERD.

All trials were completed in the US, 12 centers participated. The trial period was from Dec 2, 2002, through Dec 23, 2003. A total of 52 patients completed the trial.

B. Background

As stated in the Written Request for Pediatric trials with pantoprazole sodium (originally issued on Dec 31, 2001, amended on Dec 18, 2002; Jul 28, 2003; May 7, 2004; and 15 May 2006), the objectives for Trial 4 in children, aged 1-11 years, included:

1. To characterize the pharmacokinetic (PK) profile of single and repeated doses of pantoprazole sodium in patients 1 to 11 years of age.
2. To compare the safety and clinical outcome of pediatric patients 1 to 11 years of age with endoscopically proven GERD across different dosages of pantoprazole sodium.
3. To determine the proportion of patients showing endoscopic evidence of healing after completion of therapy across different dosages of pantoprazole sodium in those pediatric patients 1 to 11 years of age who undergo follow-up endoscopy after treatment.

To satisfy objectives 2 and 3, Wyeth conducted two safety and effectiveness trials (322 and 328) to evaluate the clinical outcome of different dosages of pantoprazole sodium in pediatric patients aged 1 to 11 years with endoscopically proven GERD. Trial 322 was designed to evaluate the safety and clinical outcomes of treatment with oral pantoprazole (10, 20, and 40 mg) in pediatric patients (5 to 11 years old) with symptomatic GERD. For the Written Request, all patients were required to have endoscopically proven GERD.

To fulfill objective 1, Wyeth conducted five pharmacokinetic trials (3001A1-109-US, 3001K1-110-US, 3001K1-117-US, 3001A1-337-US and 3001B3-334-US) to evaluate the pharmacokinetic profile of single and repeated doses of pantoprazole sodium. Dosages (pantoprazole 10 mg, 20 mg, and 40 mg) for each patient were selected because the Applicant felt these dosages were most likely to be therapeutically effective and safe based on pediatric and adult PK data. In a phase 1 pediatric trial (3001A1-109-US), the PK and safety profile of a single oral dose of pantoprazole tablet 20 or 40 mg were evaluated in children aged 5 to 10 years old and 11 to 16 years old who could benefit from acid-suppressive therapy. Pharmacokinetic data from 3001A1-109-US showed dose proportionality and similarity between the 5- to 10-years old and 11- to 16-years old age groups, with serum values similar to those from historical data obtained in adults. No significant association was observed between either clearance or $t_{1/2}$ and age or weight. The volume of distribution increased with age and weight.

Pharmacokinetics results were also evaluated from an open-label, single-dose, randomized, parallel group trial, 3001K1-110-US, in hospitalized patients aged 2 to 16 years who could benefit from acid suppression therapy. Patients were stratified into three groups according to age (2 to 4, 5 to 10, and 11 to 16 years) and then randomly assigned to receive one of the following treatments: 1) pantoprazole IV 0.8 mg/kg infused over 15 minutes, and 2) pantoprazole IV 1.6 mg/kg infused over 15 minutes.

The Applicant states that the PK results with IV pantoprazole, in children aged 2 to 16 years from trial 3001K1-110 showed that the dose-independent PK parameters CL and $t_{1/2}$ are similar to the historical data observed in adult subjects. Similar conclusions were obtained with the oral formulation of pantoprazole in the pediatric trial 3001A1-109. In conclusion, based on the results of trial 3001A1-109 and trial 3001K1-110, doses of pantoprazole 10 mg, 20 mg, and 40 mg were selected.

The assessment tool, GASP-Q, was tested in an unpublished field test conducted by Wyeth in 77 children aged 5 to 16 years. Of the 77 patients, 38 were 5 to 10 years old; 47 of the children were diagnosed as having GERD. Overall, the children with GERD had a mean symptom score of 69.2 (SD = 65.0; min – max = 0-233). In the 5 to 10-year-old group, 14 children without GERD had a mean CSS of 31.6 (SD=62.4) while 23 children with GERD had a mean symptom of 60.9 (SD=43.8).

Protocol Amendments

The original protocol, dated Jul 3, 2002, was amended once on Jan 17, 2003. The amendment was submitted to the FDA on Feb 21, 2003 (IND 35,441, Serial No. 349) and included the following modifications:

1. The number of potential sites increased to 25.
2. Exclusion Criterion 12 regarding the history of PPI treatment was modified to allow screening of subjects with a PPI usage three months before administration of the test article.
3. Some editorial changes not affecting the conduct of the trial were implemented.
4. It was indicated that all central lab and biopsy results should be recorded on the CRF using an electronic system.
5. The protocol's administrative sections 7 (Selection of Patients), 8 (Trial Material), and 9 (Trial Methods) were revised to include additional information regarding records and reports, publications, and subject injury.

C. Inclusion

1. Male and nonpregnant, nonlactating female patients aged 5 through 11 years.
2. Demonstrated ability to swallow a placebo tablet identical to the appearance of a pantoprazole tablet. The tablet was not to be crushed, chewed, or dissolved.
3. Pretrial symptom score of at least 16 on the GASP-Q.
4. Ability to undergo the required endoscopy with esophageal biopsies.
5. GERD confirmed by one of the following:

i. Positive endoscopic evidence of reflux-related esophagitis within two weeks of enrollment or
ii. Positive histologic evidence of esophagitis consistent with GERD within two weeks of enrollment; or
iii. Positive 24-hour esophageal pH-metry with pH < 4.0 for 6% of the total time, performed within 90 days of enrollment (the patient must not be on PPIs, H2RAs, or prokinetic agents during the pH-metry).

6. Weight and height greater than tenth percentile for the patient's age.
7. Female patients who had the onset of menses:
   i. were required to have a negative urine b-HCG test result before receiving test article;
   ii. And if sexually active, were required to use medically acceptable contraception, and were required to sign an IRB-approved child assent form, which reflected an awareness of the stipulations concerning the use of contraception in sexually active female patients and the use of medically acceptable contraception (including oral contraception, injectable or implantable methods, and intrauterine devices).

D. Exclusion

Similar to infant trial (Section 9.4.1-D).

E. Procedure

Patients received the trial drug once daily for eight weeks. Visits occurred at Weeks –2, 2, 4, 6, and 8 and telephone contacts were conducted at Weeks 1, 3, 5, and 7. The post treatment telephone contact occurred approximately two weeks after the final visit. A symptom questionnaire, GERD Assessment of Symptoms in Pediatrics Questionnaire (GASP-Q), was used to evaluate response. As a measure of patient well being, Composite Symptom Score (CSS) was determined on the basis of the frequency and severity of eight selected symptoms. Results of endoscopy with biopsy at week eight were compared with the baseline results.

During the pretrial screening period, an endoscopy was required to diagnose GERD and to rule out upper gastrointestinal pathology other than GERD. To confirm a diagnosis of GERD, each patient was to have either positive endoscopic evidence of reflux-related esophagitis within two weeks before enrollment (per modified Hetzel-Dent score ≥ grade 2 and/or presence of vertical lines) or positive histologic evidence of esophagitis consistent with GERD within two weeks before enrollment.

The modified Hetzel-Dent score was to be obtained before conducting the esophageal biopsies or passing the endoscope beyond the lower esophageal sphincter. The Hetzel-Dent score below was modified for use in children to include the *distal 15% of the esophagus* (instead of the distal five cm of the esophagus used in adults):

Grade 0: Normal mucosa
Grade 1: No macroscopic erosions but with visible erythema, hyperemia, or friability
Grade 2: Superficial erosions/ulcerations affecting < 10% of the distal 15% of the esophagus

Grade 3: Superficial erosions/ulcerations affecting 10% to 50% of the distal 15% of the esophagus
Grade 4: Deep peptic ulceration anywhere in the esophagus or confluent erosions/ ulcerations > 50% of the distal 15% of the esophagus.

Six biopsy samples were taken from the patient's esophagus:

1. Four biopsies from the distal esophagus (2 to 3 cm above the Z line; one biopsy circumferentially from each quadrant position at approximately 0°, 90°, 180°, and 270°).
2. Two biopsies from the mid-esophagus (at approximately 0°and 180°) GERD biopsies were analyzed for GERD-associated esophagitis by the central laboratory.

Basal cell height, papillary height, total mucosal height, eosinophils per HPF, and neutrophils per HPF were measured. From the biopsy data a non-erosive GERD (NERD) score was determined as follows:

Grade 1 (mild) –

1. Basal cell zone > 15% of total mucosal height, *or*
2. Papillary height > 66% of mucosal height.

Grade 2 (moderate or severe), requires at least two of the following:

1. Basal cell zone > 15% of total mucosal height;
2. Papillary height > 66% of mucosal height;
3. Five eosinophils/HPF or ≥ three neutrophils/HPF.

Grade 0 (normal esophagus): neither grade 1 or 2.

Endoscopy and biopsies were performed at the final visit (visit 6 or week 8) for all patients with pathology at baseline. Endoscopy with biopsy at the final visit (visit 6) was optional for the pHmetry patients if their baseline results were normal. If GERD was confirmed on the basis of pH-metry, then a repeat evaluation was to be performed at the final visit. However, no patients were enrolled under this criterion.

Treatments

Patients were randomly assigned to receive one of the following treatment regimens once daily for eight weeks: pantoprazole 10, 20, or 40 mg enteric-coated tablet. Each enrolled patient was to participate in the trial for approximately 12 weeks, including a two week screening period, an eight week treatment period, and a two week post treatment follow-up telephone contact. Visits occurred at weeks –2, 0, 2, 4, 6, and 8 and telephone contacts were conducted at weeks 1, 3, 5, and 7.

Table 59: Study Schedule (Trial 322)

Study Period	Prestudy Screening[a]		Treatment							Final Visit[b]	Post-treatment
Study Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**
Study Visit[c]	**V1**	**V2**		**V3**		**V4**		**V5**		**V6**	
Telephone Contact[c]			**T1**		**T2**		**T3**		**T4**		**T5**
Informed consent and assent forms	X										
"Swallow" test[d]	X										
Demography and medical history	X										
Inclusion and exclusion criteria	X										
Prior and current medications	X										
Complete physical examination		X								X	
Brief physical examination	X			X		X		X			
Symptom questionnaire (GASP-Q)[e]	X	X	X	X	X	X	X	X	X	X	X
Endoscopy and biopsies		X[f]								X	
Physician global assessment										X	
Routine laboratory evaluation	X					X				X	
Urine β-HCG for pregnancy[g]	X	X				X					
Serum β-HCG for pregnancy[g]										X	
Fasting serum gastrin level[h]	X					X				X	
12-lead ECG[h]	X									X	
Vital signs	X	X		X		X		X		X	
Record adverse events	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications		X	X	X	X	X	X	X	X	X	X
Dispense test article[i]		X				X					
Count and collect unused test article[j]				X		X		X		X	
Dispense study antacid	X	X				X					
Count and collect unused study antacid[j]		X		X		X		X		X	
WR Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**

Concomitant Medications

Trial antacid was provided during the pretrial and treatment periods for symptom relief. Patients were given Children's Mylanta Chewable Tablets (Johnson and Johnson, New Brunswick, NJ /Merck, West Point, PA; 400 mg calcium carbonate per tablet) for use after five or more minutes of GERD symptoms. All trial antacid given during the pretrial and treatment period had to be recorded on the patient's CRF, including the dose, the frequency, and the duration of treatment.

Patients continued with their usual medical therapies according to standard clinical practice unless prohibited. Continuous treatment with theophylline derivatives, carbamazepine, phenytoin, and digoxin was closely monitored throughout the trial to assure that proper serum levels of these drugs were maintained.

Prohibited Medications

Similar to infant trial (Section 9.4.1-E).

G. Endpoints

Effectiveness Measurements

The GASP-Q was used to assess each patient's physical well-being by measuring the signs and symptoms of pediatric GERD.

Primary Effectiveness Variables
The primary objective of this trial was to evaluate the clinical outcomes of treatment with oral pantoprazole (10 mg, 20 mg, and 40 mg once daily) in patients aged 5 to 11 years with symptomatic GERD.

The primary endpoint is the change in the CSS from the baseline to the final visit. The individual symptom score (ISS) and the CSS were calculated for each assessment.

Secondary Effectiveness Variables
The secondary objective of this trial was to evaluate the safety and tolerability of oral pantoprazole (10 mg, 20 mg, and 40 mg once daily) in patients aged 5 to 11 years with symptomatic GERD.

The secondary endpoints were:

i. Change in ISS from baseline at each assessment and the change in CSS from baseline at each assessment (other than the final visit, which constituted the primary endpoint).
ii. Need for trial antacids, as determined by a pill count at each visit.
iii. Physician global assessment at the final visit. The physician global assessment was performed at the final visit. The physician global assessment is a seven-point Likert scale of the overall impression of the effectiveness of the test drug.

Other endpoints:

iv. The number of times (frequency) each symptom occurred during the previous seven days, and each symptom's usual severity at each assessment.
v. Endoscopy and histologic assessment of esophageal biopsies for patients with pathology results at baseline and after treatment, when available, to determine the proportion of patients showing endoscopic evidence of healing after completion of therapy across different dosages of pantoprazole sodium in those pediatric patients 5 to 11 years of age who underwent follow-up endoscopy after treatment.
vi. Changes in growth parameters (i.e., weight and height). Each patient's weight was measured during the brief physical examination at the pretrial screening period, during the trial (at Weeks 2, 4, and 6), and at the final visit (Week 8). Each patient's height was measured at the prescreening period and at the final visit.

H. Data Analysis

Statistical Analytical Plan
The primary endpoint was the change in CSS from baseline to the final visit, whenever that occurred. It was analyzed by an analysis of covariance that included dose as factor and the baseline values of CSS, body mass index, age, and number of Children's Mylanta Chewable Tablets as covariates. If the effect of dose was significant at $p < 0.05$, then pairwise contrasts were used to further explore differences between treatment groups. The primary analysis was based on the intent-to-treat population.

A similar analysis was used for change in CSS at other assessments, as well as for changes in ISS at all assessments. The physician global assessment was analyzed with an analysis of

covariance with dose as factor, and baseline BMI and number of Children's Mylanta Chewable Tablets as covariates. The number of patients who improved in Hetzel-Dent score from screening to final visit was analyzed by Fisher's exact test. Patients with a score of 0 at screening were omitted from the analysis. Baseline biopsy scores were also broken down by whether or not the patient was taking an H2RA or a PPI. The baseline CSS was summarized by baseline NERD score and the final CSS was summarized by final NERD score. Changes from baseline in growth parameters were compared within dose groups by a paired t-test. All patients from the ITT population were included in the analyses of safety, which included adverse events, early discontinuations, vital signs, laboratory measurements, endoscopy an biopsy results. The proportion of patients who discontinued early was compared among dose groups by the Cochran-Armitage trend test. The incidence of AEs was analyzed similarly. The proportions of patients with potentially clinically important values or changes in vital signs and laboratory parameters were analyzed by the Cochran-Armitage trend test. Changes from baseline in vital signs and laboratory parameters were compared within dose groups by a paired t-test.

Esophageal biopsies were obtained at baseline and again at the final visit to evaluate the presence of mucosal disease and to determine if there had been a therapeutic response. The proportion of patients who had a baseline NERD score of 1 or 2 and then had a final score of 0 were compared among treatment groups by Fisher's exact test.

Baseline scores were also broken down by whether or not the patient was taking an H2RA or a PPI. The baseline CSS was summarized by baseline NERD score and the final CSS was summarized by final NERD score.

Determination of Sample Size

The Applicant based the sample size on regulatory and practical needs and was not by statistical power. With 16 patients per dose group, there was an approximately 80% chance that an AE with an incidence of 10% in patients receiving a particular dose could be observed. If the mean CSS was 70 in the pantoprazole 10 mg group, 45 in the pantoprazole 20 mg group, and 20 in the pantoprazole 40 mg group, then, with a standard deviation of 45, the power was 70% that a significant difference among the groups would be observed. The sample size estimates are based on a field test done by Wyeth in which patients were given the questionnaire without any treatment. Patients with GERD had a mean CSS of 69.2, while healthy children had a mean CSS of 20.1. Pantoprazole 40 mg has been shown to greatly reduce symptoms in adults, so with treatment symptoms should be similar to non-GERD patients. Pantoprazole 10 mg was significantly less effective and assumed to be similar to placebo in adults.

I. Results

Disposition of Patients

A total of 76 patients were screened to receive a daily dose of pantoprazole; 11 patients did not meet the initial entry criteria. A total of 65 patients underwent endoscopy; 5 did not meet entry criteria and 7 were excluded based on histology results (4 without GERD, and 3 with eosinophilic esophagitis). Overall, 23 patients did not meet all inclusion/exclusion criteria, including 3 patients with eosinophilic esophagitis, and were considered screen failures. Fifty-

three patients (ITT population) aged 5 to 11 years were randomly assigned to receive either pantoprazole 10 mg (n = 19), 20 mg (n = 18), or 40 mg (n = 16) once daily. Of the 53 randomly assigned patients, 4 had erosive esophagitis and 49 had non-erosive GERD. No patient was enrolled using 24-hour esophageal pH-metry diagnosis for confirmation of diagnosis. All 53 patients took at least one dose of trial drug (ITT/safety population) and 52 completed Visit 6 (end of treatment, Week 8). One patient in the 10 mg dose group withdrew after four weeks of treatment. Of the 53 ITT patients, 44 were in the VFE population: 15 in the 10 mg group, 15 in the 20 mg group, and 14 in the 40 mg pantoprazole group. See Figure 17 from the Applicant.

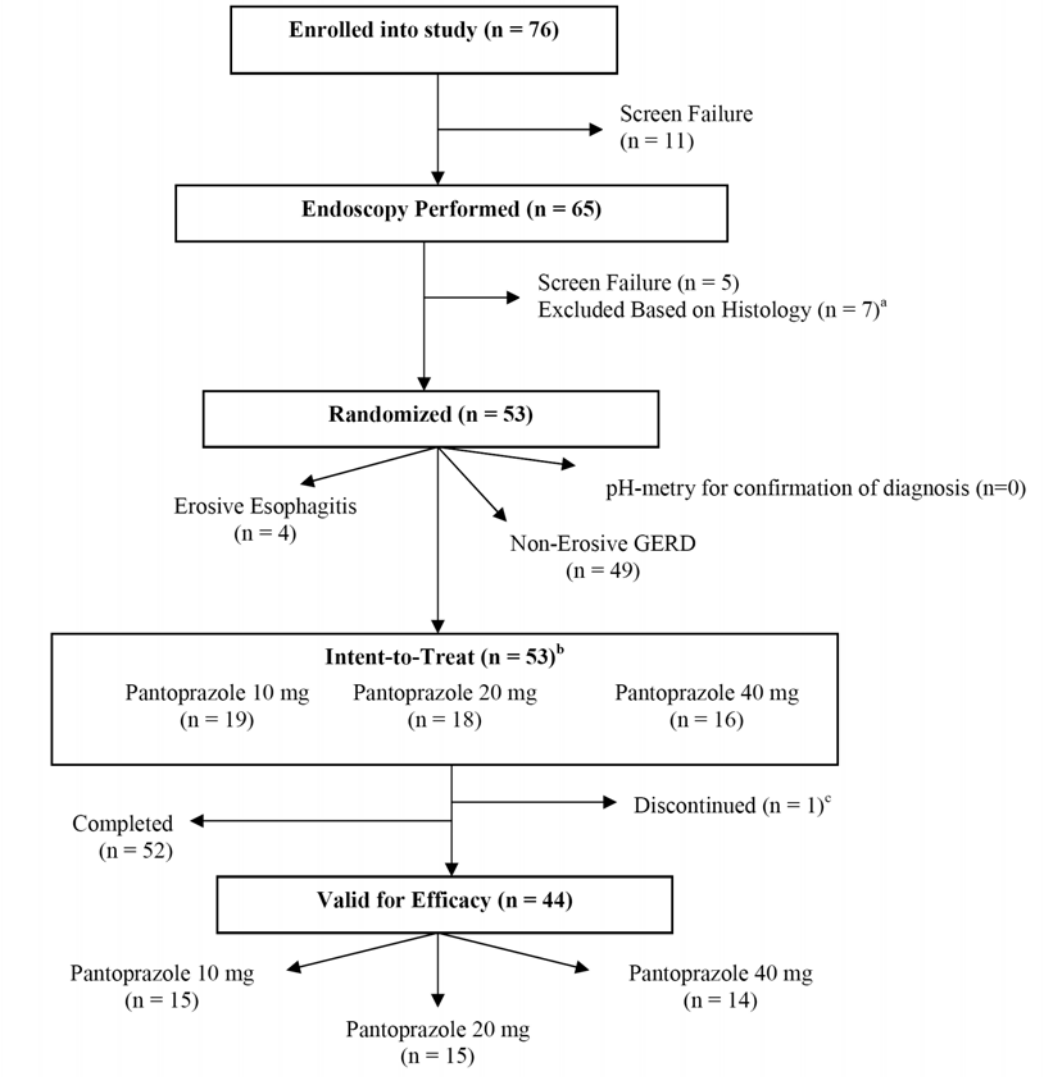


Figure 17: Patient Disposition (Trial 322)

Discontinuations

Of the 53 patients who received pantoprazole in the trial, only one (5%) withdrew from the trial. Patient 006-060 in the pantoprazole 10 mg group discontinued from the trial because the patient's mother withdrew consent because of lack of effectiveness on Day 27. The patient's

mother administered Tums (secondary reason for withdrawal) which was considered a prohibited medication; while the patient was receiving trial medication.

Compliance

The first date of trial medication was the day after Visit 2. This date was obtained from the randomization, trial test article, and antacid record of each patient CRF. The last date of trial medication was the day before the final visit (generally Visit 6=Week 8). Patient compliance with the test article regimen was assessed by an accurate count of the test article. The percentage of patient compliance was calculated from the amount of medication dispensed and the amount counted at each visit. A compliance rate ≥ 80% was expected throughout the trial.

Compliance was defined by the number of days on which a patient took trial medication divided by the duration of treatment. All 53 randomized patients took at least one dose of trial drug (ITT population), and 52 completed visit 6 (end of treatment). Of the 53 patients, five patients missed doses more than 20% of the time. The five patients (006-061, 006-063, 021-228, 022-242, and 022-244) with compliance < 80% were excluded from the VFE population. A total of 48 patients (91%) took > 80% of their daily doses of pantoprazole.

No systematic deviations in the conduct of the trial were noted. All individual violations of the protocol were evaluated by the medical monitor. Of ten patients with protocol violations, four took prohibited medications (three of which were on low dose), five missed doses more than 20% of the time, and one patient (006-061) in the pantoprazole 40 mg group took prohibited medication and missed doses of trial medication more than 30% of the time. All these patients, except 011-110 were excluded from the VFE population. No other major protocol deviations/violations occurred during this trial.

During the treatment period, a patient was able to remain in the VFE population if the patient took a prohibited medication sporadically for an AE at the discretion of medical monitor. A total of seven patients took prohibited medications during the treatment with pantoprazole. A summary of prohibited medications by dose group is given in Table 60 from the Applicant. Two of the seven patients took antacids (Tums and Alka-seltzer), three patients took an H2RA (ranitidine), one patient took Pepto-Bismol, and one patient took Mylanta during the treatment period. Six of the 7 patients (86%) taking prohibited acid reducing prohibited medications were in the 10 mg dose group.

Comment: The above pattern of protocol violations suggest that low dose pantoprazole was not helpful for a number of patients.

Table 60: Prohibited Concomitant Medications Taken (Trial 322)

Medication Classification (WHO Med Category)	Pantoprazole 10 mg (n = 19)	Pantoprazole 20 mg (n = 18)	Pantoprazole 40 mg (n = 16)	Pantoprazole Total (n = 53)
Alka-Seltzer	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)
Bismuth Subsalicylate	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)
Mylanta	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)
Ranitidine	2 (10.5)	0 (0.0)	1 (6.3)	3 (5.7)
Tums	1 (5.3)	0 (0.0)	0 (0.0)	1 (1.9)

Demographics

Demographic and other baseline characteristics of the ITT population were similar among all three treatment groups. The following table shows demographic and baseline characteristics for the 53 pediatric patients who received at least one dose of test article.

Table 61: Demographic Summary (Trial 322)

Characteristics		Pantoprazole treatment 10 mg N=19	20 mg N=18	40mg N=16
Age (years)	Mean±SD	8.5±1.7	8.2±1.5	7.6±1.9
	Min - Max	5 - 11	6 - 11	5 - 11
Age Group	Age 5	1 (5)	0	4 (25)
	Age 6 – 11 yrs	18 (95)	18 (100)	12 (75)
Sex	Female	11 (58)	14 (78)	9 (56)
	Male	8 (42)	4 (22)	7 (44)
Race	Caucasian	11 (58)	12 (67)	8 (50)
	African American	8 (42)	6 (33)	8 (50)
	Asian	0	0	0
	Other	0	0	0
Baseline Wt (kg)	Mean±SD	34.4±7.1	31.9 ±8.9	32.4±14.1
	Min - Max	22.4 – 48.9	20.4 – 48.6	18.1 – 77.3
Baseline Ht (m)	Mean±SD	1.3±0.08	1.4±0.13	1.3±0.13
	Min - Max	1.2 – 1.5	1.2 – 1.6	1.1 – 1.5
Grade of Esophagitis (Modified HD score)	Grade 0	4 (21)	6 (33)	3 (19)
	Grade 1	15 (79)	9 (50)	12 (75)
	Grade 2	0	3 (17)*	0
	Grade 3	0	0	1 (6)*
	Grade 4	0	0	0
GASP-Q CSS ≥ 16 at Visit 1		19 (100)	18 (100)	15 (94)

*EE patients

GERD Indications at Screening

All patients had positive diagnosis of GERD at baseline: including 4 (8%) patients with EE and 49 (92%) patients with non-erosive GERD (NERD). Of the patients with NERD, the majority had endoscopic evidence of erythema (80%) and a NERD score of 2 at baseline. Three (17%) patients in the 20 mg group and 1 patient (6%) in the 40 mg group had Hetzel-Dent scores of 2

and 3 at the baseline visit, respectively, consistent with EE. Fifty-two (98%) patients had GASP-Q ≥16 on their GERD assessment at Visit 2.

Concomitant Therapy/Medications

Prior medication was defined as any medication administered on a date before the first dose of pantoprazole. Post-trial medication was defined as medication administered the day after Visit 6 (Week 8). Concomitant medication was defined as medication administered during the eight weeks of treatment with pantoprazole. During treatment with pantoprazole, the majority of patients in the three dose groups received diphenhydramine, fentanyl, ibuprofen, lidocaine, midazolam, nitrous oxide, paracetamol, propofol, salbutamol, and sevoflurane, which were used for pain relief, sedation, or as anesthetic agents during the endoscopy and biopsy procedures.

EFFECTIVENESS EVALUATION

Primary Effectiveness Analysis

The primary endpoint was the change in the CSS as a measure of wellbeing from baseline to the final visit (week 8). The following table copied from the Applicant summarizes the mean CSS values at baseline and Week 8, along with the changes in the mean from baseline to the final evaluation. The mean CSS values improved significantly from baseline to the final visit both for the ITT ($p < 0.001$) and VFE ($p < 0.001$) populations in all three dose groups. No significant differences were seen in the mean CSS change from baseline among the treatment groups at Week 8 ($p > 0.05$).

Table 62: Summary of CSS for Baseline and Final Evaluation (Trial 322)

	Pantoprazole		
Population			
Visit	10 mg (N = 19)	20 mg (N = 18)	40 mg (N = 16)
Intent-to-treat			
Baseline			
n	19	18	16
Mean ± Standard deviation	129.2 ± 107.12	134.6 ± 108.19	132.4 ± (37.09
Min - Max	13 - 427	20 - 394	0 - 543
Week 8			
n	18	18	16
Mean ± Standard deviation	28.1 ± 42.90	32.6 ± 38.88	42.8 ± 68.42
Min - Max	0 - 140	0 - 116	0 - 258
Change from baseline at week 8			
Mean[a] ± Standard error	-97.33 ± 11.756	-100.06 ± 11.888	-93.31 ± 12.443
p-Value[b]	< 0.001	< 0.001	< 0.001

Endoscopy and Biopsy Data

Of the 53 patients randomized, 4 had erosive esophagitis (EE) and 49 had non-erosive GERD (NERD). Of the patients with NERD, 80% had endoscopic evidence of erythema and 65% had moderate or severe esophagitis on biopsy at baseline. After treatment, 70% of the endoscopy results were normal and 72% of the biopsy results were normal or showed mild esophagitis. The

following table from the Applicant presents the number of patients with improvement in NERD score from screening to the final visit. Most of the patients in the three treatment groups showed improvement in NERD scores. No statistically significant findings related changes in Hetzel-Dent score or NERD score were seen with change in CSS (baseline to Week 8).

Table 63: Patients with Improvement in NERD Disease Score (Trial 322)

Pantoprazole Dose Group	n/N[a] (%)	Overall p-Value[b]	vs Pan 20 mg[b]	vs Pan 40 mg[b]
10 mg	14/19 (73.7)	0.243	0.448	0.151
20 mg	9/17 (52.9)			0.722
40 mg	8/16 (50.0)			

Note: The non-erosive gastroesophageal reflux disease (NERD) score = 0 at screening was excluded.
a. n = Number of subjects whose NERD score decreased from screening to final visit (2 to 1, 2 to 0, or 1 to 0); N = Number of subjects with NERD score > 0 at screening.
b. Fisher's exact-test.

Table 64: NERD Score Outcome for All Doses (Trial 322)

NERD Score Outcome All Doses Total=49 patients		
Unchanged	Improved	Worse
14 (29%) ave. Protonix exposure=0.9 mg/kg	31 (63%) ave. Protonix exposure=0.7 mg/kg	4 (8%) ave. Protonix exposure=0.9 mg/kg

Four patients, including three patients in the 20 mg and one patient in the 40 mg dose groups, had EE and Hetzel-Dent scores ≥ grade 2 at baseline. At the end of the trial, all of these patients had a score of 0 (normal) or 1 and were considered healed. No significant differences were seen in changes among or between the treatment groups in Hetzel-Dent scores.

Table 65: Patients with EE Endoscopy Results (Trial 322)

Patient	Age (Years)	Weight (kg)	Assigned Dose	Treatment	Study Week	HD Grade
021-225	9	44	Med	20 mg (0.5 mg/kg)	Baseline	2
					Final	1
021-232	8	37	Med	20 mg (0.5 mg/kg)	Baseline	2
					Final	1
027-316	11	45	Med	20 mg (0.5 mg/kg)	Baseline	2
					Final	0
011-107	9	30	High	40 mg (0.8 mg/kg)	Baseline	3
					Final	0

Secondary Endpoints

The following secondary endpoints were evaluated and analyzed for the three treatment groups:

- Change in ISS from baseline at each assessment and the change in CSS from baseline at each assessment (other than the final visit, which constitutes the primary endpoint).
- Amount of antacid taken between visits.
- Physician global assessment at the final visit.

Individual Symptom Improvement

At the baseline visit (Week –1), the majority of patients reported abdominal pain/belly pain, burping/belching, and pain after eating. Chest pain/ heartburn was also reported in a majority of patients in the 20 mg and 40 mg groups. Of the eight symptoms, abdominal pain/belly pain, nausea, burping/belching, and pain after eating contributed the most to the overall CSS results. The number and percentage of patients with these symptoms decreased from baseline to the last visit at Week 8 after treatment with pantoprazole 10, 20, or 40 mg.

Table 66: % of Patients with Each Symptom for Baseline and Wk 8 (Trial 322)

	Pantoprazole					
	10 mg (N = 19)		20 mg (N = 18)		40 mg (N = 16)	
Symptom Visit	N[a]	n (%)[a]	N[a]	n (%)[a]	N[a]	n (%)[a]
Abdominal Pain/Belly Pain						
Baseline	19	18 (94.7)	18	17 (94.4)	16	12 (75.0)
Week 8	18	11 (61.1)	18	12 (66.7)	16	7 (43.8)
Chest Pain/Heartburn						
Baseline	19	8 (42.1)	18	10 (55.6)	16	9 (56.3)
Week 8	18	5 (27.8)	18	7 (38.9)	16	5 (31.3)
Difficulty Swallowing						
Baseline	19	8 (42.1)	18	6 (33.3)	16	4 (25.0)
Week 8	18	3 (16.7)	18	3 (16.7)	16	2 (12.5)
Nausea						
Baseline	19	15 (78.9)	18	12 (66.7)	16	7 (43.8)
Week 8	18	7 (38.9)	18	3 (16.7)	16	4 (25.0)
Vomiting/Regurgitation						
Baseline	19	8 (42.1)	18	9 (50.0)	16	7 (43.8)
Week 8	18	3 (16.7)	18	6 (33.3)	16	5 (31.3)
Burping/Belching						
Baseline	19	16 (84.2)	18	14 (77.8)	16	10 (62.5)
Week 8	18	8 (44.4)	18	6 (33.3)	16	7 (43.8)
Choking When Eating						
Baseline	19	5 (26.3)	18	2 (11.1)	16	4 (25.0)
Week 8	18	2 (11.1)	18	0 (0.0)	16	1 (6.3)
Pain After Eating						
Baseline	19	13 (68.4)	18	10 (55.6)	16	10 (62.5)
Week 8	18	5 (27.8)	18	4 (22.2)	16	2 (12.5)

ISS Improvement

For each symptom, the ISS was defined as the product of the number of times the individual symptom occurred (frequency) and the severity of that individual symptom (ranging from mild =1 to most severe = 7) in the previous seven days. Although there were some fluctuations from week to week, the mean symptom scores tended to decrease steadily over time. No clear dose response is noted, however. See Table 67 from the Applicant for details.

Table 67: ISS for GERD Assessment at Baseline and Wk 8 (Trial 322)

	Pantoprazole		
Symptom Visit	10 mg (N = 19)	20 mg (N = 18)	40 mg (N = 16)
Abdominal pain/Belly pain			
Baseline			
n	19	18	16
Mean ± Standard deviation	27.2 ± 27.02	28.8 ± 31.12	31.1 ± 45.39
Min - Max	0 - 110	0 - 105	0 - 140
Week 8			
n	18	18	16
Mean ± Standard deviation	5.9 ± 7.53	4.7 ± 5.02	11.8 ± 19.64
Min - Max	0 - 24	0 - 15	0 - 72
Change from baseline at week 8			
Mean[a] ± Standard error	-20.62 ± 2.661	-24.26 ± 2.687	-17.20 ± 2.817
p-Value[b]	<0.001	<0.001	<0.001
Chest Pain/Heartburn			
Baseline			
N	19	18	16
Mean ± Standard deviation	6.2 ± 9.81	15.7 ± 33.03	11.6 ± 15.86
Min - Max	0 - 35	0 - 140	0 - 57
Week 8			
N	18	18	16
Mean ± Standard deviation	2.9 ± 6.22	5.6 ± 14.13	2.3 ± 4.19
Min - Max	0 - 20	0 - 60	0 - 14
Change from baseline at week 8			
Mean[a] ± Standard error	-7.71 ± 2.323	-6.71 ± 2.334	-8.71 ± 2.427
p-Value[b]	0.002	0.006	<0.001
Difficulty Swallowing			
Baseline			
N	19	18	16
Mean ± Standard deviation	7.1 ± 19.26	4.8 ± 9.92	1.7 ± 4.11
Min – Max	0 - 84	0 - 36	0 - 15
Week 8			
N	18	18	16
Mean ± Standard deviation	0.9 ± 2.32	1.1 ± 3.01	1.0 ± 3.10
Min – Max	0 - 9	0 - 12	0 - 12
Change from baseline at week 8			
Mean[a] ± Standard error	-3.58 ± 0.678	-3.89 ± 0.682	-3.53 ± 0.721
p-Value[b]	<0.001	<0.001	<0.001
Nausea			
Baseline			

	Pantoprazole		
Symptom			
Visit	10 mg (N = 19)	20 mg (N = 18)	40 mg (N = 16)
N	19	18	16
Mean ± Standard deviation	24.5 ± 46.42	17.7 ± 35.40	9.8 ± 16.69
Min - Max	0 - 196	0 - 147	0 - 56
Week 8			
N	18	18	16
Mean ± Standard deviation	4.7 ± 9.06	5.8 ± 17.35	1.9 ± 5.07
Min - Max	0 - 30	0 - 70	0 - 20
Change from baseline at week 8			
Mean[a] ± Standard error	-12.46 ± 2.914	-12.78 ± 2.929	-15.79 ± 3.091
p-Value[b]	<0.001	<0.001	<0.001
Vomiting/Regurgitation			
Baseline			
N	19	18	16
Mean ± Standard deviation	8.7 ± 18.09	9.9 ± 16.57	12.8 ± 27.76
Min - Max	0 - 72	0 - 60	0 - 112
Week 8			
N	18	18	16
Mean ± Standard deviation	3.5 ± 9.82	7.2 ± 12.91	10.0 ± 27.02
Min - Max	0 - 35	0 - 40	0 - 108
Change from baseline at week 8			
Mean[a] ± Standard error	-5.12 ± 4.011	-3.10 ± 4.049	-2.76 ± 4.248
p-Value[b]	0.208	0.448	0.520
Burping/Belching			
Baseline			
N	19	18	16
Mean ± Standard deviation	37.6 ± 50.20	40.7 (39.78)	40.4 ± 76.57
Min - Max	0 - 210	0 - 140	0 - 246
Week 8			
N	18	18	16
Mean ± Standard deviation	5.6 ± 9.15	6.8 ± 14.25	9.6 ± 19.59
Min - Max	0 - 30	0 - 45	0 - 70
Change from baseline at week 8			
Mean[a] ± Standard error	-32.95 ± 2.914	-32.08 ± 2.948	-31.16 ± 3.084
p-Value[b]	<0.001	<0.001	<0.001
Choking When Eating			
Baseline			
N	19	18	16
Mean ± Standard deviation	2.1 ± 4.22	0.6 ± 2.15	1.4 ± 4.03
Min - Max	0 - 15	0 - 9	0 - 16

Time to Improvement

Overall, significant improvements in the mean CSS of GERD symptoms were seen from baseline to all visits during and after treatment with pantoprazole 20 mg and 40 mg (Table 68 from Wyeth). Significant decreases from baseline in the mean CSS of GERD symptoms were observed for all three treatment groups, starting at Week 3 and continuing to Week 10 ($p < 0.05$). These results indicate that symptoms improved faster in the 20 and 40 mg dose groups compared with the 10 mg dose group. But by end of treatment, there was similar dose response across all groups.

Table 68: CSS of GERD Assessment for Baseline and Weekly Time Points (Trial 322)

	---------- Pantoprazole ----------		
Visit[a]	10 mg (n = 19)	20 mg (n = 18)	40 mg (n = 16)
Baseline			
N	19	18	16
Mean ± Standard deviation	129.2 ± 107.12	134.6 ± 108.19	132.4 ± 37.09
Min - Max	13 - 427	20 - 394	0 - 543
Week 1			
N	19	18	16
Mean ± Standard deviation	101.0 ± 80.15)	77.4 ± 91.44)	48.0 ± 45.80
Min - Max	6 - 260	0 - 294	0 - 151
Change from baseline at week 1			
Mean[b] ± Standard error	-25.55 ± 17.858	-57.37 ± 18.469	-87.37 ± 19.409
p-Value[c]	0.159	0.003	< 0.001
Week 2			
N	19	18	16
Mean ± Standard deviation	101.7 ± 173.04	60.4 ± 66.21	48.8 ± 52.60
Min - Max	6 - 775	3 - 274	0 - 198
Change from baseline at week 2			
Mean[b] ± Standard error	-32.20 ± 27.666	-70.03 ± 28.613	-82.73 ± 30.070
p-Value[c]	0.251	0.018	0.008
Week 3			
N	19	18	16
Mean ± Standard deviation	52.1 ± 60.87	56.9 ± 60.53	34.6 ± 36.94
Min - Max	0 - 207	0 - 187	0 - 117
Change from baseline at week 3			
Mean[b] ± Standard error	-77.83 ± 12.808	-73.02 ± 13.247	-102.24 ± 13.921
p-Value[c]	< 0.001	< 0.001	< 0.001
Week 4			
N	19	18	16
Mean ± Standard deviation	79.7 ± 127.90	50.6 ± 62.03	33.6 ± 44.16
Min - Max	0 - 574	2 - 257	0 - 158
Change from baseline at week 4			
Mean[b] ± Standard error	-51.34 ± 21.558	-83.72 ± 22.297	-96.92 ± 23.432
p-Value[c]	0.021	< 0.001	< 0.001
Week 5			
N	18	18	16
Mean ± Standard deviation	51.4 ± 64.78	44.7 ± 43.16	38.6 ± 55.49

	Pantoprazole		
Visit[a]	10 mg (n = 19)	20 mg (n = 18)	40 mg (n = 16)
Min - Max	0 - 258	0 - 147	0 - 172
Change from baseline at week 5			
Mean[b] ± Standard error	-75.78 ± 13.140	-86.28 ± 13.287	-97.31 ± 13.909
p-Value[c]	< 0.001	< 0.001	< 0.001
Week 6			
n	18	18	15
Mean ± Standard deviation	39.3 ± 35.49	37.6 ± 36.55	37.5 ± 53.09
Min - Max	1 - 106	0 - 130	0 - 165
Change from baseline at week 6			
Mean[b] ± Standard error	-86.61 ± 9.586	-88.94 ± 9.726	-94.21 ± 10.456
p-Value[c]	< 0.001	< 0.001	< 0.001
Week 7			
n	18	18	15
Mean ± Standard deviation	34.1 ± 47.59	40.9 ± 48.12	28.1 ± 45.11
Min - Max	0 - 175	0 - 161	0 - 165
Change from baseline at week 7			
Mean[b] ± Standard error	-84.46 ± 11.264	-87.57 ± 11.438	-94.11 ± 12.414
p-Value[c]	< 0.001	< 0.001	< 0.001
Week 10			
n	18	17	15
Mean ± Standard deviation	35.7 ± 44.79	20.4 ± 29.73	29.3 ± 44.0
Min - Max	0 - 126	0 - 121	0 - 143
Change from baseline at week 10			
Mean[b] ± Standard error	-89.42 ± 9.577	-111.35 ± 10.022	-99.30 ± 10.458
p-Value[c]	< 0.001	< 0.001	< 0.001

Use of Antacid

A total of 24 Mylanta tablets were dispensed to each patient for a two-week period. Patients in 20 mg and 40 mg groups used slightly fewer Mylanta tablets at Weeks 7 to 8 than they had at baseline. However, there was no change in antacid use in the 10 mg group.
Comment: This information combined with the fact that three patients had protocol violations of using prohibited antacid medications in the 10 mg dose group suggest that this dose is not effective for symptom improvement of GERD.

Physician Global Assessment at the Final Visit

Pantoprazole effectiveness was evaluated by the investigators at the end of treatment. In the opinion of the investigators, a majority of patients in the pantoprazole 10 mg (58%) and 40 mg (56%) groups had improved greatly at the end of treatment. Eight (44%) patients in the 20 mg group showed improvement in their GERD symptoms at the end of treatment. None of the patients in this trial worsened. Similar results were obtained for the VFE population. In the opinion of the investigators, the patients had significant disease improvement at the end of therapy within all three dose groups of pantoprazole ($p < 0.001$), although no significant difference was seen among the dose groups ($p > 0.433$).

Other Effectiveness Endpoints

Frequency of symptoms

The number of times that each individual symptom occurred (frequency) and the severity of that individual symptom (ranging from mild = 1 to most severe = 7) were evaluated before the baseline visit and in the week before the patient's last visit. In general, the incidence of each symptom decreased from the baseline to the last visit.

Effectiveness Conclusions

Analysis of the trial report indicates that pantoprazole 10 mg, 20 mg, and 40 mg all improved GERD symptoms in patients aged 5 to 11 years, although there is no comparator arm such as active or placebo-control. The time to symptom resolution and rates of symptom response was significantly better at Week 1 in the 20 mg and 40 mg group compared with 10 mg group, although by Week 3 there was significant improvement in symptom resolution in all dose groups. The only patient who discontinued treatment because of lack of effectiveness was in the 10 mg dose group. In addition, 6 of the 7 (87%) of patients taking prohibited acid reducing medications were in the 10 mg group. All four patients with EE were healed by the end of the trial as shown by the Hetzel-Dent score. In conclusion, the data supports extrapolation of efficacy from the adult population to pediatric patients ages 5 to 11 years.

SAFETY EVALUATION

Exposure

All 53 patients received pantoprazole for ≥ 21 days. Only patient 006-060 in the pantoprazole 10 mg group discontinued from trial because of lack of effectiveness on Day 27. All other patients completed eight weeks of treatment with pantoprazole; 34 (65%) of these patients received trial medication.

Of the 19 patients who were randomized to the 10 mg dose group, all received about 0.3 mg/kg pantoprazole. Of the 18 patients who were randomized to the 20 mg dose group, 15 (83%) received about 0.6 to 0.9 mg/kg pantoprazole and three patients received about 0.3 mg/kg pantoprazole. Of the 16 patients who were originally assigned to the 40 mg dose group, 13 (81%) received about 1.2 mg/kg pantoprazole or more and three received about 0.6 to 0.9 mg/kg pantoprazole.

Serious Adverse Events

No deaths or other serious adverse events occurred during this trial.

Adverse Events

A total of 48 patients (91%) reported one or more AEs, including 17 patients (90%) in the 10 mg group, 16 patients (89%) in the 20 mg group, and 15 patients (91%) in the 40 mg group. The incidence of AEs was similar among the treatment groups (p = 0.639). An AE was considered a TEAE if (1) it was not present at baseline and was not a chronic condition that was part of the patient's medical history, or (2) it was present at baseline or as part of the subject's medical history but the severity or frequency increased during treatment. TEAEs were reported by 48

(91%) patients treated with pantoprazole: 17 (90%) in the 10 mg group, 16 (89%) in the 20 mg group, and 15 (91%) in the 40 mg group; the differences among the different dose groups were not statistically significant.

The most common TEAEs in the pantoprazole 10 mg group were headache (7; 37%), rhinitis (5; 26%), accidental injury and infection (4 each; 21%), and nausea (3; 16%). The most common TEAEs in the pantoprazole 20 mg group were headache (5; 28%), infection and rhinitis (3 each; 17%). The most common TEAEs in the pantoprazole 40 mg group were headache (4; 25%), accidental injury (5; 31%), abdominal pain, infection, asthma, and pharyngitis (3 each; 19%).

The majority of TEAEs were mild or moderate and considered by the investigator to be unrelated to the trial medication. There were four patients total (21%) in the 10 mg group reported TEAEs including headache (3; 16%), nausea (1; 5%), and urinary incontinence (1; 5%) that were considered to be related to the trial drug. There were also four (22%) patients in the 20 mg group that reported TEAEs including abdominal pain (1; 6%), increased appetite (1; 6%), nausea (1; 6%), dizziness (1; 6%), and insomnia (1; 6%). There was one patient (6%) with headache in the 40 mg group that was considered to be related to the trial medication.

Overall, in the total population, the most frequent TEAEs were headache, accidental injury, infection, and rhinitis. The frequency of the occurrence of TEAEs did not increase with increasing dose. Incidence rates of AEs for patients treated with pantoprazole were not significantly different among the different dose groups. The trends seen for the incidence of AEs in this trial are similar to those seen in the approved package insert for pantoprazole with the exception of accidental injury, which is likely more common in the pediatric population as compared to adults.

Table 69: TEAEs Reported (Trial 322)

Body System		Panto 10mg N= 19	Panto 20mg N=18	Panto 40mg N=16
Any AE		17 (90%)	16 (89%)	15 (94%)
Body as Whole	Total	16 (84)	12 (67)	11 (69)
	Abd pain	2 (11)	2 (11)	3 (19)
	Abscess	2 (11)	0	0
	Accidental Injury	4 (21)	4 (22)	5 (31)
	Asthenia	1 (5)	1 (6)	0
	Back pain	0	2 (11)	0
	Cellulitis	1 (5)	0	0
	Chest pain	1 (5)	0	0
	Fever	1 (5)	1 (6)	2 (13)
	Flu syndrome	1 (5)	0	0
	Headache	7 (37)	5 (28)	5 (31)
	Infection	4 (21)	3 (17)	3 (19)
	Neoplasm	1 (5)	0	0
	Pain	3 (16)	1 (6)	1 (6)
CV System	Total	1 (5)	1 (6)	0
	Hemorrhage	1 (5)	1 (6)	0
Digestive	Total	8 (42)	6 (33)	6 (38)

Body System		Panto 10mg N= 19	Panto 20mg N=18	Panto 40mg N=16
System	Diarrhea	2 (11)	1 (6)	1 (6)
	Dyspepsia	2 (11)	0	0
	Gastroenteritis	0	1 (6)	1 (6)
	Increased appetite	0	1 (6)	0
	Nausea	4 (21)	2 (11)	1 (6)
	Tooth caries	1 (5)	0	0
	Tooth disorder	0	0	1 (6)
	Tooth malformation	0	1 (6)	0
	Ulcerative stomatitis	1 (5)	0	0
	Vomiting	3 (16)	3 (17)	2 (13)
Hemic and Lymphatic System	Total	0	2 (11)	1 (6)
	Echhymosis	0	2 (11)	1 (6)
Metabolic & Nutritional	Total	1 (5)	0	0
	Hyperlipidemia	1 (5)	0	0
Musculo-Skeletal System	Total	1 (5)	1 (6)	1 (6)
	Arthralgia	1 (5)	1 (6)	0
	Bone Pain	0	0	1 (6)
Nervous System	Total	2 (11)	3 (17)	2 (13)
	Agitation	0	0	1 (6)
	Anxiety	1 (5)	0	0
	Dizziness	1 (5)	2 (11)	0
	Hypertonia	0	0	1 (6)
	Insomnia	0	1 (6)	0
	Nervousness	1 (5)	0	0
	Vertigo	1 (5)	0	0
Respiratory System	Total	12 (63)	8 (44)	8 (50)
	Asthma	1 (5)	0	3 (19)
	Bronchitis	0	1 (6)	0
	Cough inc	1 (5)	3 (17)	0
	Dyspnea	1 (5)	0	0
	Pharyngitis	4 (21)	0	4 (25)
	Pulm physical finding	1 (5)	0	0
	Rhinitis	5 (26)	3 (17)	1 (6)
	Sinusitis	1 (5)	2 (11)	0
	URI	0	2 (11)	1 (6)
Skin	Total	2 (11)	2 (11)	2 (13)
	Contact Dermatitis	0	0	1 (6)
	Eczema	0	0	1 (6)
	Fungal Dermatitis	1 (5)	0	0
	HSV	0	1 (6)	0
	Miliaria	1 (5)	0	0
	Rash	1 (5)	1 (6)	0
	Skin Ulcer	0	0	0
Special Senses	Total	4 (21)	4 (22)	1 (6)
	Ear Disorder	1 (5)	1 (6)	1 (6)
	Ear pain	2 (11)	1 (6)	0
	Lacrimation d/o	1 (5)	1 (6)	0
	Otitis Media	0	1 (6)	0

Body System		Panto 10mg N= 19	Panto 20mg N=18	Panto 40mg N=16
Urogenital	Total	2 (11)	2 (11)	0
	Urinary incontinence	1 (5)	0	0
	UTI	0	2 (11)	0
	Urine abn	1 (5)	0	0
	Vulvovaginitis	0	1 (6)	0
AE assoc with misc factors	Total	1 (5)	1 (6)	1 (6)
	Local rxn to procedure	1 (5)	0	0
	Surgical procedure	0	1 (6)	1 (6)

Safety Related Discontinuations

None

Other Clinically Important Adverse Events

All laboratory data were examined to identify individual subjects who had findings of potential clinical importance (PCI). Individual results were examined if the values were outside the PCI criteria delineated in Table 70 at any time other than the pretreatment baseline visit.

Table 70: PCI Criteria

Test	Criteria
Hematology	
Hemoglobin	Decrease of ≥ 20 g/L
Hematocrit	Decrease of ≥ 0.05 L/L
White Blood Cell count	Increase or decrease of ≥ 2.0 x 10^9/L and ONR
Platelet count	Increase ≥20% above baseline value and abnormally high or decrease of ≥20% below baseline value and abnormally low
Blood Chemistry	
Sodium, Chloride	Increase or decrease of ≥5.0 mmol/L and ONR
Potassium	Increase or decrease of ≥0.5 mmol/L and ONR
Calcium	Increase or decrease of ≥0.499 mmol/L and ONR
Carbon dioxide	Increase of ≥4.0 mmol/L and ONR
BUN, Creatinine, Total bilirubin	≥1.5 x ULN
ALT/SGPT, AST/SGOT, Alkaline phosphatase	≥3 x ULN
Glucose	≥9.9918 mmol/L or <2.7755 mmol/L
Uric acid	Increase of ≥ 0.177 mmol/L and ONR
Total protein	Decrease or increase of ≥10 g/L and ONR
Albumin	Decrease of ≥ 10 g/L and ONR
Urinalysis	
Acetone/ketones, Protein/albumin, Glucose/sugar, Hemoglobin/blood	Any value not negative

Notable differences were seen among the groups in the total number of patients with PCI laboratory test results. A higher number of patients (6 of 16; 38%) in pantoprazole 40 mg group

had PCI laboratory values compared with the patients in 20 mg (3 of 18; 17%) or 10 mg (1 of 19; 5%) groups. However, the range of reported abnormalities was very low and no patients were withdrawn from the trial because of abnormal laboratory test results. For each patient with laboratory test results identified as PCI, the WR medical monitor reviewed the data and pertinent sections of the CRF adverse event record and determined that none of the abnormal laboratory values were reported to be of clinical importance.

Table 71: Patients with PCI Lab Results (Trial 322)

	Pantoprazole			
Category				
Values	10 mg (N = 19)	20 mg (N = 18)	40 mg (N = 16)	
Increase/Decrease	n/N (%)[a]	n/N (%)[a]	n/N (%)[a]	p-Value[b]
Total	1/19 (5.3)	3/18 (16.7)	6/16 (37.5)	0.014
Increase	1/19 (5.3)	2/18 (11.1)	4/16 (25.0)	
Decrease	0/19 (0.0)	2/18 (11.1)	2/16 (12.5)	
Hematology				
Hematocrit	0/18 (0.0)	1/17 (5.9)	1/16 (6.3)	0.398
Increase	0/18 (0.0)	0/17 (0.0)	0/16 (0.0)	
Decrease	0/18 (0.0)	1/17 (5.9)	1/16 (6.3)	
White blood cell	0/18 (0.0)	2/17 (11.8)	2/16 (12.5)	0.222
Increase	0/18 (0.0)	1/17 (5.9)	1/16 (6.3)	
Decrease	0/18 (0.0)	1/17 (5.9)	1/16 (6.3)	
Platelet count	0/18 (0.0)	1/17 (5.9)	0/16 (0.0)	0.823
Increase	0/18 (0.0)	1/17 (5.9)	0/16 (0.0)	
Decrease	0/18 (0.0)	0/17 (0.0)	0/16 (0.0)	
Blood Chemistry				
Chloride	0/19 (0.0)	0/18 (0.0)	1/16 (6.3)	0.149
Increase	0/19 (0.0)	0/18 (0.0)	1/16 (6.3)	
Decrease	0/19 (0.0)	0/18 (0.0)	0/16 (0.0)	
Uric Acid	1/19 (5.3)	1/18 (5.6)	2/16 (12.5)	0.392
Increase	1/19 (5.3)	1/18 (5.6)	2/16 (12.5)	
Decrease	0/19 (0.0)	0/18 (0.0)	0/16 (0.0)	

Table 72: Comparison of Statistically Significant Mean Changes from Baseline (Trial 322)

10 mg	20 mg	40 mg
Alk Phos @ Wk 4 (21.7±28.6 U/L, p=0.005) Bili @ Wk 8 (-1.3±2.3µmol/L, p=0.03) Blood glucose @ Wk 4 (-0.2±mmol/L, p=0.02) BUN @ Wk 8 (-0.6±mmol/L, p=0.04) Cholesterol @ Wk 4 (0.2±0.4 mmol/L, p=0.33)	Serum Gastrin @ Wk 4, 8 (52±80 ng/L, p=0.02), (21±34 ng/L, p=0.02)	Albumin @ Wk 4 (1.9±2.7 g/L, p=0.01) BUN @ Wk 4 (1±0.9 mmol/L, p=0.001) Calcium @ Wk 4 (0.1±mmol/L, p=0.02) Gastrin @ Wk 4, 8 (36.3±66.2 ng/L, p=0.04) (26.3±47.1 ng/L, p=0.04) PTT @ Wk 8

10 mg	20 mg	40 mg
Triglyceride @ Wk 4 (-0.3±0.6 mmol/L, p=0.04) Uric Acid @ Wk 4, 8 (-17.3±27µmol/L, p=0.02) UA Spec Grav @ Wk 4 (1±0.01, p=0.03)		(-0.7±2.5 sec, p=0.05) Total Protein @ Wk 4 (3.2±5.6, p=0.04)

Comment: All lab values that were noted as PCI abnormal above only at Week 4 normalized by Week 8. The Week 8 bilirubin mean level was lower on therapy than compared to baseline. There do not appear to be any clinically significant laboratory abnormalities.

Vital Signs

The criteria for determining PCI changes in vital signs are shown in Table 10.5.1-1. The changes refer to comparisons with pretrial values.

Table 73: PCI Criteria for Vital Signs

Variable	Criteria[a]
Pulse rate	Increase of ≥ 15 beats/min to ≥ 120 beats/min or decrease of ≥ 15 beats/min to ≤ 50 beats/min
Systolic BP	Increase of ≥20 mm Hg to ≥ 180 mm Hg or decrease of ≥ 20 mm Hg to ≤ 90 mm Hg
Diastolic BP	Increase of ≥ 15 mm Hg to ≥ 105 mm Hg or decrease of ≥ 15 mm Hg to ≤ 50 mm Hg
Temperature	≥ 101°F and a change from baseline of ≥ 2°F
Weight	Change of ≥ 7% in body weight

Information on the seven patients identified as having PCI changes in weight was examined by the medical monitor. The Applicant speculates that the weight gain observed in the 6 (11%) patients may have been due to increased food intake that resulted from the improved symptoms. This is an optimistic interpretation by Wyeth, I am unable to evaluate the conclusion given the limited information available.

No significant differences were observed in vital signs among the treatment groups. The vital sign results for individual patients with potentially clinical important changes were examined over time and for possible other etiologies related to these elevations. The changes were not considered to be of clinical significance. In addition, the elevations were not statistically significant among the treatment groups weight, temperature, systolic and diastolic blood pressure, and pulse.

Electrocardiograms

Patients with ECG findings of PCI were identified and were evaluated by the medical monitor. One patient (023-0256) in the 40 mg dose group had an abnormal mild intraventricular delay at Visit 8 which was considered to be a PCI. The patient's ECG was normal otherwise and reviewed by the medical monitor indicated that the mild intraventricular delay not to be of actual clinical significance. No abnormal QTc changes were reported.

Growth Parameter Analyses

BMI and Height: BMI and height values were measured at the pretrial screening period (visit 2) and at the final visit of the treatment period (Week 8). There was significant height increase seen in the 10 mg and 40 mg treatment groups for height. For the mean height z-scores calculated there were no significant changes were seen in any treatment group. There was no significant changes from baseline to the end of treatment were seen in any treatment group in BMI Z-score.

Weight: Each patient's weight was measured during the pretrial screening period, during the trial (Weeks 2, 4, and 6), and at the final visit (Week 8), and mean weight z-scores were calculated.

Statistically significant increases from baseline were noted in mean values for weight and height at Week 8 in the pantoprazole 10 mg and 40 mg dose groups ($p < 0.04$). The patients in the 20 mg group had a significant mean increase in weight at Week 8 ($p = 0.02$). Small increases in weight and height would be expected in growing children aged 5 to 11 years of age. It is likely that increases in weight and height were related to the expected growth in these children. The Applicant states that in addition, it is possible that improvements in GI symptoms could be associated with increased food intake. Longer term data with more patients would be required to make such an association.

Comment: Overall, short term treatment on pantoprazole does not appear to negatively impact the growth parameters measured.

Safety Conclusions

No deaths, SAEs, or discontinuations due to AE were reported in this trial. The incidence of AEs reported in this trial are similar to those reported in the current package insert for pantoprazole. The incidence of AEs was similar among the treatment groups ($p = 0.639$), and no concerning signal of dose response was noted. The most frequent AE for all treatment groups was headaches. There does not appear to be negative impact of short term drug treatment on growth parameters.

CONCLUSIONS

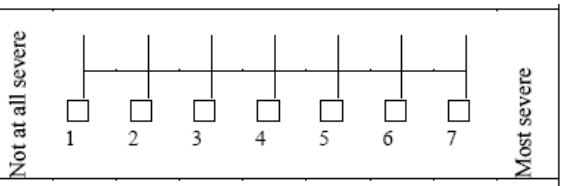
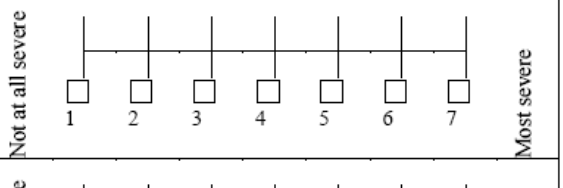
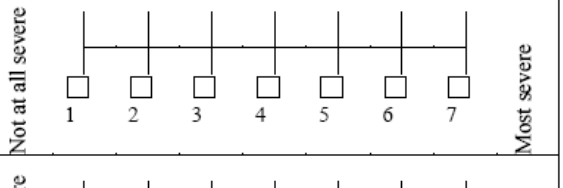
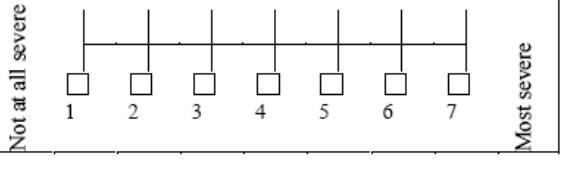
For the patient population ages 5 to 11 years, a pantoprazole dose of 20 mg or 40 mg appears to have acceptable safety profile and to support effectiveness in the short-term treatment of EE.

(b) (4)

Pantoprazole GERD Assessment of Symptoms in Pediatrics Questionnaire (GASP-Q)

SYMPTOMS	QUESTION A How many times did each symptom occur in the past 7 days? *(such as 0, 1, 2, 3, etc)*	QUESTION B On a scale of 1 to 7 how severe was the symptom usually? 1 = Not at all severe 7 = Most severe *(leave question B blank if your answer to question A is "0")*
ABDOMINAL PAIN / BELLY PAIN *it hurts, aches or burns in the middle of your belly but not in your chest.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe
CHEST PAIN / HEARTBURN *it hurts, aches or burns in the middle of your chest behind your breast bone but not in your belly.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe
DIFFICULTY SWALLOWING *foods or liquids feel like they are getting stuck and you have to swallow many times or drink more liquids to "unstick" them.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe
NAUSEA *feeling sick to your stomach or that you may throw-up.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe

Pantoprazole GERD Assessment of Symptoms in Pediatrics Questionnaire (GASP-Q) (continued)

VOMITING / REGURGITATION *throwing up or having food come up into your mouth and swallowing it.*	____ Times in the past 7 days	
BURPING / BELCHING *air coming up from your stomach and out of your mouth.*	____ Times in the past 7 days	
CHOKING WHEN EATING *coughing when you are swallowing foods or liquids.*	____ Times in the past 7 days	
PAIN AFTER EATING *it hurts, aches or burns in the middle of your belly but not in your chest after you eat.*	____ Times in the past 7 days	

9.4.4 Trial 3001A1-326-US: Ages 12 to 16 year – Clinical Outcome and Safety

A. General Design and Objective

Trial 3001A1-326-US (Trial 326) is a Phase 3, multicenter, out-patient, randomized, double-blind, parallel treatment group trial of the safety, tolerability, and clinical outcomes of two doses (20 and 40 mg) of oral pantoprazole in children (12 to 16 yrs old) with symptomatic GERD. Patients received the trial drug once daily for eight weeks. Safety assessments were based on reports of adverse events (AEs) and results of routine physical examinations, laboratory determinations, and vital sign measurements. The GERD Assessment of Symptoms-Pediatric Questionnaire (GASP-Q) was used as a measure of patient well being to evaluate symptom response.

This trial took place between Oct 4, 2002, and Sep 30, 2004. A total of 24 of 35 sites enrolled patients. There were 159 patients who were screened and 130 patients completed the trial.

Primary Objective

The primary objective of this trial was to evaluate the safety and tolerability of oral pantoprazole (20 mg and 40 mg once daily) in patients aged 12 to 16 years with symptomatic GERD.

Secondary Objective

The secondary objective of this trial was to evaluate the clinical outcomes of treatment with oral pantoprazole (20 mg and 40 mg once daily) in patients aged 12 to 16 years with symptomatic GERD.

B. Background

As stated in the Written Request for Pediatric Trials with Pantoprazole Sodium, Trial 5 requires enrollment of patients: a) aged 12 to 16 years inclusive, b) with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Endoscopy was not required for trial entry or participation. For both sexes, outcome measures will be assessed weekly: at the clinical visits at least once every other week as well as by other appropriate means during weeks in which no clinic visit is scheduled. For example, telephone evaluations may be made to assess the incidence of adverse events, and other clinical outcomes. At least 100 patients will complete at least eight weeks of treatment. The objectives of Trial 5 are: (a) to characterize the pharmacokinetic (PK) profile of single and repeated doses of pantoprazole sodium in pediatric patients 12-16 years of age, and (b) to collect information on the safety of single and repeated doses of pantoprazole sodium in pediatric patients 12 to 16 years of age.

Protocol Amendments

Amendment 1 (submitted to IND No. 35,441 on Feb 21, 2003, Serial No. 350): The following key revisions to the protocol were made:

1. The number of sites was increased from 25 to approximately 35.

2. Exclusion criterion 11 was amended to exclude patients who had been on PPIs within three months prior to administration of test article.
3. Specified that once test article has been assigned to a patient, it must not be reassigned to another patient.
4. Added a paragraph to the AE section about the Health Outcome Assessment Survey to be administered, explaining that its purpose was to explore the patients' own perception about their quality of life.

Amendment 2 (submitted to IND No. 35,441 on Jul 3, 2003, Serial No. 364): The protocol was amended primarily to revise the exclusion criteria, as requested by correspondence from the FDA dated May 28, 2003.

1. The duration of time for pretrial PPI use was shortened to 28 days before receipt of trial drug.
2. Revised height and weight inclusion criteria to be within the 5th percentile for age.
3. Patients were excluded if they had a positive urine drug toxicology test.
4. Patients were excluded if they had a known history of life-threatening drug sensitivity.
5. Patients were excluded if they had a known history of acute life-threatening event.
6. Patients were excluded if they used special diets, or herbal or alternative medication that might affect the metabolism of the trial drug.
7. Revised the definition of evaluable patient to include patients who were withdrawn because of lack of effectiveness.

C. Inclusion

1. Male and nonpregnant, nonlactating female patients aged 12 through 16 years.
2. Demonstrated ability to swallow a placebo tablet identical in appearance to a pantoprazole tablet.
3. Pretrial CSS symptom score of at least 16 on the GERD Assessment of GASP-Q.
4. Clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD.
5. Weight and height ≥ 5th percentile for the patient's age.
6. Female patients who had had the onset of menses:
    a) Were required to have a negative urine b-HCG test result before receiving test article;
    b) And if sexually active, were required to use medically acceptable contraception, and were required to sign an IRB-approved child assent, which reflected an awareness of the stipulations concerning the use of contraception in sexually active females and the use of medically acceptable contraception (including oral contraception, injectable or implantable methods, and intrauterine devices).

D. Exclusion

Similar to infant trial (Section 9.4.1-D).

E. Treatment

Patients were randomized to receive one of the following regimens daily for eight weeks:
1. Pantoprazole 20 mg enteric-coated tablet.
2. Pantoprazole 40 mg enteric-coated tablet.

Concomitant Medications

Patients were allowed to use only the oral antacid provided for this trial (Mylanta Gelcaps). Patients continued with their usual medical therapies unless prohibited. Continuous treatment with theophylline derivatives, carbamazepine, phenytoin, and digoxin were closely monitored throughout the trial to assure that proper serum levels of these drugs were maintained.

Prohibited Medications

Similar to infant trial.

F. Safety Considerations/Monitoring

The trial schedule for this protocol was similar to those for the 1 to 11 year old patients. The following is a table with the details of the trial schedule from the Applicant's submission.

Table 74: Study Schedule (Trial 326)

Study Period	**Prestudy Screening[a]**		**Treatment**							**Final Visit[b]**	**Post-treatment**
Study Week	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**10**
Study Visit [c]	**V1**	**V2**		**V3**		**V4**		**V5**		**V6**	
Telephone Contact[c]			**T1**		**T2**		**T3**		**T4**		**T5**
Informed consent and assent	X										
"Swallow" test[d]	X										
Demography and medical history	X										
Inclusion and exclusion criteria	X										
Prior and current medications	X										
Complete physical exam		X								X	
Brief physical exam	X			X		X		X			
Symptoms questionnaire (GASP-Q)[e]	X	X	X	X	X	X	X	X	X	X	X
Physician global assessment										X	
Routine laboratory evaluation	X					X				X	
Urine drug screen	X										
Urine ß-HCG for pregnancy[f]	X	X				X					
Serum ß-HCG for pregnancy[f]										X	
Fasting serum gastrin level[g]	X					X				X	
12-lead ECG[g]	X									X	
Vital signs	X	X		X		X		X		X	
Record adverse events	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications		X	X	X	X	X	X	X	X	X	X
Dispense test article[h]		X				X					
Collect and count unused test article[i]				X		X		X		X	
Dispense study antacid	X	X				X					
Collect and count unused study antacid[i]		X		X		X		X		X	

G. Endpoints

Effectiveness Measurements
The GERD Assessment of Symptoms Pediatrics Questionnaire (GASP-Q explained in Section 6.1.4) was used to evaluate the effectiveness of pantoprazole in relieving symptoms associated with GERD. The GASP-Q assessed each patient's physical well being by measuring the signs and symptoms of pediatric GERD. The frequency and usual severity of the following GERD symptoms over the preceding seven days were assessed using the GASP-Q: abdominal pain/belly pain, chest pain/heartburn, difficulty swallowing, nausea, vomiting/regurgitation, burping/belching, choking when eating, and pain after eating.

Symptoms were assessed both individually and collectively. The Individual Symptom Score (ISS) for each symptom was defined as the product of the frequency times the severity score for a given symptom at a given assessment. The Composite Symptom Score (CSS) was calculated as the sum of all individual ISS at a given assessment. Both the ISS and the CSS were calculated for each assessment, which was weekly. To be eligible for the trial, the CSS at Visit 1 had to be at least 16. Baseline for symptom scores was the last assessment before the first dose of trial medication.

The Physician Global Assessment (PGA) is a seven-point Likert scale of the overall impression of the effectiveness of the test article at the end of treatment compared with baseline. This was performed at the final visit (Visit 6). The physician checked 1 of 7 boxes, indicating how he/she assessed the impact of pantoprazole on the patient's disease compared with baseline. Choices included the following: disease improved greatly (=1), disease improved moderately, disease improved slightly, no impact, disease worsened slightly, disease worsened moderately, or disease worsened greatly (=7).

Primary Effectiveness Variables

The primary endpoint was the change in the CSS from the baseline to the last on-treatment evaluation at Week 8. The ISS and the CSS were calculated for each assessment.

Secondary Effectiveness Variables

Other endpoints included:

1. Change in CSS from baseline to other assessments.
2. Change in ISS from baseline to each assessment.
3. Whether or not the CSS was < 16 at each assessment.
4. Time in weeks when the CSS fell below 16, the entry threshold, and stayed below 16 through week 8.
5. The number of times each symptom occurred in the 7 days prior to an assessment.
6. The severity of each symptom in the 7 days prior to an assessment.
7. Amount of antacid taken between visits.
8. Physician global assessment.

Clinical Laboratory Evaluations

A central lab was used for all required trial laboratory tests. The following parameters were obtained: CBC, comprehensive metabolic panel, urinalysis, and coagulation studies.

Vital Signs and Growth Parameters

Complete physical examinations with vital signs, growth parameters (ht and wt), and ECG were done.

H. Data Analysis

Statistical Analytical Plan

Analyses for Week 8 were based on the last on-therapy questionnaire submitted for each patient, that is, a last-observation-carried forward analysis. For time point analyses, missing data were excluded. On symptom questionnaires, if the frequency was shown to be zero, then any response for severity was ignored. If the frequency was shown to be zero but the severity was missing, the severity was assumed to be zero. If frequency was missing, but any value of severity was checked, then the frequency was assumed to be one. If frequency was not zero and was not missing but severity score was missing, then the severity score was assumed to be seven.

Determination of Sample Size

The number of patients was based on the Pediatric Written Request and practical needs and was not set by statistical power. With at least 50 patients per dose group, there was approximately an 80% chance that an AE that has an incidence of 3% in patients receiving a particular dose would be observed. Thus, the trial was not powered to be able to detect a treatment difference, rather it is a safety trial.

Analysis Populations

The safety population consisted of all patients who received any amount of trial medication. The intent-to-treat (ITT) population consisted of all patients who took any amount of pantoprazole provided for the trial, were not screen failures, and had at least one questionnaire filled out from Week 1 to 8. This was the primary analysis population. The valid-for-efficacy (VFE) population consisted of patients from the ITT population who completed eight weeks of treatment (at least 50 days), took at least 80% of scheduled trial medication, had a completed GASP-Q at Week 8, and did not violate the protocol in a major way as determined by the medical monitor.

I. Results

Disposition of Patients

A total of 159 patients were screened for this trial. Of these, 23 patients were screen failures and were not randomized to treatment. Of the remaining 136 patients, 68 patients were randomly assigned to the pantoprazole 20 mg group and 68 patients were randomly assigned to the pantoprazole 40 mg group. All 136 patients randomized to treatment received at least one dose of trial drug and completed at least one GASP-Q, and are included in the safety/ITT population.

From the ITT population, 106 patients were valid for efficacy. Per inclusion criteria (# 4), all 136 patients were enrolled with clinical diagnosis of symptomatic GERD. See Figure 18 from the Applicant for details.

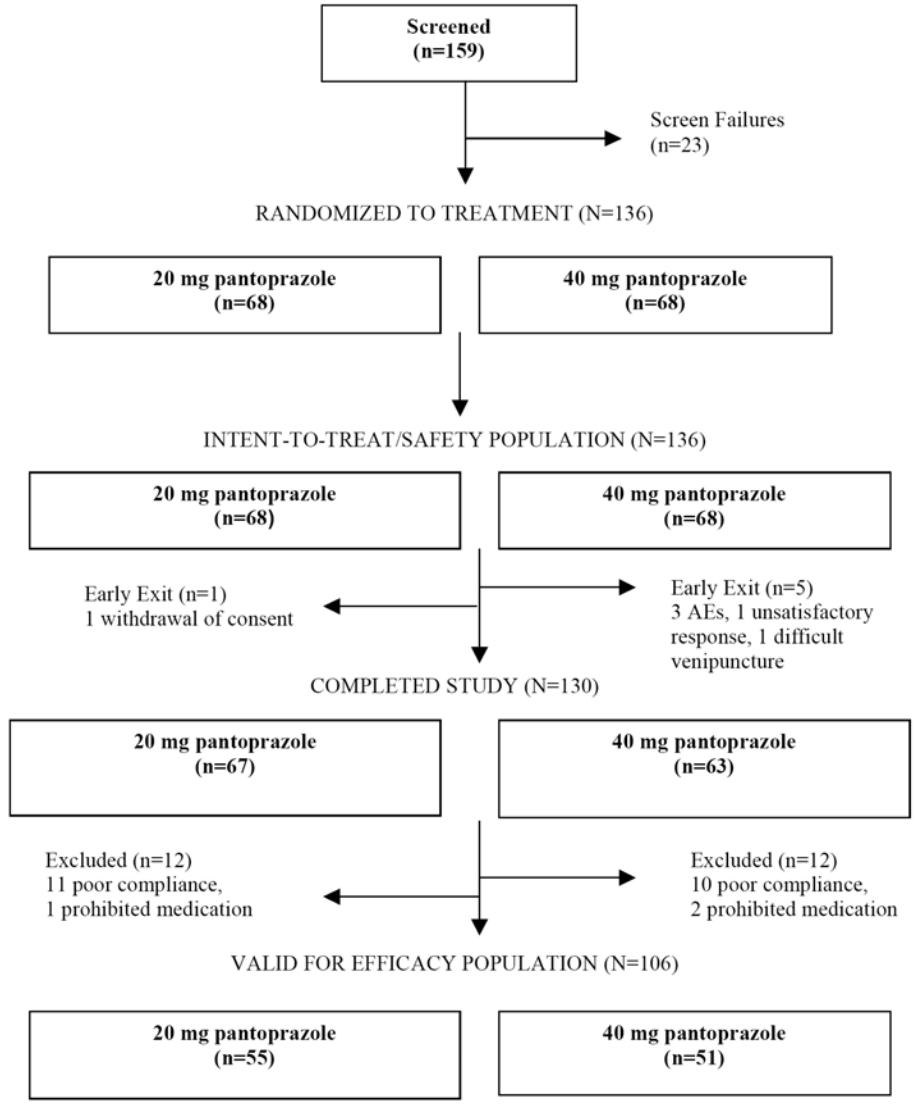


Figure 18: Disposition of Patients (Trial 326)

Discontinuations

Six patients discontinued from the trial prematurely. On the 40 mg treatment, three patients discontinued because of AE of headache (patients 326-003-057, 326-021-377, and 326-040-852). Patient 326-008-127 (40 mg) discontinued because of lack of effectiveness, Patient 326-002-028 (20 mg) discontinued by request ("tired of being in the study"), and Patient 326-024-450 (40 mg) discontinued after multiple unsuccessful attempts at venipuncture.

Table 75: Reasons for Discontinuation of Patient Participation

	Treatment on pantoprazole	
	20 mg N=68	40 mg N=68
All reasons	1 (2%)	5 (7%)
Adverse Event	0	3 (4%)
Poor Efficacy	0	1 (2%)
Patient request	1 (2%)	0
Other event		1 (2%)

Protocol Deviations

Protocol deviations were noted for the following patients who violated inclusion/exclusion criteria. Patient 326-022-401 had weight, and Patients 326-003-056 and 044-976 had height that was below the fifth percentile for their age at screening. Patient 326-031-627 was enrolled simultaneously in another trial (an NIH outcomes trial involving Flu-Mist). Since these deviations were not expected to affect the results of this trial or patient safety, exceptions were granted to enroll these patients. Other deviations from the protocol consisted mainly of prohibited concomitant medications, trial visits that occurred outside the specified time window, or laboratory specimens that were missing or could not be analyzed.

Compliance

Overall drug compliance was calculated as the number of tablets taken throughout the trial divided by 56 days. In the ITT population, mean drug compliance was 91 ± 15%, with the 20 mg group slightly higher (93± 12%) than the 40 mg group (88± 17%). In the VFE population, mean drug compliance was 95% ± 7% with no difference between dose groups. On an individual basis, compliance was calculated as the number of tablets taken divided by days on treatment. A total of 21 patients were less than 80% compliant, seven patients were less than 70% compliant.

Demographics

The majority of patients in the trial were white adolescent females. The median age of the trial population was 14 years (range 12-16 years) for both groups. The mean GASP-Q CSS score at screening was 187, and at baseline was 176. Demographic characteristics were similar between the dose groups. The most common symptom at baseline was burping/belching, with an ISS of 41.5, abdominal pain/belly pain was also common, with a baseline ISS of 32.1. Baseline symptoms were comparable between dose groups.

Table 76: Pt Demographics (Trial 326)

Characteristics		Pantoprazole treatment	
		20 mg N=68	40 mg N=68
Age (years)	Mean±SD	13.9±1.4	14.1±1.3
	Min, Max	12, 16	12, 16
Sex	Female	46 (68)	46 (68)
	Male	22 (32)	22 (32)
Race	Caucasian	53 (78)	52 (77)
	African American	8 (12)	8 (12)
	Hispanic	7 (10)	5 (7)
	Asian	0	1 (2)
	Other	0	1 (2)
Baseline Wt (kg)	Mean±SD	61.3±18.8	60.6±16.8
	Min, Max	34.1, 143.7	34, 100.9
Baseline Ht (cm)	Mean±SD	160.9±11.1	159.2±19.5
	Min, Max	109, 179	56, 185
Baseline GASP-Q CSS ≥ 16	Mean±SD	177.7±172.31	174.1±332.2
	Min, Max	12, 973	2, 2037

GERD Symptoms at Screening

Baseline symptoms at screening are comparable between treatment groups.

Table 77: Summary of Baseline Sxs (Trial 326)

	Pantoprazole						
	20 mg (N = 68)			40 mg (N = 68)			
Symptom	Freq	Severity	ISS	Freq	Severity	ISS	p value for ISS
Abdominal pain/belly pain							
N	68	57	68	68	57	68	
Mean	6.5	4.5	30.0	6.8	4.5	34.2	0.6741
Chest pain/heartburn							
N	68	47	68	68	50	68	
Mean	6.5	4.3	30.7	4.5	4.0	20.6	0.1899
Difficulty swallowing							
N	68	25	68	68	22	68	
Mean	1.9	2.9	6.7	2.8	3.5	12.8	0.3616
Nausea							
N	68	43	68	68	39	68	
Mean	3.6	3.6	15.8	4.6	4.5	24.9	0.3413
Vomiting /regurgitation							
N	68	28	68	68	31	68	
Mean	3.8	4.1	17.2	4.1	4.0	20.4	0.7868
Burping/belching							
N	68	57	68	68	54	68	
Mean	14.6	3.2	50.3	11.9	3.3	41.5	0.5374
Choking when eating							
N	68	11	68	68	8	68	
Mean	0.3	3.1	1.0	0.3	2.9	0.9	0.8434
Pain after eating							
N	68	42	68	68	39	68	
Mean	5.4	4.3	25.9	4.3	4.2	18.8	0.2576

Concomitant Therapy/Medications

Acetaminophen (59, 43%), ibuprofen (51, 38%), and albuterol (18, 13%) were the non-trial medications that were most frequently taken during the trial. Other concomitant medications were taken by at most 9 patients (7%) that included: advair, cetirizine hydrochloride, diphenhydramine hydrochloride, fluticasone, Miralax, naproxen, and pseudoephedrine hydrochloride. The treatment groups appear relatively comparable.

Effectiveness Evaluation

Primary Effectiveness Results

The primary endpoint was the change in the CSS from baseline to the last on-treatment evaluation at Week 8. For the ITT population, the CSS decreased approximately 100 points after eight weeks of treatment in both dose groups (Applicant Table 78). This was a statistically significant change indicating improvement in symptoms for each group ($p<0.001$). Results for the VFE population were comparable, with an even larger decline observed for the 40 mg VFE patients.

Table 78: Summary of CSS for Baseline and Final Evaluation (Trial 326)

	---------- Pantoprazole ----------	
Population Visit	20 mg (N = 68)	40 mg (N = 68)
Intent-to-treat		
Baseline		
N	68	68
Mean ± standard deviation	177.7 ± 172.31	174.1 ± 332.20
Min - Max	(12 - 973)	(2 - 2037)
Week 8		
N	67	63
Mean ± standard deviation	67.2 ± 108.02	58.2 ± 119.30
Min - Max	(0 - 600)	(0 - 854)
Change from baseline at week 8		
Mean[a] ± standard error	-103.03 ± 11.300	-110.91 ± 11.664
p-Value[b]	<0.001	<0.001
Valid for efficacy		
Baseline		
N	55	51
Mean ± standard deviation	177.7 ± 181.89	185.2 ± 372.64
Min - Max	(12 - 973)	(2 - 2037)
Week 8		
N	55	51
Mean ± standard deviation	71.3 ± 114.13	57.4 ± 123.79
Min - Max	(0 - 600)	(0 - 854)
Change from baseline at week 8		
Mean[a] ± standard error	-104.54 ± 12.528	-121.65 ± 13.025
p-Value[b]	<0.001	<0.001

Secondary Effectiveness Endpoints

The GASP-Q was administered weekly during the trial, either in person or by telephone. The following secondary endpoints on the GASP-Q were analyzed:

- CSS: change from baseline each week
- CSS < 16 at each assessment.
- ISS: symptom frequency, severity, change from baseline to each assessment.

In addition to the GASP-Q, other secondary endpoints included the following:

- Amount of antacid taken between visits.
- Physician global assessment.

Change in CSS by Trial Week

A steady decline in mean CSS was observed in the ITT population throughout the course of this trial. A lower CSS was observed as early as Week 1. Results for the VFE population were comparable with the ITT population.

The number of patients with a CSS below the entry criteria (less than 16) increased in both dose groups as the trial progressed. More patients in the 40 mg group achieved CSS below entry threshold at Week 1 (p = 0.048) and Week 6 (p =0.041) but not at Week 8 (p = 1.00).

Table 79: % of Patients with CSS < 16 (Trial 326)

	Pantoprazole		
Week	20 mg (N = 68) n/N (%)	40 mg (N = 68) n/N (%)	p-Value
Screening	0/68 (0.0)	0/68 (0.0)	-
Baseline	2/68 (2.9)	3/68 (4.4)	1.000
Week 1	8/68 (11.8)	17/67 (25.4)	0.048
Week 2	11/68 (16.2)	13/68 (19.1)	0.822
Week 3	18/68 (26.5)	22/66 (33.3)	0.452
Week 4	19/68 (27.9)	18/63 (28.6)	1.000
Week 5	24/68 (35.3)	24/63 (38.1)	0.856
Week 6	17/68 (25.0)	27/63 (42.9)	0.041
Week 7	27/68 (39.7)	31/63 (49.2)	0.295
Week 8	31/67 (46.3)	29/63 (46.0)	1.000
Week 10	26/67 (38.8)	23/66 (34.8)	0.720

Individual Symptoms Assessed on the GASP-Q

The number of patients reporting each symptom decreased from baseline to Week 8 in the ITT population in both dose groups. The most common symptoms were abdominal pain/belly pain and burping/belching, reported by approximately 80% of patients in both treatment groups at baseline. At Week 8 these symptoms were reported by approximately 50% of patients.

Difficulty swallowing showed the largest improvement, being reported by approximately 35% of patients at baseline and 10% of patients at Week 8.

In addition to the number of patients with each symptom, the frequency with which these symptoms occurred during each one-week period decreased from baseline to week 8 in both dose groups. After eight weeks of treatment, the frequency with which each symptom occurred had decreased in most cases by half. However, the severity of symptoms did not change much after eight weeks of treatment. See Applicant's Table 80 for details.

Table 80: Individual Symptom Frequency and Severity at Baseline and Final Evaluation (Trial 326)

	Pantoprazole			
	20 mg (N = 68)		40 mg (N = 68)	
Symptom	Baseline	Week 8	Baseline	Week 8
Abdominal pain/belly pain				
Mean frequency	6.5	2.8	6.8	3.7
Mean severity	4.5	3.4	4.5	4.1
Chest pain/heartburn				
Mean frequency	6.5	1.5	4.5	1.7
Mean severity	4.3	2.8	4.0	4.1
Difficulty swallowing				
Mean frequency	1.9	0.5	2.8	0.4
Mean severity	2.9	2.9	3.5	3.5
Nausea				
Mean frequency	3.6	2.0	4.6	2.0
Mean severity	3.6	3.9	4.5	3.7
Vomiting/regurgitation				
Mean frequency	3.8	2.0	4.1	1.5
Mean severity	4.1	3.9	4.0	3.1
Burping/belching				
Mean frequency	14.6	8.5	11.9	5.0
Mean severity	3.2	2.8	3.3	2.5
Choking when eating				
Mean frequency	0.3	0.2	0.3	0.2
Mean severity	3.1	2.8	2.9	2.7
Pain after eating				
Mean frequency	5.4	2.1	4.3	1.5
Mean severity	4.3	3.3	4.2	3.7

Consistent with the decreased number of patients reporting each symptom and the decreased frequency, the mean ISS for each symptom was significantly lower at Week 8 compared with baseline in both dose groups for the ITT population. The results for the ISS in the VFE population were comparable with the ITT population. There was no difference between dose groups.

Antacid Use

Mylanta Gelcaps were provided for use as antacid rescue medication. There was no difference between treatment groups in antacid use or the number of patients taking antacids in any two-week period. Antacid use decreased slightly at the end of the trial, but the change was not significant in the ITT population (p=0.16 and 0.78 for the 20 mg and 40 mg groups, respectively).

Comment: The use of antacid tablets was lower at baseline for the 40mg group, so the comparative change is hard to detect. The clinical significance of these changes from baseline to week 8 even though statistically significant is questionable.

Physician Global Assessment

The physician global assessment, performed at Week 8, rated most patients (>75%) as moderately or greatly improved (Table 81). Both groups demonstrated significant improvement compared with baseline ($p<0.001$). No patients were rated as having moderately or greatly worsened. Results for the VFE population were comparable with the ITT population.

Table 81: PGA (Trial 326)

	Pantoprazole	
Assessment of Disease	20 mg (N = 68)	40 mg (N = 68)
Worsened greatly	0 (0.0)	0 (0.0)
Worsened moderately	0 (0.0)	0 (0.0)
Worsened slightly	2 (2.9)	1 (1.5)
No change	3 (4.4)	3 (4.5)
Improved slightly	10 (14.7)	10 (15.2)
Improved moderately	19 (27.9)	21 (31.8)
Improved greatly	34 (50.0)	31 (47.0)
Total patients with assessment completed	68 (100.0)	66 (100.0)

Effectiveness Conclusions

There was GASP-Q score improvement in symptoms by Week 1 ($p<0.001$ from Week 1 through 10; except Week 2 with $p = 0.017$ for CSS for the 40 mg dose group). The number of patients with a CSS below the entry criteria (less than 16) increased as the trial progressed. The ISS and the frequency of symptoms decreased, but the severity of symptoms did not change. The use of antacid as rescue medication decreased slightly at the end of the trial, but there were no differences between groups in antacid use or the number of patients taking antacids. The physician global assessment, performed at Week 8, demonstrated improvement compared to baseline.

Safety Evaluation

Exposure

All 136 randomized patients are included in the safety analysis. Patients were in the trial for an average of 56 days of therapy, and received an average of 51 tablets of treatment. Compliance was above 90% on average. Although almost all the patients in the 20 mg group stayed in the trial through Week 8, five patients in the 40 mg group discontinued midway through the trial. Table 82 from the Applicant shows the comparison between treatment groups with regards to compliance which was similar at approximately 90%.

Table 82: Mean Duration in Study and Use of Drug (Trial 326)

	---------- Pantoprazole ----------		
	20 mg (N = 68)	40 mg (N = 68)	Total (N = 136)
Mean number of days in study[a]	67.6 (6.00)	65.1 (11.85)	66.3 (9.44)
Mean number of days[b] on therapy[c]	56.8 (2.26)	54.4 (8.21)	55.6 (6.12)
Mean number of tablets taken	52.0 (6.80)	49.4 (9.30)	50.7 (8.23)
Mean percent compliance	91.7 (11.95)	90.5 (9.53)	91.1 (10.79)

In the 20 mg group, the majority of patients received 0.3 mg/kg pantoprazole as seem in the Applicant's Table 83. In the 40 mg group, the majority of patients received 0.6-0.9 mg/kg pantoprazole. There was considerable overlap between dose groups in the 0.3 to 0.6 mg/kg dose range. On a dose-by-weight basis, only 28 patients in the 40 mg group received 0.9 mg/kg or higher, which is the dose level that was unique to the higher dose group and not shared with the 20 mg group.

Table 83: Number of Patients by Dose per Weight (Trial 326)

	---------- Pantoprazole ----------	
Dose per Weight (mg/kg)	20 mg (N = 68)	40 mg (N = 68)
<0.15	1 (1.5)	0 (0.0)
0.3	57 (83.8)	6 (8.8)
0.6	10 (14.7)	34 (50.0)
0.9	0 (0.0)	23 (33.8)
1.2	0 (0.0)	5 (7.4)
1.5	0 (0.0)	0 (0.0)
1.8	0 (0.0)	0 (0.0)
≥1.95	0 (0.0)	0 (0.0)

Adverse Events

A total of 113 patients (83%) reported one or more AEs, including 60 patients (88%) in the 20 mg group and 53 patients (78%) in the 40 mg group. The incidence of AEs was similar between treatment groups with the exception of diarrhea, which had a higher incidence in the 40 mg group. An AE was considered a TEAE if (1) it was not present at baseline and was not a chronic condition that was part of the patient's medical history, or (2) it was present at baseline or as part of the patient's medical history but the severity or frequency increased during treatment. TEAEs were reported by 112 patients (82%) during the trial: 59 (87%) in the 20 mg group and 53 (78%) in the 40 mg group; differences between the two dose groups were not statistically significant.

The most common TEAE was headache, reported by 47 patients (35%), 25 in the 20 mg group and 22 in the 40 mg group. Other common TEAEs were infection (32 patients total, 23%), and pharyngitis (26 patients total, 19%). Accidental injury was more common in the 20 mg group (13 patients compared with 4 patients in the 40 mg group, p=0.036) and diarrhea was more common in the 40 mg group (7 patients compared with 1 patient in the 20 mg group, p=0.062). All other AEs occurred with comparable frequency between the dose groups.

Headache was considered to be related to trial medication for 24 (35%) of the 47 patients reporting this TEAE. The majority of headaches were mild. Severe headaches considered to be related to trial drug were reported for four patients, and two additional patients had severe headaches that were not related to trial drug. Headache led to early discontinuation of three patients. Overall, TEAEs were mild or moderate in intensity. Abdominal pain was severe for three patients, for two of whom the pain was severe and considered to be related to trial drug. Flu syndrome, cholecystitis, flatulence, myalgia, dizziness, and ovarian cyst were severe for one patient each; only severe flatulence and severe dizziness were considered to be related to trial drug. In addition to headache, other related TEAEs were abdominal pain (4), diarrhea and dizziness (3 each), and ALT/SGPT increased (2). Lab test abnormal (increased gastrin), anorexia, constipation, flatulence, hyperlipidemia, hyperuricemia, AST/SGOT increased, insomnia, furunculosis, and abnormal vision were considered to be related to trial drug for one patient each.

Diarrhea, reported by one patient in the 20 mg group and by seven patients in the 40 mg group, was the only AE for which the incidence increased with increasing dose ($p = 0.062$). Accidental injury, unrelated to trial medication, was more common in patients in the 20 mg group ($p = 0.036$).

Table 84: TEAEs ≥ 3% of All Patients (Trial 326)

Body System		Panto 20mg N (%)	Panto 40mg N (%)	Total N (%)
Any AE		60 (88)	53 (78)	113 (83)
Body as Whole	Total	50 (74)	43 (63)	93 (68)
	Abd pain	8 (12)	7 (10)	15 (11)
	Allergic rxn	1 (2)	2 (3)	3 (2)
	Asthenia	1 (2)	0	1 (2)
	Back pain	2 (3)	1 (2)	3 (2)
	Cellulitis	1 (2)	0	1 (1)
	Chest pain	3 (4)	1 (2)	4 (3)
	Face edema	2 (3)	0	2 (2)
	Fever	1 (2)	3 (4)	4 (3)
	Flu syndrome	3 (4)	3 (4)	6 (4)
	Headache	26 (38)	23 (34)	49 (36)
	Infection	19 (28)	13 (19)	32 (24)
	Injection site pain	0	3 (4)	3 (2)
	Lab test abn	3 (4)	0	3 (2)
	Malaise	0	1 (2)	1 (1)
	Neck pain	0	1 (2)	1 (1)
	Pain	6 (9)	4 (6)	10 (7)
	Sepsis	0	1 (2)	1 (1)
CV System	Total	3 (4)	0	3 (2)
	Migraine	1 (2)	0	1 (1)
	Palpitation	1 (2)	0	1 (1)
	Syncope	1 (2)	0	1 (1)
Digestive System	Total	10 (15)	16 (24)	26 (19)
	Anorexia	1 (2)	1 (2)	2 (2)
	Apthous Stomatitis	0	1 (2)	1 (1)
	Cholecystitis	1 (2)	0	1 (1)
	Constipation	0	2 (3)	2 (2)
	Diarrhea	1 (2)	8 (12)	9 (7)
	Dyspepsia	1 (2)	0	1 (1)
	Esophagitis	0	1 (2)	1 (1)
	Flatulence	1 (2)	1 (2)	2 (2)
	Gastroenteritis	1 (2)	1 (2)	2 (2)
	LFT abn	0	1 (2)	1 (1)
	Melena	1 (2)	0	1 (1)
	Mouth Ulceration	1 (2)	1 (2)	2 (2)
	Nausea	3 (4)	2 (3)	5 (4)
	Stomatitis	0	1 (2)	1 (1)
	Vomiting	0	2 (3)	2 (2)
Hemic and Lymphatic System	Total	1 (2)	3 (4)	4 (3)
	Echhymosis	1 (2)	2 (3)	3 (2)
	Leukocytosis	0	1 (2)	1 (1)
Metabolic & Nutritional	Total	2 (3)	3 (4)	5 (4)
	Hyperlipidemia	0	1 (2)	1 (1)
	Hyperuricemia	0	2 (3)	2 (2)
	SGOT inc	0	1 (2)	1 (1)

Body System		Panto 20mg N (%)	Panto 40mg N (%)	Total N (%)
	SGPT inc	2 (3)	0	2 (2)
Musculo-Skeletal System	Total	9 (13)	5 (7)	14 (10)
	Arthralgia	3 (4)	1 (2)	4 (3)
	Leg cramps	1 (2)	1 (2)	2 (2)
	MS anomaly	1 (2)	0	1 (1)
	Myalgia	4 (6)	3 (4)	7 (5)
Nervous System	Total	9 (13)	1 (2)	10 (7)
	Dizziness	6 (9)	1 (2)	7 (5)
	Hypertonia	1 (2)	0	1 (1)
	Insomnia	2 (3)	1 (2)	3 (2)
Respiratory System	Total	23 (34)	29 (43)	52 (38)
	Asthma	1 (2)	2 (3)	3 (2)
	Bronchitis	0	1 (2)	1 (1)
	Cough inc	4 (6)	3 (4)	7 (5)
	Hemoptysis	1 (2)	0	1 (1)
	Laryngismus	0	1 (2)	1 (1)
	Pharyngitis	12 (18)	16 (24)	28 (21)
	Rhinitis	10 (15)	7 (10)	17 (13)
	Sinusitis	4 (6)	4 (6)	8 (6)
	URI	1 (2)	6 (9)	7 (5)
	Voice alteration	0	1 (2)	1 (1)
Skin	Total	6 (9)	10 (15)	16 (12)
	Acne	1 (2)	1 (2)	2 (2)
	Alopecia	0	1 (2)	1 (1)
	Contact Dermatitis	0	1 (2)	1 (1)
	Dry Skin	0	1 (2)	1 (1)
	Eczema	0	1 (2)	1 (1)
	Furunculosis	1 (2)	0	1 (1)
	HSV	0	1 (2)	1 (1)
	Rash	1 (2)	2 (3)	3 (2)
	Sunburn	3 (4)	0	3 (2)
	Vesiculobullous rash	0	2 (3)	2 (2)
Special Senses	Total	6 (9)	10 (15)	16 (12)
	Abn vision	2 (3)	0	2 (2)
	Conjunctivitis	0	3 (4)	3 (2)
	Ear pain	2 (3)	4 (6)	6 (4)
	Eye disorder	2 (3)	0	2 (2)
	Otitis externa	0	2 (3)	2 (2)
	Otitis media	0	1 (2)	1 (1)
Urogenital	Total	8 (12)	12 (18)	20 (15)
	Albuminuria	2 (3)	1 (2)	3 (2)
	Dysmenorrhea	3 (4)	7 (10)	10 (7)
	Dysuria	0	1 (2)	1 (1)
	Hematuria	1 (2)	0	1 (1)
	Ovarian cyst	0	1 (2)	1 (1)
	UTI	1 (2)	2 (3)	3 (2)
	Urine abnormality	1 (2)	2 (3)	3 (2)

Serious Adverse Events

There were no deaths in this trial. There was one SAE reported in this trial. Patient 326-013-0228, a 12-year-old white female, had a history of seasonal allergies, reactive airway disease, and constipation. Her baseline visit was on Nov 18, 2003, and she started treatment with pantoprazole 20 mg the next day. At Week 5, she complained of abdominal pain. An inflamed gall bladder was diagnosed, and a cholecystectomy was performed on (b) (6). The patient was hospitalized overnight and discharged on (b) (6), with Vicoden and Tylenol. The patient fully recovered and completed the trial on Jan 12, 2004 with 98.2% trial drug compliance. The event was considered to be unrelated to the trial medication.

Comment: The narrative on this patient is very short on the CRF, and it does not allow for any firm evaluation to be made regarding the association of the SAE to the trial treatment. The patient was not at any known risk for developing cholecystitis, and given the timing of the SAE, it is possible that there is an association with trial treatment.

Safety Related Discontinuations

Headache, in all cases considered related to trial medication, led to the withdrawal of three patients in the 40 mg group. Patient 326-03-0057 discontinued because of mild headache "definitely related" to trial drug after receiving 19 doses of pantoprazole 40 mg. Patient 326-021-0377 discontinued because of moderate headache "possibly related" to trial drug after receiving 20 doses of pantoprazole 40 mg. Patient 326-040-0852 discontinued because of severe headache "definitely related" to trial drug after receiving 25 doses of pantoprazole 40 mg. These patients all received ≥ 0.8 mg/kg of pantoprazole. All headaches resolved after discontinuation of trial drug.

Clinical Laboratory Evaluations

During the trial, 53 patients had laboratory values of potential clinical importance. The most frequent PCI laboratory value was platelet count increased for five patients (4%). For urinalysis, increased hemoglobin was recorded for 27 patients (20%) and increased protein/albumin recorded for 20 patients (15%). All other PCI laboratory values were reported for one or two patients only. There were no significant differences in values of PCI between the 20 mg and 40 mg treatment groups. None of these findings was considered to be clinically significant and they did not appear to pose a safety risk to the patients.

Mean changes in laboratory tests that were statistically significant compared with baseline ($p<0.05$) but were not clinically important included the following:

Table 85: Lab Value Abnormalities Compared by Dose (Trial 326)

20 mg	40 mg
WBC dec @ Wk 4 PTT inc @ Wk 4 Gastrin inc @ Wk 4, 8 Bili inc @ Wk 4, 8 Bicarbonate inc @ Wk 4, 8 Chloride dec @ Wk 8 Creatinine inc @ Wk 8 Uric acid inc @ Wk 8	BUN inc @ Wk 4 Phosphorous inc @ Wk 4 Hb dec @ Wk 8 Uric acid inc @ Wk 8

*All lab values that are noted as PCI abnormal only at Week 4 normalized by Week 8

Liver enzymes did not change significantly from baseline during the trial. Three patients had liver enzyme values that were reported as AEs: patient 326-026-509 (40 mg group) with mildly elevated AST, and patients 326-005-878 and 326-027-533, both in the 20 mg group, with elevated ALT values. Urinalysis at Week 4 and 8 showed that protein/albumin, hemoglobin/blood, nitrites, and leukocyte esterase were positive for up to five patients in the 20 mg group. In the 40 mg group, hemoglobin/blood was positive for up to seven patients and leukocyte esterase was positive for one patient. There was no difference between the groups.

Vital Signs and Other Parameter Analyses

During the trial, 24 patients had changes from baseline in vital signs that met the PCI criteria. None of these was considered clinically important. Weight gain was the most common change, reported for 10 patients. Weight loss sufficient to meet the PCI criteria was reported for four patients. It is difficult to explain the wide variability in weight. Decreases in sitting systolic and diastolic blood pressure were noted for five patients each. Low heart rate for one patient (326-047-1056, 41 bpm) was preceded by low pulse measurements of 49-59 bpm at earlier visits. No adverse event was reported. There were no significant differences in PCI values between the treatment groups. None of these findings was considered clinically significant by the investigators and they did not appear to pose a safety risk to the patients.

Weight: An increase in mean weight during the trial was statistically significant compared with baseline, but this was not considered clinically important.

Table 86: Descriptive Statistics and Comparisons to Baseline for Weight (kg) During the Trial 326

		Panto 20 mg		Panto 40 mg	
		Baseline	Week 8	Baseline	Week 8
Weight (kg)	N	68	67	68	62
	Mean (SD)	61.3 (18.8)	61.9 (18.9)	60.7 (16.8)	62.2 (17.2)
	Mean change		0.7		0.5
Height (cm)	N	28 pairs		30 pairs	
	Mean (SD)	161.9 (8.6)	162.3 (8.4)	161.9 (9.0)	162.9 (8.8)
	Mean change	0.42 (2.0)		0.92 (1.2)	

Height: Each patient's height was measured during the pretrial period (visit 2) and at the final visit (Week 8). However, 28 of the 68 patients treated with 20 mg pantoprazole and 30 of the 68 patients treated with 40 mg pantoprazole had height evaluation at or before Week 8. Therefore, patients' records were evaluated to obtain their height for up to six months and up to two years after the first dose of pantoprazole. No statistically significant differences between groups were seen in the mean height at various times.

BMI: Body mass index (BMI) was evaluated for each patient with available weight and height during pretrial screening (baseline), at final visit (Week 8), Week 8 up to six months, and Week 8 up to two years. The BMI Z-scores were calculated based on the available results from these time points. No between groups statistically significant difference were seen in the mean BMI at various visits ($p > 0.61$). There were no significant changes in the mean BMI from baseline to Week 8, up to six months, or up to two years in any treatment group.

Comment: Overall, there were no significant alterations in growth factors as measured by weight, height, BMI and their corresponding Z-scores in this eight week trial in adolescents patients with GERD treated with either 20 or 40 mg pantoprazole. In this short term trial, growth does not appear to be negatively impacted by treatment with pantoprazole.

ECG: Four patients in the 40 mg group had ECG findings that were normal at screening but abnormal at Week 8. Patients 326-022-0414 and 326-037-0776 were observed to have sinus bradycardia, and patient 326-026-0507 had sinus arrhythmia. The abnormal change for patient 326-026-0510 was not specified. These findings were not considered clinically significant by the investigators.

Comment: ECG results were reviewed for those whose readings were normal at baseline but abnormal at end of trial. Four patient results fit this description, three of which do not appear to be clinically significant from the description of the abnormality. One of the patient ECG results are not specified and only "not clinically significant" is listed, therefore, no additional evaluation can be made.

Safety Conclusions

In general, no major safety signals were detected from use of pantoprazole 20 mg and 40 mg in reducing symptoms of GERD in children aged 12-16 years. A total of 112 patients (82%)

reported one or more TEAEs. The most common TEAE was headache, reported by a total of 47 patients (35%).

AEs occurred with comparable frequency between dose groups. Diarrhea was the AE for which there was the biggest increase in incidence increased with increasing dose, reported by one patient in the 20 mg group and by seven patients in the 40 mg group. Headache, abdominal pain, diarrhea, dizziness, and SGPT increased were the TEAEs considered related to trial drug that were experienced by two or more patients. The majority of TEAEs was mild or moderate in intensity and not related to trial drug. No deaths were reported in this trial, however, there was one SAE of cholecystectomy. This was reported by the investigator as not related to trial drug.

There were more safety related discontinuations in the 40 mg dose group. Three patients in the 40 mg group discontinued from the trial prematurely because of the related AE of headache. One patient in the 40 mg group withdrew prematurely from the trial because of lack of effectiveness. Changes in laboratory values, vital signs, and ECGs do not appear clinically significant and did not appear to pose a safety risk to patients.

CONCLUSIONS

(b) (4)

The pathophysiology of EE associated with GERD in adults and pediatric patients is thought to be the same, as such, efficacy of pantoprazole should be extrapolated to this age group. Pantoprazole doses of 20 mg and 40 mg appear to have an acceptable safety profile in this age group, thus I recommend that the dosage used for adult EE, 40 mg, be used as a reference to dose pediatric patients ages 12 to 16 years for short term treatment of EE associated with GERD. Final labeling recommendations will need to take into account results of PK studies in pediatric patients.

GERD ASSESSMENT OF SYMPTOMS IN PEDIATRICS QUESTIONNAIRE (GASP-Q)

patient identification: ☐☐☐ ☐☐☐ (Protocol no. / Site no. / Patient no.)		patient initials: ☐☐☐ ☐☐☐
patient date of birth: ☐☐ ☐☐ ☐☐ (mm dd yy)		patient gender: ☐ male ☐ female
person completing questionnaire: _____ (eg, mother, father)		date completed: ☐☐ ☐☐ ☐☐ (mm dd yy)
SYMPTOMS	QUESTION A How many times did each symptom occur in the past 7 days? *(such as 0, 1, 2, 3, etc)*	QUESTION B On a scale of 1 to 7 how severe was the symptom usually? 1 = Not at all severe 7 = Most severe *(leave question B blank if your answer to question A is "0")*
ABDOMINAL PAIN / BELLY PAIN *it hurts, aches or burns in the middle of your belly but not in your chest.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe
CHEST PAIN / HEARTBURN *it hurts, aches or burns in the middle of your chest behind your breast bone but not in your belly.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe
DIFFICULTY SWALLOWING *foods or liquids feel like they are getting stuck and you have to swallow many times or drink more liquids to "unstick" them.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe
NAUSEA *feeling sick to your stomach or that you may throw-up.*	____ Times in the past 7 days	Not at all severe ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 Most severe

Figure 19: GASP-Q

patient identification: Protocol no. Site no. Patient no. patient initials:

SYMPTOMS	QUESTION A How many times did each symptom occur in the past 7 days? *(such as 0, 1, 2, 3, etc)*	QUESTION B On a scale of 1 to 7 how severe was the symptom usually? 1 = Not at all severe 7 = Most severe *(leave question B blank if your answer to question A is "0")*
VOMITING / REGURGITATION *throwing up or having food come up into your mouth and swallowing it.*	____ Times in the past 7 days	Not at all severe 1 2 3 4 5 6 7 Most severe
BURPING / BELCHING *air coming up from your stomach and out of your mouth.*	____ Times in the past 7 days	Not at all severe 1 2 3 4 5 6 7 Most severe
CHOKING WHEN EATING *coughing when you are swallowing foods or liquids.*	____ Times in the past 7 days	Not at all severe 1 2 3 4 5 6 7 Most severe
PAIN AFTER EATING *it hurts, aches or burns in the middle of your belly but not in your chest after you eat.*	____ Times in the past 7 days	Not at all severe 1 2 3 4 5 6 7 Most severe

Please check one box

How would you assess the impact of pantoprazole on this patient's disease?

1	2	3	4	5	6	7
Disease Improved Greatly	Disease Improved Moderately	Disease Improved Slightly	No Impact	Disease Worsened Slightly	Disease Worsened Moderately	Disease Worsened Greatly

Figure 20: Physician Global Assessment Tool

9.4.5 Study 3001B3-331-WW: Neonates - PK/PD, and Safety Trial

A. General Design and Objective

Study 3001B3-331-WW (Study 331) is a multicenter, open-label, randomized, single-dose and multiple-dose trial to assess PK, clinical GERD, respiratory symptoms, and safety of two dose levels of pantoprazole (1.25 mg and 2.5 mg), and the PD at one dose level (2.5 mg) in neonates and preterm infants with a clinical indication for acid suppression to treat a presumed diagnosis of GERD. All patients received five days of treatment. Patients were neonates and preterm infants that had been admitted to an NICU or special care nursery prior to enrollment.

The primary objective of this study was to determine whether consistent exposures to pantoprazole in neonates and preterm infants with presumed GERD could be achieved by using oral doses of pantoprazole.

Secondary objectives of the study were:

1. To characterize the PK of oral pantoprazole after a single dose and at steady state when consistent exposures are achieved in neonates and preterm infants with presumed GERD at doses expected to produce exposures similar to those achieved in older children and adults given standard doses of pantoprazole.
2. To provide the PD assessment of oral pantoprazole at baseline and steady state by using pH-metry to measure intragastric and intraesophageal pH in neonates and preterm infants with presumed GERD.
3. To characterize the change from baseline in clinical GERD and respiratory symptoms after single and multiple doses of oral pantoprazole have been administered to neonates and infants with presumed GERD.
4. To describe the safety of pantoprazole in neonates and preterm infants with presumed GERD throughout the study.

B. Background

This study was conducted in response to the Study 1 requirement of the FDA's Pediatric Written Request (PWR) for PROTONIX Delayed-Release Tablets (NDA 20-987) and PROTONIX IV for Injection (NDA 20-988), initially issued on Dec 31, 2001.

C. Inclusion

1. Male and female hospitalized patients admitted to an NICU or special care nursery at the time of enrollment.
2. A clinical indication for acid suppression in patients with a presumptive diagnosis of GERD based on clinical symptoms suggestive of GERD and/or objective tests diagnostic of GERD.

3. Term and postterm infants within the neonatal period (≤28 days postnatal age), or preterm infants with a corrected age of less than 44 weeks.
4. Body weight of at least 1500 g.
5. Ability to tolerate oral feeding and swallow the pantoprazole doses.

D. Exclusion

1. Cardiovascular instability, life-threatening arrhythmias, or previous cardiopulmonary arrest, or mechanical ventilation.
2. Known HIV or clinical manifestations of AIDS or other significant immunodeficiency disorder or malignancy.
3. Disorders associated with or worsened by GERD, objective tests suggestive of GERD, and/or aspiration in conjunction with GERD were also noted as supportive documentation of the clinical diagnosis.
4. Clinically significant laboratory test abnormality:
    a. AST or ALT level ≥2 times the upper limit of normal (ULN).
    b. Alkaline phosphatase level ≥2 times ULN (age-corrected).
5. Known history of positive serologic test for the hepatitis B surface antigen (HBsAg) or the hepatitis C virus (HCV) antibody or RNA.
6. Known hypersensitivity to PPIs, including pantoprazole.
7. Use of antacids within two hours before or after pantoprazole administration and two hours before and during pH-metry.
8. For patients in the PK stratum, a history of treatment with PPIs or H2RAs within 24 hours before the first dose of pantoprazole.
9. For patients in the PK/PD stratum, a history of treatment with PPIs within seven days before the first dose of pantoprazole, use of H2RAs within three days before the first dose of pantoprazole, or receiving 24-hour continuous enteral feeding or any feeding more frequently than every three hours.
10. Significant renal or hepatic disease.
11. Any life-threatening condition that would make it unlikely that the patient would be discharged from the hospital.
12. Participation in any other investigational study within 30 days before the administration of pantoprazole without prior approval of the medical monitor.

E. Treatment

Pantoprazole delayed-release granules were provided in an inert powder blend in foil pouches in 1.25- and 2.5-mg dose strengths. At the time of administration, 2.5 mL of water was added to the content of the foil pouch to form a grape-flavored suspension. The appropriate doses were then administered to patients by using an oral syringe approximately 30 minutes before the first feeding each day at approximately the same time as on study day 1. Dose administration via NG tube was prohibited. Feeding began approximately 30 minutes after dose administration. Doses of 1.25 and 2.5 mg correspond to 0.6 to 1.2 mg/kg, respectively. The labeled dose in adults is 40 mg, which corresponds to approximately 0.5 to 0.6 mg/kg.

Concomitant Medications

Concomitant medications were permitted where appropriate. Patients were to continue their usual medical therapies according to standard clinical practice. Medications that were not prohibited and were deemed necessary because of intercurrent acute or chronic disease could be administered, provided that no dose adjustment was likely to be necessary during the study.

Continuous treatment with theophylline derivatives or digoxin was closely monitored throughout the study to assure that proper serum levels of these drugs were maintained.
All patients were permitted to use antacids on a daily basis as needed with the exception of:

- For patients in the PK stratum, two hours before and after pantoprazole administration on days when PK blood samples were scheduled to be obtained.
- For patients in the PK/PD stratum, two hours before and during pH-metry on the days of PD procedures.

Prohibited Medications

The following medications were prohibited during the study:
1. Antacids were prohibited except as described under "Permitted medications".
2. PPIs (other than the study medication, pantoprazole) and H2RAs.
3. Use of warfarin, carbamazepine, phenytoin, or rifampin for any disorder from at least 24 hours before the first use of pantoprazole until after the final study procedure.

Patients given an acid suppressant other than pantoprazole during the active treatment phase of the study were withdrawn from the study.

F. Safety Considerations/Monitoring

There were different study schedules for the PK, PD, and PK/PD treatment groups. In general there was a screening visit, baseline visit, active treatment period on Days 1 to 6 with a final study evaluation, then a post study visit on Day 23.

G. Endpoints

Efficacy Measurements
The worksheet for collecting GERD and respiratory symptoms was derived from the GERD Symptoms Questionnaire in Infants (GSQ-I) and the Infant Gastroesophageal Reflux Questionnaire (I-GERQ). The GSQ-I was previously developed for use by parents to assess GERD symptoms in infants aged 1 through 11 months, at the request of the FDA. The GSQ-I was shortened to five items, and severity assessments were removed. The GSQ-I was further modified using questions from the validated I-GERQ developed by Orenstein and colleagues, and the resulting items were converted into an electronic diary (eDiary) that was used daily in trial 3001B3-329-WW (see section 9.4.1-G).

Comment: The use of a daily GERD symptom diary in preterm infants and neonates is exploratory. Preterm infants taking oral feedings have GERD symptoms very similar to those in

infants under one year of age, but these symptoms have not been systematically described in the medical literature.

PK Endpoints

1. Plasma concentrations of pantoprazole were determined after single and multiple-dose administration.
2. AUC and Cl/F of pantoprazole was estimated for patients using a population PK approach.

Safety Evaluations

The safety assessments of the study were:

1. AEs, TEAEs, and SAEs.
2. Comorbidities of prematurity (sepsis, pneumonia/aspiration pneumonia, apnea, necrotizing enterocolitis [NEC], bronchopulmonary dysplasia, upper GI bleeding, and retinopathy of prematurity).
3. Physical examination, body weight (g), length (cm), and head circumference (cm).
4. Vital sign measurements, including potentially clinically important (PCI) results.
5. Laboratory evaluations, including PCI results.
6. Standard 12-lead ECG recordings, including HR and QRS, QT, and RR intervals.
7. Premature terminations for safety reasons
8. Nonstudy medications.

H. Data Analysis

Statistical Analytical Plan

Patients were summarized by age groups (preterm versus full term) and CYP genotypes to explore PK results. Exploratory presentations for subpopulations or subgroups were prepared after final presentation of planned statistical analyses was completed for the entire study population. Because of the limited size of the study population, these exploratory analyses are presented only as additional descriptive information.

Baseline demographics, disease characteristics, and other background medical history information of the safety population were summarized to evaluate comparability. The Fisher exact test was used for variables reported as nominal attributes. Analysis of variance (ANOVA) with treatment as a factor in the model was used for continuous variables such as age, corrected age, weight, length and head circumference.

Safety Analysis

All AEs, TEAEs, PCI laboratory test results, PCI vital sign measurements, and PCI ECG results were summarized by dose group. The Fisher exact test was used to compare all AEs and TEAEs between dose groups. The frequencies of PCI laboratory test results, vital sign measurements, and ECG results were summarized. Continuous safety parameters were analyzed using ANCOVA with treatment as a factor and baseline value as a covariate.

I. Results

Disposition of Patients

A total of 68 patients were screened for the study. Of these, 59 patients were randomized to the two treatment groups (19 for 1.25 mg and 20 for 2.5 mg) as shown in Figure 21 (copied from the Applicant).

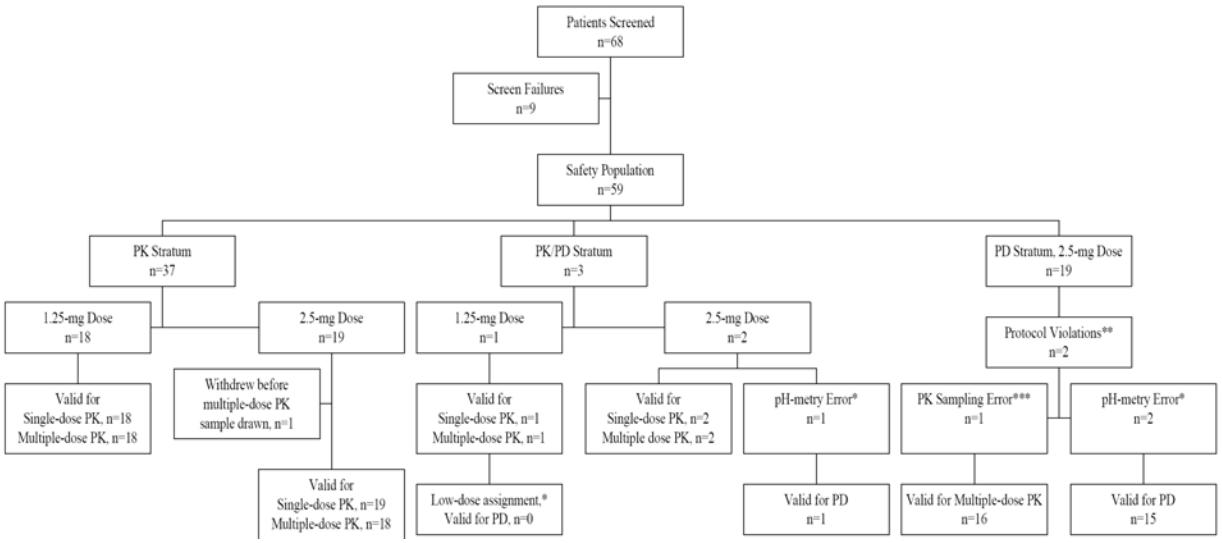


Figure 21: Disposition of Patents (Study 331)

Discontinuations

Two patients were withdrawn during the study. Patient 331-031-003051 (PD stratum) was withdrawn because of a protocol violation. Patient 331-085-003501 (PK stratum) was withdrawn early because of parental request. Both infants had received 2.5-mg doses of pantoprazole.

Demographics

There were no statistically significant differences between the dose groups in terms of baseline demographics. All the patients participating in the study were neonates (aged ≤28 days) or preterm infants with a corrected age of less than 44 weeks. Most (54 of 59; 91.5%) were born prematurely. The median gestational age was 29 weeks. The median corrected age of the infants born prematurely was 37.5 weeks. The majority (41 of 59; 69.5%) of the patients were male. Race and ethnicity were predominantly white, non-Hispanic, but other races and ethnicities were represented in the study population.

Table 87: Patient Demographics (Study 331)

Characteristic	Overall p-Value	1.25 mg n=19	2.5 mg n=40	Total n=59
Gestational Age (weeks)				
Mean	0.992	30.2	30.3	30.3
SD		4.7	4.7	4.6
Min		23.5	23	23
Max		40	41	41
Sex				
Female	0.77	5 (26%)	13 (33%)	18 (31%)
Male		14 (74%)	27 (68%)	41 (70%)
Race				
Asian	0.766	0	1 (3%)	1 (2%)
Black		3 (16%)	6 (15%)	9 (15%)
Other		0	3 (8%)	3 (5%)
White		16 (84%)	30 (75%)	46 (78%)
Type of Birth				
Full Term		1 (5%)	4 (10%)	5 (9%)
Premature		18 (95%)	36 (90%)	54 (92%)
Baseline Length (cm)				
Mean	0.53	46.6	45.8	46.1
SD		3.8	4.6	4.3
Min		42	39	39
Max		53	57	57
Baseline Weight (g)				
Mean	0.92	2661	2679	2673
SD		586	696	658
Min		2060	1570	1570
Max		4100	4570	4570
Baseline Head Circumference (cm)				
Mean	0.58	33	32.7	32.8
SD		2.3	2.2	2.2
Min		29	28	28
Max		38.6	38	38.6

GERD Indications at Screening

Results of four upper GI series, one esophagram, two video swallowing studies, and three laryngoscopies were consistent with GERD or showed erythema. Thus, 15% patients had test results at screening that were consistent with GERD, and nearly 85% of the patients entered the study based on clinical symptoms of GERD.

Concomitant Therapy/Medications

All but 1 of the 59 (98%) patients received concomitant medication during the study. Iron preparations were the most widely used products and were given to 32 (54%) patients. The second most common medications were propulsives, which were given to 18 (31%) patients, indicated for feeding intolerance as well as GERD. At least 12 (20%) patients received vitamin supplements, including multivitamin and plain vitamin preparations. Other concomitant products provided to at least 10% of the patients in the study were mydriatics or cycloplegics (11

patients; 19%); caffeine for the treatment of apnea (9 patients; 15%), nasal decongestants (8 patients; 14%); and antifungals for topical use, ascorbic acid, and laxatives (7 patients each; 12%). There were no statistically significant differences between the dose groups.

Congenital History of Patients

The most common congenital anomaly at birth was congenital heart disease, which was observed in 16 (27%) patients in the study population (8 patients in each dose group).
For the 54 preterm infants in this study, medical history included the presence or absence of a history of any of prespecified comorbidities of prematurity. A history of complications of prematurity was reported at screening and again during the treatment period.

Effectiveness Evaluation

From baseline to the last day on-therapy, the mean total daily GERD symptom score decreased from 3.26 to 2.19 in the 1.25-mg dose group and from 2.94 to 2.17 in the 2.5-mg dose group. The decreases in both dose groups approached did not meet statistical significance and the decrease in total daily GERD symptom score was not significantly different between groups. Table 88 from the Applicant summarizes the results.

Table 88: Total Daily GERD Symptom Score Baseline vs. Final Day

		-------- Pantoprazole 1.25 mg --------			-------- Pantoprazole 2.5 mg ---------			
Visit	Statistics	Actual	Change from Baseline	p-Value[a]	Actual	Change from Baseline	p-Value[a]	p-Value[b]
Baseline								
	N	17			35			
	Mean ± SD	3.26 ± 2.55			2.94 ± 2.10			
	Median	2.00			3.00			
	Min, Max	0.00, 10.00			0.00, 7.00			
Last on Therapy	N	17	17		35	35		
	Mean ± SD	2.19 ± 2.00	-1.07 ± 2.59	0.107	2.17 ± 1.54	-0.77 ± 2.29	0.054	0.915
	Median	2.00	-1.00		2.00	-1.00		
	Min, Max	0.00, 8.00	-6.00, 5.50		0.00, 5.00	-5.00, 4.00		

Safety Evaluation

Exposure

There were 59 patients in the safety population. Exposure to test drug is summarized in Table 89 from the Applicant:

Table 89: Summary of Pantoprazole Exposure (Study 331)

Cumulative Days Exposed	Pantoprazole 1.25 mg (n=19)	Pantoprazole 2.5 mg (n=40)
≥1 Day	19 (100)	40 (100)
≥2 Days	19 (100)	40 (100)
≥3 Days	19 (100)	39 (97.5)
≥4 Days	19 (100)	39 (97.5)
≥5 Days	19 (100)	38 (95.0)
≥6 Days	11 (57.9)	31 (77.5)
≥7 Days	6 (31.6)	6 (15.0)
≥8 Days	3 (15.8)	3 (7.5)
≥9 Days	2 (10.5)	3 (7.5)
10 Days	2 (10.5)	2 (5.0)

Errors

There was one minor test drug administration error which did not result in an AE.

Adverse Events

AEs were reported for 30 (51%) of the 59 patients. TEAEs were reported for 23 (39%) of 59 patients, including 5 (26%) of 19 patients in the 1.25-mg dose group and 18 (45%) of 40 patients in the 2.5-mg dose group. The difference between groups was not statistically significant.

Overall, the most common TEAEs were anemia (6 patients; 10 %), hypoxia (4 patients; 7%), constipation (3 patients; 5%), and rhinitis (3 patients; 5%). In the 1.25-mg dose group, the most common TEAE was contact dermatitis (diaper rash), which was reported in 2 (11%) patients. In the 2.5-mg dose group, the most common TEAE was anemia, which occurred in 5 (13%) patients. Between-group differences were not statistically significant.

The TEAEs were mild to moderate in severity, and most were considered not related to the test article. Two (3%) TEAEs were considered related to the test article: one was an abnormal liver test result (elevated liver enzyme) in patient 331-054-003222, and the other was contact dermatitis (diaper rash) in patient 331-054-003225. Both TEAEs were mild in severity, and both resolved.

Table 90: TEAEs (modified from the Applicant for Study 331)

Body System Adverse Event	p-Value	1.25 mg Total=19 N (%)	2.5 mg Total=40 N (%)	All Treated Total=59 N (%)
Any Adverse Event	0.254	5 (26.3)	18 (45.0)	23 (39.0)
Body as a Whole	1.000	0	2 (5.0)	2 (3.4)
Fever	1.000	0	1 (2.5)	1 (1.7)
Hernia	1.000	0	1 (2.5)	1 (1.7)
CV System	0.653	2 (10.5)	3 (7.5)	5 (8.5)
Bradycardia	0.544	1 (5.3)	1 (2.5)	2 (3.4)
Cardiovascular Physical Finding	0.322	1 (5.3)	0	1 (1.7)

Body System Adverse Event	p-Value	1.25 mg Total=19 N (%)	2.5 mg Total=40 N (%)	All Treated Total=59 N (%)
Tachycardia	1.000	0	2 (5.0)	2 (3.4)
Ventricular Extrasystoles	0.322	1 (5.3)	0	1 (1.7)
Digestive System	1.000	1 (5.3)	4 (10.0)	5 (8.5)
Constipation	1.000	1 (5.3)	2 (5.0)	3 (5.1)
Flatulence	1.000	0	1 (2.5)	1 (1.7)
Liver Function Tests Abnormal	1.000	0	1 (2.5)	1 (1.7)
Hemic/Lymphatic	0.163	0	6 (15.0)	6 (10.2)
Anemia	0.165	0	5 (12.5)	5 (8.5)
Iron Deficiency Anemia	1.000	0	1 (2.5)	1 (1.7)
Metabolic	1.000	0	1 (2.5)	1 (1.7)
Peripheral Edema	1.000	0	1 (2.5)	1 (1.7)
Musculoskeletal	0.100	2 (10.5)	0	2 (3.4)
Musculoskeletal Anomaly	0.322	1 (5.3)	0	1 (1.7)
Osteopenia	0.322	1 (5.3)	0	1 (1.7)
Respiratory	1.000	2 (10.5)	4 (10.0)	6 (10.2)
Apnea	0.322	1 (5.3)	0	1 (1.7)
Hypoxia	1.000	1 (5.3)	3 (7.5)	4 (6.8)
Lung Disorder	1.000	0	1 (2.5)	1 (1.7)
Pulmonary Physical Finding	0.322	1 (5.3)	0	1 (1.7)
Rhinitis	1.000	1 (5.3)	2 (5.0)	3 (5.1)
Skin	0.240	2 (10.5)	1 (2.5)	3 (5.1)
Site Reaction	1.000	0	1 (2.5)	1 (1.7)
Contact Dermatitis	0.100	2 (10.5)	0	2 (3.4)
Special Senses	0.240	2 (10.5)	1 (2.5)	3 (5.1)
Conjunctivitis	0.322	1 (5.3)	0	1 (1.7)
Retinal Disorder	0.544	1 (5.3)	1 (2.5)	2 (3.4)
Urogenital	0.544	1 (5.3)	1 (2.5)	2 (3.4)
UTI	1.000	0	1 (2.5)	1 (1.7)
Urine Abnormality	0.322	1 (5.3)	0	1 (1.7)

Serious Adverse Events

There were no deaths reported during the study. SAEs were reported in 2 (3%) of 59 patients: patients 331-039-003071 and 331-217-006116. Both of the SAEs occurred after the treatment period of the study, and neither was considered related to test drug by the investigator.

Patient 331-039-003071 was a preterm (gestational age, 23 weeks) white male infant aged 16.4 weeks (corrected age, 39.4 weeks) who developed a urinary tract infection during the follow-up portion of the study (day 11), five days after the last dose of study medication. After developing a fever, he was taken to the emergency room, and a culture of urine was positive for *E coli*. He was hospitalized and discharged three days after admission. The patient was in the PK stratum

and had received six 2.5-mg daily doses of pantoprazole. The investigator did not consider the SAE to have been related to the test article.

Patient 331-217-006116 was a preterm (gestational age, 36 weeks) white male infant aged 1.9 weeks (corrected age, 37.9 weeks) who developed hematochezia without a fever or other bowel problems during the follow-up portion of the study (day 33), 27 days after the last dose of study medication. He was hospitalized; hematochezia due to colitis (not further specified) was diagnosed; and he was treated with diosmectite (Smecta). The SAE resolved three days later, and the patient was discharged. The patient was in the PD stratum and had received six 2.5-mg daily doses of pantoprazole. The investigator considered the SAE to have been not related to the test drug.

Comment: Given the timing of the events and known half life of the study drug, it is unlikely that the test drug was associated with the SAEs. I agree with the investigator assessments given the information provided in the narratives.

Safety Related Discontinuations

None.

Laboratory evaluations

One patient developed a PCI elevation in AP while on treatment with pantoprazole. Patient 331-054-003221 was a preterm (gestational age, 25 weeks), 14-week-old (corrected age, 39 weeks), white male patient whose medical history included alkaline phosphatasemia and cutis aplasia congenita. At screening he had a moderately elevated AP at 1042 mU/mL (normal range, 150 to 420 mU/mL) with a mildly elevated AST of 39 mU/mL (normal range, 0 to 37 mU/mL) and normal ALT. At the final evaluation eight days later (study Day 6), the patient's AP had risen to a PCI level of 1312 mU/mL, whereas AST and ALT remained unchanged.
Comment: This patient had a baseline abnormality in AP and the change from screen given this history is not as concerning. No further f/u information is available for this patient.

One patient (331-054-003222) developed a PCI elevated AST (182 mU/mL) while on treatment with pantoprazole. This patient was preterm (gestational age, 27 weeks), 7.9-week-old (corrected age, 34.9 weeks), other-race male patient whose medical history included neonatal cholestasis with direct hyperbilirubinemia, which was reported as ongoing at study entry. The laboratory evaluation at screening showed normal AST and alkaline phosphatase levels and an elevated ALT of 90 mU/mL (normal range, 0 to 41 mU/mL); bilirubin levels were not reported. At the final evaluation, the patient's AST was elevated to a PCI level of 182 mU/mL (normal range, 0 to 37 mU/mL), ALT had risen slightly to 121 mU/mL, and alkaline phosphatase (AP) and bilirubin remained within the normal range. There was no evidence of hemolysis. No other AEs were reported for this patient.
Comment: The timing of events makes it possible for there to be a relationship between AST elevation and pantoprazole treatment. There is no further information available regarding changes in the AST for this patient.

One patient developed a PCI elevated CPK and had PCI high carbon dioxide while on treatment with pantoprazole. Patient 331-073-003383 was a preterm (gestational age, 23.5 weeks), 13.6-week-old (corrected age, 37.1 weeks), black male patient with an extensive medical history. At screening the patient had a low-normal CPK of 8 mU/mL (normal range, 2 to 129 mU/mL), and a slightly elevated AP. At final evaluation on day 6, the patient's CPK had increased to a high of 462 mU/mL, whereas his AP had returned to within the normal range. Apart from PCI high carbon dioxide levels reflecting respiratory acidosis at both evaluations, the patient had no notable blood chemistry abnormalities.
Comment: No further follow-up information is available. From the eCRF it is notable that this patient had a history of seizures, apnea, and multiple congenital anomalies. There is a possible relationship betweeb CPK increase and drug treatment, however, there could have been confounding factors given this patient's complex medical history.

Hematology abnormalities:
Patient 331-039-3073 was a preterm (gestational age, 27 weeks), 7-week-old (corrected age, 34 weeks), white male patient who received six 2.5-mg daily doses of pantoprazole. Despite a history of ongoing anemia, at screening the patient's hemoglobin was 123 g/L (normal range, 115 to 165 g/L) and hematocrit was 0.358 L/L (normal range, 0.36 to 0.52 L/L). At final evaluation, the patient's hemoglobin had decreased to a PCI low of 84 g/L with a PCI low hematocrit of 0.26 L/L.

Patient 331-054-3227 was a preterm (gestational age, 27 weeks), 9-week-old (corrected age, 36 weeks), white male patient who received ten 1.25-mg daily doses of pantoprazole. At screening, the patient's hemoglobin (normal range, 125 to 205 g/L) and hematocrit (normal range, 0.31 to 0.55 L/L) were both low at 107 g/L and 0.289 L/L, respectively. At final evaluation, laboratory tests were done at a different laboratory with different normal ranges for hemoglobin (100 to 180 g/L) and hematocrit (0.31 to 0.55 L/L). The final evaluation showed that the patient had a PCI hemoglobin of 77 g/L and a PCI low hematocrit of 0.22 L/L.

Patient 331-209-6021 was a preterm (gestational age, 28 weeks), 7-week-old (corrected age, 35 weeks), white male patient who received six 2.5-mg daily doses of pantoprazole. At screening, the patient's hemoglobin was 101 g/L (normal range, 94 to140 g/L) with a hematocrit of 0.29 L/L (normal range, 0.28 to 0.42 L/L). At final evaluation, the patient's hemoglobin had dropped to a PCI low of 79 g/L with a PCI low hematocrit of 0.232 L/L. On follow-up at study day 15, the hemoglobin had recovered to 99 g/L with a hematocrit of 0.293 L/L.

During the study, there were five TEAE reports of anemia and one report of iron deficiency anemia; however, none were considered to be related to the test article by the investigators.

In general there were more PCI lab test results in the prestudy results than in the postbaseline laboratory tests (46% vs 40% total). The tests for which there were slightly increased abnormalities in the postbaseline group were: AST (1/57 post vs. 0 pre), Alk Phos (1/57 post vs. 0 pre), CPK (1/46 post vs. 0 pre), and anemia (14/57 post vs. 7/59 pre). Other than for the low hematocrit levels in which there is a more clear discrepancy between prestudy and postbaseline, the number of patients affected is too small to make any general conclusions. There does not

appear to be any between treatment group differences. None of these lab abnormalities resulted in SAEs.

Vital signs:
Altogether, 22 (37% vs. 24% prestudy) of 59 patients had PCI vital sign measurements during the study, including 7 (37%) patients in the 1.25-mg dose group and 15 (38%) patients in the 2.5-mg dose group. It appears that the PCI vital sign abnormality in most cases was an isolated event not sustained through subsequent measurements and not associated with corresponding changes in other vital sign parameters. The parameters in the PCI category were diastolic BP, respiratory rate, and pulse.

ECG:
There were a total of five patients (9%) with ECG PCI abnormalities. One was in the low dose group and four were in the high dose group. Of these, three had the abnormalities only at screening. There was only one abnormality which was new at final evaluation: Patient 331-081-003471 was a 1.3-week-old white male infant who received seven 1.25-mg daily doses of pantoprazole. The patient's QRS interval was 55 ms at baseline and 118 ms at final evaluation. The patient had no relevant medical history, and had no AEs during the study. The investigator considered the QRS interval prolongation to be not clinically significant.

Growth Parameter Analyses

Mean patient weight increased from 2661 g at baseline to 2855 g in the 1.25-mg dose group and from 2679 g at baseline to 2859 g in the 2.5-mg dose group ($p<0.001$, both groups). The increase was not significantly different between dose groups. The baseline z-scores for weight were -3.78 and -3.47 in the 1.25- and 2.5-mg dose groups respectively, likely reflecting the prematurity and associated disorders of the study patient population. At the end of the treatment period the z-scores remained unchanged at -3.74 and -3.49 respectively, indicating that over the short treatment period, the patients' growth rates for weight remained unchanged.

Mean length increased from 46.8 cm at baseline to 47.5 cm in the 1.25-mg group (not significant) and from 46.0 cm at baseline to 47.9 cm in 2.5-mg group ($p<0.001$). The increase was not significantly different between dose groups. The baseline z-scores for length were -4.70 and -5.23 in the 1.25-mg and 2.5-mg dose groups respectively, again likely reflecting the prematurity of the study patient population. At the end of the treatment period the z-score in the 1.25-mg group was largely unchanged at -4.87, whereas in the 2.5-mg dose group the increase to -4.75 was possibly significant ($p= 0.047$).

Head circumference increased from 32.9 cm at baseline to 33.7 cm in the 1.25-mg dose group ($p=0.02$) and from 32.8 cm at baseline to 34.0 cm in the 2.5-mg dose group ($p<0.001$). The increase was not significantly different between dose groups. The baseline z-scores for head-circumference were -3.73 and -3.68 in the 1.25-mg and 2.5-mg dose groups respectively. At the end of the treatment period, the z-score was not significantly changed at -3.60 in the 1.25-mg dose group, but there was a statistically significant increase to -3.29 in the 2.5-mg dose group ($p=0.019$).

The patients' growth parameters during the study do not appear to have been negatively impacted and there were no differences between groups in growth parameters.

CONCLUSIONS

A. **Pharmacokinetics**

- The concentration values were highly variable after single and multiple doses of pantoprazole in this study population.
- Exposures observed with the 2.5-mg dose were slightly higher compared with that of adults who received 40-mg doses.
- The half-life of pantoprazole appeared to be longer in neonates and preterm infants, compared with that seen in adults and children aged 1 through 16 years.
- The mean apparent total clearance normalized to body weight was similar to that of adults and children aged 6 through 16 years but lower than that of infants aged 1 through 11 months and children aged 1 through 5 years.
- There was no evidence of accumulation after multiple doses of pantoprazole.

B. Symptom Evaluation

Based on the analyses of GERD and respiratory symptom frequency, pantoprazole treatment resulted in some clinical improvements in this patient population; however, improvement did not reach the 0.05 level of significance, as follows:

In the 1.25-mg dose group, the total daily GERD symptom score decreased from a mean of 3.26 at baseline to 2.19 at the last day on therapy (p=0.107). In the 2.5-mg dose group, the total daily GERD symptom score improved from 2.94 at baseline to 2.17 at the last day on therapy (p=0.054). These data include all patients (PK, PK/PD, and PD) with only a clinical diagnosis of GERD. These clinical outcome results are based on a short term study with no control and should be considered exploratory. The clinical meaningfulness of the decrease in symptom score seen in either treatment group is questionable.

C. Safety

Based on the analysis of patient safety data, daily doses of pantoprazole (1.25 mg to 2.5 mg) were relatively safe in neonates and preterm infants with a clinical diagnosis of GERD.

- AEs were reported in 30 (51%) of 59 patients. TEAEs were reported in 5 (26%) of 19 patients in the 1.25-mg dose group and in 18 (45%) of 40 patients in the 2.5-mg dose group; the difference between groups was not significant.
- No patients were withdrawn from the study because of AEs and no deaths occurred.
- There were two reports of SAEs, both of which occurred in the follow-up period of the study and were not related to pantoprazole in the opinion of the investigators. One patient had a urinary tract infection and the other had hematochezia.
- The most frequently reported TEAE was anemia, which occurred in 5 (9%) patients. Other TEAEs occurring in at least 5% of patients were hypoxia, rhinitis, and constipation.
- PCI laboratory test result abnormalities were common at baseline and decreased over the period of the study. There were no clear dose-related abnormalities identified.

- The patients grew in weight, length, and head circumference during the study.

This was the only study done for the PWR in the neonates and preterm NICU population. These infants have confounding complexities given their population. Without a placebo group, it is difficult to ascertain which adverse events are most likely due to study drug versus prematurity or disease process that has caused them to be in the NICU. In general, the drug appears to be well tolerated.

9.4.6 Study 3001B3-333-WW: Ages 1 to 11 months – PK/PD and safety study

A. General Design and Objective

Study 3001B3-333-WW (Study 333) is a Phase 3, multicenter, randomized, open-label, single-dose and multiple-dose PK, safety, and multiple-dose PD study in infants aged 1 month through 11 months with presumed GERD. Hospitalized patients or outpatients participated in one of two strata: PK or PD. Patients participated in the study for a total of approximately four weeks. There were 56 patients planned for enrollment in the study; 32 patients in the PK portion and 24 patients in the PD portion of the study.

The primary objective of the study was to characterize the PK profile of single and repeated oral doses of pantoprazole and the PD profile at baseline and at steady state after multiple doses of pantoprazole in infants aged 1 month through 11 months with presumed GERD.

The secondary objective was to assess the safety and tolerability of pantoprazole in infants aged 1 month through 11 months with presumed GERD. Growth parameters (length, weight, and head circumference) were also to be assessed as part of the safety evaluation. This review focuses on the safety data for the study. Please refer to the biopharmacology reviews for further details of the PK/PD analysis.

B. Background

This study was designed and conducted in response to the Study 2 requirements of the FDA's Pediatric Written Request (PWR) for PROTONIX, issued May 17, 2008. The PROTONIX PWR Study 2 requirements are for single-dose and multiple-dose PK data and PD, and safety data of two dose levels of pantoprazole for patients of both sexes, aged 1 month through 11 months, with a presumptive diagnosis of GERD.

C. Inclusion

1. Male or female term or postterm infants beyond the neonatal period more than four weeks but less than 12 months of (postnatal) age, or preterm infants with a corrected age of at least 44 weeks (postmenstrual) but less than 12 months at the time the ICF was signed.
2. A presumptive diagnosis of GERD requiring pharmacologic treatment. The method by which the presumptive diagnosis of GERD was made was recorded on the eCRF.
3. Body weight at least 2.5 kg but not more than 15 kg.
4. Hospitalized patients or outpatients at the time of study entry.
5. Able to swallow the pantoprazole suspension.

D. Exclusion

Similar to Study 331 (Section 9.4.5).

E. Treatment

Patients were randomized to receive either a low dose (0.6 mg/kg) or high dose (1.2 mg/kg) of pantoprazole sodium enteric-coated spheroid suspension, with each patient to receive at least five consecutive daily doses.

Concomitant Medications

Concomitant medications were permitted as appropriate. Eligible patients were permitted to continue their usual medications according to standard clinical practice. Continuous treatment with theophylline (or its derivatives) or digoxin were to be closely monitored throughout the study to assure that proper serum levels of these drugs were maintained.

Medications used to treat nongastrointestinal conditions were allowed, provided that no dose adjustment was likely to be necessary during the study.

Prohibited Medications

Patients were required to discontinue any acid suppressant therapy, including the use of PPIs or H2RAs, at the time that the ICF was signed, and they were not to be given any acid suppression therapy other than pantoprazole during the active treatment period. During the two-week post-treatment period, patients were permitted to receive acid suppression therapy as well as any other treatments that were discontinued for the study if such treatments were clinically indicated. Use of warfarin, carbamazepine, phenytoin, or rifampin for any disorder is prohibited.

F. Safety Considerations/Monitoring

Throughout the study period, routine safety monitoring of pantoprazole was based on reported signs and symptoms, and the results of scheduled physical examinations, vital signs, length, weight, head circumference, standard 12-lead ECGs, and clinical laboratory tests. Table 91 from the Applicant details the study visits.

Table 91: Study Schedule (Study 333)

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

G. Data Analysis

Clinical outcomes, PK parameters, and safety analysis were summarized in a descriptive manner.

H. Results

Disposition of Patients
A total of 81 patients were enrolled in the study. Fourteen patients were screen failures. Sixty-seven were randomly assigned to treatment and received at least one dose of pantoprazole. Thirty-three patients were randomly assigned in a 1:1 fashion to receive the low dose (0.6 mg/kg), and 34 patients were randomly assigned to the high-dose (1.2 mg/kg) group.

The safety population consisted of 39 male and 28 female infants aged 1 month through 11 months with presumed GERD. Sixty-seven patients who received at least one dose of pantoprazole were included in the safety analysis population. From this, 42 patients were included in the all-patient population for single-dose PK analysis, 35 patients were included in the valid for PK evaluation population for single-dose PK analysis, and 31 patients were included in the valid for PK evaluation population for multiple-dose PK analysis.

Discontinuations
The study was completed by more than 90% of the enrolled patients. Reasons for violations during patient participation as detailed in Table 92 from the Applicant. Most are a result of study procedure deviations.

Table 92: Patients with Protocol Violations (Study 333)

Patient	Postnatal Age (Months)/ Corrected age (Months)/Sex[a]	Dose	Comments
333-013-002130	1.1/F	1.2 mg/kg	During multiple-dose PD analysis, the pH-metry equipment malfunctioned.
333-024-002256	3.6/1.6/M	1.2 mg/kg	At the time of randomization, patient's ALT was greater than twice the upper limit of normal.
333-024-002263	2.3/F	1.2 mg/kg	Patient had multiple-dose PK blood sample but only received 4 consecutive daily doses of pantoprazole.
333-024-002265	10.3/8.5/M	1.2 mg/kg	Patient's screening evaluation did not include determinations of ALT, AST, and alkaline phosphatase.
333-024-002268	10.8/7.6/M	0.6mg/kg	Patient failed to return for the multiple-dose PK evaluation.
333-024-002269	4.2/1.1/F	0.6mg/kg	Patient failed to return for the multiple-dose PK evaluation.
333-033-002382	4.1/3.2/M	1.2 mg/kg	Patient returned to study site 1 day past the study window allowed by the protocol.
333-230-005181	7/M	0.6mg/kg	During multiple-dose PD analysis, the probe was pulled out, but replacement was not confirmed by X-ray.

Demographics

A total of 45 (67%) patients participating in the study were full-term infants and 22 (33%) patients were premature infants, with 36 (54%) patients less than six months of age (postnatal age), and 31 (46%) patients were aged six months or older. The mean age of patients was 5.3 months in the low-dose group and 5.4 months in the high-dose group. The mean gestational age of the patients was 36.6 weeks and the mean corrected age for preterm infants was 4.5 months. Patient 333-013-002126 had the ICF signed before her first birthday, and her demographic interview date was three days after her first birthday, so the maximum patient age is 12.1 months. A total of 39 (58%) male patients and 28 (42%) female patients were randomized to the study. The majority of patients (72%) were Caucasian.

Table 93: Pt Demographics (Study 333)

		0.6 mg/kg	1.2 mg/kg	Total
Characteristic	**P-Value**	**N=33**	**N=34**	**N=67**
Age (month)				
Mean	0.920a	5.98	5.91	5.94
Standard Deviation		2.98	3.42	3.19
Min – Max		1.3 – 13.9	1.1 – 12.6	1.1 – 13.9
Gestational Age (week)				
Mean	0.425a	36.2	36.9	36.6
SD		4.38	3.30	3.86
Min – Max		26 - 41	28 - 41	26 - 41
Type of Birth	0.609b			
Full Term		21 (64%)	24 (71%)	45 (67%)
Premature	0.806b	12 (36%)	10 (29%)	22 (33%)
Sex				
Female		13 (39%)	15 (44%)	28 (42%)
Male	0.064b	20 (61%)	19 (56%)	39 (58%)
Race				
African American		7 (21%)	7 (21%)	14 (21%)
Other		5 (15%)	0	5 (7%)
Caucasian	1.000b	21 (64%)	27 (79%)	48 (72%)
Hispanic or Latino		1 (3%)	1 (3%)	2 (3%)
Non-Hispanic and Non-Latino		32 (97%)	33 (97%)	65 (97%)
Length (cm)				
Mean	0.576a	64.8	63.8	64.3
SD		7.53	7.25	7.35
Min – Max		52 – 80	50 - 76	50 - 80
Weight (kg)				
Mean	0.744a	6.9	6.8	6.9
SD		1.98	1.92	1.94
Min – Max		3.8 – 10.8	3.4 – 9.8	3.4 – 10.8
Head Circ (cm)				
Mean	0.748a	42.4	42.1	42.2
SD		2.99	3.08	3.02
Min – Max		37 – 47	35 - 46	35 - 47
Age Group	0.466b			
≥ 1 and < 6 month		16 (48%)	20 (59%)	36 (54%)
≥ 6 month		17 (52%)	14 (41%)	31 (46%)

Concomitant Therapy/Medications

Only a few medications were used by patients during this study and appear unrelated to GERD.

PK Evaluation

The PK results were presented as:

1. Single–dose PK results in all-patient PK population
2. Single–dose PK results in valid-for-PK evaluation population

3. Multiple–dose PK results in all-patient PK population
4. Multiple–dose PK results in valid-for-PK evaluation population

Safety Evaluation

Adverse Events
A total of 30 patients had TEAEs, 13 (39%) patients in the 0.6 mg/kg dose group and 17 (50%) patients in the 1.2 mg/kg dose group. TEAEs reported for more than one patient included fever (7, 10%), diarrhea (6, 9%), contact dermatitis (5, 8%), rhinitis (4, 6%), gastroenteritis (3, 5%), infection (3, 5%), otitis media (3, 5%), abdominal pain (2, 3%), tooth disorder (2, 3%); flatulence (2, 3%), rash (2, 3%); and vomiting (2, 3%).

Four patients had TEAEs that were considered by the reporting investigator to be possibly or probably related to their treatment with pantoprazole, including two patients with diarrhea (1 in each dose group), one patient with eructation (0.6-mg/kg dose group), and one patient with flatulence (1.2-mg/kg dose group). These TEAEs were all considered to be mild in severity; the two cases of diarrhea resolved in two days or less.

A 4.6-month-old male patient (333-008-002061) had injection site pain on study day 5 after receiving an intramuscular injection of an unspecified anti-infammatory medication for treatment of croup. The event resolved the same day. This event was described as mild and was considered by the investigator to be not related to pantoprazole.

There were no statistically significant differences in the incidence of TEAEs between the two dose groups.

Table 94: TEAEs (Study 333)

Body System Adverse event	overall p-value	Pantoprazole 0.6 mg/kg total= 33 N (%)	Pantoprazole 1.2 mg/kg total= 34 N (%)	All treated Total = 67 N (%)
Any adverse event	0.464	13 (39.4)	17 (50.0)	30 (44.8)
Body as a Whole	1.000	6 (18.2)	6 (17.6)	12 (17.9)
Abdominal pain	1.000	1 (3.0)	1 (2.9)	2 (3.0)
Fever	1.000	3 (9.1)	4 (11.8)	7 (10.4)
Infection	1.000	1 (3.0)	2 (5.9)	3 (4.5)
Injection site pain	1.000	0	1 (2.9)	1 (1.5)
Sepsis	0.493	1 (3.0)	0	1 (1.5)
CV System	0.493	1 (3.0)	0	1 (1.5)
ASD	0.493	1 (3.0)	0	1 (1.5)
Digestive system	0.369	5 (15.2)	9 (26.5)	14 (20.9)
Diarrhea	0.673	2 (6.1)	4 (11.8)	6 (9.0)
Eructation	0.493	1 (3.0)	0	1 (1.5)
Flatulence	0.493	0	2 (5.9)	2 (3.0)
Gastroenteritis	1.000	1 (3.0)	2 (5.9)	3 (4.5)
Tooth disorder	0.493	0	2 (5.9)	2 (3.0)
Vomiting	0.239	2 (6.1)	0	2 (3.0)
Metabolic and Nutritional	0.614	2 (6.1)	1 (2.9)	3 (4.5)
CPK increased	0.493	1 (3.0)	0	1 (1.5)
Dehydration	0.493	1 (3.0)	0	1 (1.5)
Weight loss	1.000	0	1 (2.9)	1 (1.5)
Resp System	0.197	1 (3.0)	5 (14.7)	6 (9.0)
Apnea	1.000	0	1 (2.9)	1 (1.5)
Cough increased	1.000	0	1 (2.9)	1 (1.5)
Laryngitis	1.000	0	1 (2.9)	1 (1.5)
Rhinitis	0.614	1 (3.0)	3 (8.8)	4 (6.0)
SkinAppendages	1.000	4 (12.1)	5 (14.7)	9 (13.4)
Contact derm	1.000	2 (6.1)	3 (8.8)	5 (7.5)
Dermatitis atopic	0.493	1 (3.0)	0	1 (1.5)
Eczema	1.000	0	1 (2.9)	1 (1.5)
Maculopapular rash	0.493	1 (3.0)	0	1 (1.5)
Rash	1.000	1 (3.0)	1 (2.9)	2 (3.0)
Special Senses	0.239	0	3 (8.8)	3 (4.5)
Otitis media	0.239	0	3 (8.8)	3 (4.5)
Urogenital Sys	1.000	0	1 (2.9)	1 (1.5)
Urine abn	1.000	0	1 (2.9)	1 (1.5)

Serious Adverse Events

There were no deaths in this study. There were five patients (8%) that reported SAEs. Three of the patients were in the lower dose group and two were in the higher dose group. None of the SAEs was considered by the reporting investigator to be related to drug treatment.

0.6 mg/kg dose group

1. Patient 333-013-002131, a ten-month-old, White, non-Hispanic, non-Latino, female patient, had vomiting and dehydration on study Day 5. The dehydration was of moderate severity and the vomiting was considered severe. These events resolved after three days and were considered by the investigator as definitely not related to pantoprazole.

Comment: According to the CRF, the patient was diagnosed with gram positive cocci positive blood culture and gastroenteritis. The patient was treated with IV fluids, ceftriaxone, and clarithromycin. The study drug was temporarily halted during the hospitalization and resumed after discharge (b) (6) *for a total of ten non consecutive doses and completed the study on Nov 20, 2007. I agree with the investigator's assessment that study drug is likely unrelated to this SAE.*

2. Patient 333-021-002211, a three-month-old Hispanic or Latino male patient with a history of laryngomalacia, had respiratory distress (stridor) on study Day 18, during the follow-up period. This event was considered as life threatening, and the patient was hospitalized. The event resolved after 60 days and was considered by the investigator as definitely not related to pantoprazole.

Comment: More detailed narrative of this patient's history in the CRF indicates that this patient has a complex medical history and it is likely from this description that the respiratory distress that lead to the prolonged hospitalization is a consequence of his congenital upper airway malformation (Pierre Robin Sequence).

3. Patient 333-033-002377, a seven-month-old, White, non-Hispanic, non-Latino, male patient, had gastroenteritis on study Day 2. This event was considered by the investigator to be severe, and the patient was hospitalized and received concomitant medication. The event resolved after nine days and was considered as definitely not related to pantoprazole.

Comment: This patient was diagnosed with Rotavirus. The test drug was continued through the hospitalization and the patient recovered without further complications. It is unlikely that the test drug caused the rotavirus infection, which is a highly contagious and common viral disease in this age group.

1.2 mg/kg dose group

4. Patient 333-201-005002, a six-month-old, White, non-Hispanic, non-Latino, female patient vomited the dose of pantoprazole and was found to have rotavirus gastroenteritis on study Day 1. She was withdrawn from the study and hospitalized. This event was of moderate severity, resolved after four days, and was considered by the investigator as definitely not related to pantoprazole.

Comment: As the SAE occurred concomitantly with the administration of test drug, it is unlikely that the study drug caused this infectious disease. Likely, the patient was exposed a few days prior to rotavirus.

5. Patient 333-235-005216 a nine-month-old, White, non-Hispanic, non-Latino, male patient was found to have apnea on study day 2. The patient took the first dose of test article on Sep 12, 2007. On (b) (6) (study day (b)), approximately (b) (6) after his

initial dose of pantoprazole, the patient developed apnea and cyanosis. His mother picked him up and shook him causing him to vomit. He recovered within a minute, and was admitted to the hospital for observation. A chest x-ray was normal. The day after admission, the apnea having resolved and the patient was started back on continuous feeds. Study medication was continued during the hospitalization. The patient continued to improve and he was discharged from the hospital to home, five days after admission on study day (b) (6). Following the episode of apnea, the patient;s mother did not want to resume the bolus feeding as required by the protocol in order to obtain the second pH metry. The patient received the last dose of test article on Sep 18, 2007 and was withdrawn from the study per the investigator's request to honor the mothers wishes. During the telephone contact on Oct 9, 2007, the mother confirmed that apnea episodes had resolved, but the GERD was ongoing. The investigator considered this event life threatening and probably not related to test article. The investigator attributed the SAE to the washout period, when the patient discontinued the previous GERD medication as required by the protocol.

Comment: I can not rule out a possible association of the study drug to the apneic event. However, acute life-threatening events such as these are not uncommon in infants and an underlying diagnosis is not often found.

Safety Related Discontinuations

One patient (333-201-005002) was withdrawn after being admitted to hospital because of a rotavirus gastroenteritis which was considered by the investigator not to be related to treatment with pantoprazole.

Laboratory Evaluations

Altogether, 27 (40%) of 67 patients had PCI laboratory test results, including 14 (42%) patients in the 0.6 mg/kg dose group and 13 (38%) patients in the 1.2 mg/kg dose group. Moderate increases in the mean fasting gastrin levels were seen in both treatment groups; this is consistent with findings from adult clinical studies. There were no statistically significant between-dose-group mean changes in laboratory test results. At *screening*, 18 (27%) patients in the safety population had a PCI laboratory test result, 9 (27%) in the 0.6-mg/kg and 9 (27%) in the 1.2-mg/kg treatment groups. The most common PCI finding overall was a urine leukocyte esterase ≥ 2+ (15%), which might be a result of the collection methodology (bags were used for collection) rather than an actual abnormal finding. The next most common PCI finding at baseline was a PCI-abnormal platelet count (13%).

At the post baseline evaluation, 17 (27%) of 63 patients had PCI laboratory test results, including 9 (27%) patients in the 0.6 mg/kg dose group and 8 (27%) patients in the 1.2 mg/kg dose group. Again, the most common PCI finding was an abnormally high level of urine leukocyte esterase (6/57, 11%). The second most common PCI finding was the same as in prescreen.

A 7.3 month-old, 6.5 kg, White, non-Hispanic/non-Latino, male patient (333-202-005017) in the 0.6 mg/kg dose group with a presumptive diagnosis of GERD had an elevated CPK value (310 mU/mL, normal range: 18 to 183 mU/mL) at screening and had a PCI-elevated CPK value (593 mU/mL, PCI: ≥ ULN [183 mU/mL]) at the final evaluation. No adverse events were reported

during this period. The Applicant reports that there is no obvious reason for this increase in the creatine kinase value.

One PCI-abnormal lab result was reported as a TEAE. A six-month-old female patient (333-033-002381) had an elevated CPK of 333 mU/mL at the screening evaluation. On repeat evaluation (study day 6), the patient's CPK value was 385 mU/mL (> 3 x ULN). In reporting this elevation as a TEAE, the reporting investigator considered it to be mild in severity and definitely not related to treatment with pantoprazole.

Patient 027-2286 was preterm (33 weeks gestational age), 10.9 month old, 9.8 kg, White, non-Hispanic/non-Latino, male with a presumptive diagnosis of GERD. Prior to study entry, the patient did not receive any medication for the treatment of GERD. In addition to GERD, the patient's medical history included sleep apnea which resolved prior to study entry and mild intermittent asthma that was ongoing at study entry. At study entry the patient was not taking any other medications. Laboratory evaluations at screening on study Day -3 showed an elevated triglyceride level of 1.35 mmol/L (NL=0.34-1.13 mmol/L), which increased to a PCI level of 5.69 mmol/L at the final evaluation on study Day 8. No laboratory adverse events were reported during this period; however, the patient did have an adverse experience of fever on study day 4, loose stools on study Day 6, and roseola on study Day 8. There is no obvious reason for this increase in the patients triglycerides while on test article. It was confirmed that a four hour fast was completed prior to the collection of the screening labs and a three hour fast prior to the final evaluation lab tests. The PI did not consider this timeframe fasting and dismissed the elevated levels. The investigator did not consider these clinically significant. The triglyceride levels decreased over the following four weeks.

Overall, there do not appear to be a notable safety signal in terms of laboratory abnormalities with short term use of pantoprazole. Triglyceride level changes with pantoprazole use should be reviewed in other studies for comparison.

ECG

Two (3%) patients in the safety population had a PCI ECG result at screening. They were both in the 0.6 mg/kg dose group. Three (5%) patients in the safety population had a PCI ECG result at the final evaluation, 2 (6%) in the 0.6 mg/kg and 1 (3%) in the 1.2 mg/kg treatment groups.

Patient 333-013-002129 had a prolonged QRS interval (88 msec, PCI limits: < 40 msec or > 84 msec) at the screening evaluation, and at the final evaluation, it remained 88 msec.

Patient 333-091-002556 had a prolonged QRS interval (85 msec, PCI limits: <40 msec or >84 msec) and a prolonged QTc interval (557.2 msec, PCI limits: <200 or >550 msec) at the screening evaluation. At the final evaluation, the patient's QRS interval remained prolonged (91 msec), and the QTc interval was 408.7 msec.

Patient 333-217-005236 had a QTc interval just short of PCI length (> 550 msec) of 548.2 msec at the screening evaluation. At the final evaluation, the QTc interval was PCI-prolonged (> 550 msec) at 636.4 msec. The patient had no associated clinical AEs and was receiving no

concomitant medications. The reported overall evaluation on the ECG was normal on the case report form.

The medical monitor reviewed the records of the patients with PCI changes in ECG parameters and in each case determined that these findings had no actual clinical importance.

Comment: In both cases of the QTc prolongation, there was an abnormality at baseline. For one patient the QTc interval slightly decreased, whereas in the other, it was slightly increased at the final evaluation. It is unlikely that the drug treatment has an association.

Growth Parameter Analyses

Patients were monitored for changes in growth parameters (length, weight, and head circumference) during the study. Z-scores for each parameter were calculated. Despite the short duration of this study, analyses of growth parameters showed statistically significant increases from baseline to final visit for weight, length, and head circumference. There were no significant changes from baseline in the z-score for any parameter indicating that the increases in length, weight, and head circumference were consistent with those expected for patients of this age. No statistically significant differences between the two dose groups were observed for the change from baseline in growth parameters and their z-scores.

The safety results were as follows:

1. A total of 30 patients had TEAEs: 13 (39%) patients in the 0.6 mg/kg and 17 (50%) patients in the 1.2 mg/kg group. Specific AEs reported as TEAEs in more than one patient included fever, diarrhea, contact dermatitis, rhinitis, gastroenteritis, infection, otitis media, abdominal pain, tooth disorder, flatulence, rash, and vomiting. The difference in the incidence of TEAEs between treatments was not statistically significant.
2. Five patients reported SAEs: 3 (9%) patients in the 0.6 mg/kg and 2 (6%) patients in the 1.2 mg/kg group; none of the SAEs were considered by the reporting investigator to be related to treatment with pantoprazole. I agree with the investigator opinion that four of five of these events are not related to the study drug, however, the SAE involving the patient with an apneic episode is more difficult to rule-out an association.
3. One patient in the 1.2 mg/kg group was withdrawn from the study because of an SAE (rotavirus gastroenteritis), deemed not to be related to the study drug.
4. A total of 17 (27%) of patients, including 9 (27%) in the 0.6 mg/kg and 8 (27%) in the 1.2 mg/kg group, were identified as having post baseline PCI values for laboratory tests. None of the PCI changes was considered to be of actual clinical importance.
5. Five (8%) patients had post baseline abnormalities in VS that met the PCI criteria, 3 (9%) in the 0.6 mg/kg dose group and 2 (6%) in the 1.2 mg/kg dose group. None of the PCI changes was considered to be of actual clinical importance. Three (5%) patients had post baseline abnormalities in ECG findings that met the PCI criteria, 2 (6%) patients in the 0.6 mg/kg dose group and 1 (3%) patient in the 1.2 mg/kg dose group, the abnormalities were also noted at screening to some degree.
6. There was no negative impact on growth parameters during the study.

CONCLUSIONS

A. Pharmacokinetics

- Plasma concentrations increased with increasing doses of pantoprazole, but the increase was not exactly dose proportional.
- There was no evidence of accumulation of pantoprazole after once-daily, multiple-dose administration.
- There appears to be no apparent trend for CL/F versus age or CL/F versus BSA in children, aged 1 month through 11 months.
- The exposures observed with the 1.2-mg/kg dose regimen were generally similar to those seen in adults receiving 40 mg of pantoprazole.

B. Safety

- Overall, no new safety signals were reported during this study with pantoprazole.

9.4.7 Study 3001B3-334-US: Ages 1 to 11 year – PK and Safety Study

A. General Design and Objective

Study 3001B3-334-US (Study 334) is a multicenter, randomized, open-label, single-dose and multiple-dose PK study in children ages 1 through 11 years with endoscopically proven GERD.

The primary objective was to characterize the PK profile of single and repeated doses of pantoprazole in children ranging in age from 1 through 11 years with endoscopically proven GERD. The secondary objective was to assess the safety and tolerability of pantoprazole in children ranging in age from 1 through 11 years with endoscopically proven GERD. Growth parameters (weight, height/length, and weight for height) were also assessed.

B. Background

The PROTONIX PWR requires a PK, exposure/response, and safety study in pediatric patients 1 through 11 years of age with endoscopically proven GERD in Study 4. This current study was designed to meet this requirement.

C. Inclusion

1. Male or female children ranging in age from 1 through 11 years.
2. Had endoscopically proven GERD diagnosed within six months before study entry confirmed by one of the following: positive endoscopic evidence of reflux-related EE (Hetzel-Dent score ≥2 or Los Angeles (LA) grade A or above), or nonerosive GERD with positive histologic evidence of esophagitis consistent with GERD confirmed by the study.
3. Weight ≥8.3 kg for patients ranging in age from 1 through 5 years, and ≥25 kg for patients ranging in age from 6 through 11 years.
4. Patients might have been hospitalized or been outpatients at the time of study entry.
5. Patients ≤5 years old had to be willing to consume applesauce or apple juice or have a nasogastric (NG)/percutaneous endoscopic gastronomy (PEG) tube that was ≥16 French.

D. Exclusion

Similar to Study 331 and also excludes pregnant females.

Treatments

Single and multiple oral doses of pantoprazole (low [0.6 mg/kg] and high [1.2 mg/kg]) were evaluated. For ages 1 through 5 years, the two dosage levels (low and high) of pantoprazole spheroids were provided in four strengths: 5-, 10-, 15-, and 20-mg capsules containing spheroids according to the patient's weight for administration. Spheroids were sprinkled on applesauce or in apple juice. For patients ages 6 through 11 years whose weight was ≥25 kg, the low and high

dosage levels were achieved using pantoprazole tablets in strengths of 20 and 40 mg. See the tables below from the Applicant's submission for dosing.

Table 95: Dose Strength Based on Weight Group (Study 334)

	Dose Group	
Weight (kg)	Low	High
≤12.5	5.0 mg	15 mg
>12.5 to <25	10 mg	20 mg

	Dose Group	
Weight (kg)	Low	High
≥25	20 mg	40 mg

Concomitant Medications

Patients continued their usual medical therapies according to standard clinical practice. None of the patients was taking theophylline derivatives or digoxin. Medications used to treat nongastrointestinal conditions were allowed, provided that no dose adjustment was likely to be necessary during the study.

Prohibited Medications

Patients stopped their use of PPIs, H2RAs, prokinetics, anticholinergics, and bismuth preparations at least 24 hours before beginning test article and did not take these drugs throughout the treatment period. Use of antacids was prohibited from two hours before until two hours after administration of each dose of test article. Treatment requiring chronic use of warfarin, carbamazepine, or phenytoin for any disorder was prohibited. Special diets or herbal or alternative medication that might affect the metabolism of test article could not be used without prior approval of the medical monitor.

F. Safety Considerations/Monitoring

Safety and tolerability were evaluated using the reported AEs, scheduled physical examinations, vital sign measurements, growth parameters (height/length and weight), 12-lead ECG recordings, and clinical laboratory test results.

The study schedule was as follows from the Applicant submission:

Table 96: Study Schedule (Study 334)

Study Phase	Screening[a]			Treatment Period				Final Study Evaluation	Early Termination	Follow-up Contact
				PK	PK					
Study Day	-21 through -2	-1	1	1	7±2	14±3	21±3	28±3		42±3
Study Hour			-2							
Informed consent	X									
Visit	X	X		X	X		X	X	X	
Telephone contact						X				X
Medical history	X									
Physical examination[b]	X	X			X		X	X	X	
Endoscopy[c]	X									
Vital signs[d]	X	X	X	X	X		X	X	X	
ECG (12-lead)	X							X	X	
Laboratory evaluation[c,e]	X				X			X	X	
Urine pregnancy test[f]	X	X						X	X	
Buccal cell collection[g]	X									
Randomization			X							
Swallow test[h]	X									
Dispense test article				X	X		X			
Test article administration[i]				X----------X						
Medication diary collection				X----------X						
PK blood sample collection			X	X[j]	X[k]					

G. Data Analysis

Statistical Analytical Plan
Descriptive statistics (e.g., mean, standard deviation, and coefficient of variation) were calculated for the PK parameters for each dose group.

Safety data (vital sign measurements, ECG readings, and routine laboratory test results) were summarized by descriptive statistics and were analyzed using an analysis of covariance (ANCOVA) with predose data as the baseline covariate and treatment as a factor. Growth parameters (weight, length/height, weight z-score, length/height z-score, and weight-for-height z-score) were summarized and analyzed in the same way. Changes from baseline were reported. Individual data for vital sign measurements, ECG readings, and laboratory test results were evaluated for potential clinical importance (PCI) using predetermined criteria. Data were to be presented for overall, by three age groups (<2 years, ≥2 years to <6 years, and ≥6 years), and by two age groups (<6 years and ≥6 years).

H. Results

Disposition
A total of 41 patients were enrolled and are in the safety analysis. Two patients discontinued from the study. Patient 334-016-001226 was given spheroids instead of tablets, and this was considered a major protocol violation. Patient 334-017-001243 requested to be withdrawn from the study because of an inadequate response to GERD.

Demographics

The study population of the younger age group (<6 years/spheroid) consisted of 17 patients, 6 females and 11 males, ages 1 year through 5 years. The study population of the older age group (≥6 years/tablet) consisted of 24 patients, 10 females and 14 males, ages 6 years through 11 years. All patients had a clinical diagnosis of GERD that was confirmed endoscopically. Overall, the study population consisted of 41 patients, 16 females and 25 males, ages 1 year through 11 years. Data from all patients who took at least one dose were included in the safety analysis.

Table 97: Demographics for Age < 6 years (Study 334)

Characteristic	p-Value	0.6 mg/kg (n=7)	1.2 mg/kg (n=10)	Total (n=17)
Age (years)	0.177			
Mean		3.86	2.80	3.24
SD		1.46	1.55	1.56
Min – Max		1 – 5	1 – 5	1 – 5
Sex (%)	1.000			
Female		2 (29)	4 (40)	6 (35)
Male		5 (71)	6 (60)	11 (65)
Race (%)	0.309			
Asian		0	2 (20)	2 (12)
Other		1 (14)	0	1 (6)
White		6 (86	8 (80)	14 (82)
Ethnicity (%)	1.000			
Hispanic		2 (29)	2 (20)	4 (24)
Non-Hispanic		5 (71)	8 (80)	13 (76)
Baseline Ht	0.131			
Mean (cm)		104.37	93.42	97.93
SD		13.46	14.21	14.57
Min – Max		76.8 – 116	68.9 – 116.8	68.9 – 116.8
Baseline Wt	0.232			
Mean (kg)		17.9	15.0	16.2
SD		3.84	5.19	4.78
Min – Max		11.9 – 23.4	8.9 – 25.5	8.9 – 25.5
Study duration	0.555			
Mean (days)		58.43	60.90	59.88
SD		10.6	6.4	8.1
Min – Max		44 - 74	51 - 71	44 - 74

Table 98: Demographics for Age ≥6 years (Study 334)

Characteristic	p-Value	0.6 mg/kg (n=7)	1.2 mg/kg (n=10)	Total (n=17)
Age (years)	0.728			
Mean		8.6	8.8	8.7
SD		2.0	1.1	1.52
Min – Max		6 - 11	7 - 11	6 – 11
Sex (%)	0.697			
Female		4 (36)	6 (46)	10 (42)
Male		7 (64)	7 (54)	14 (58)
Race (%)	1.000			
Black		2 (18)	2 (15)	4 (17)
White		9 (82)	11 (85)	20 (83)
Ethnicity (%)				
Non-Hispanic				100%
Baseline Ht	0.632			
Mean (cm)		134.3	136.3	135.4
SD		14.0	6.2	10.3
Min – Max		110 - 157	129 – 147.6	110 – 157
Baseline Wt	0.435			
Mean (kg)		33.6	37.2	35.6
SD		10.8	11.1	10.9
Min - Max		20.4 – 57.1	24.4 - 60	20.4 – 60
Study duration	0.770			
Mean (days)		55.0	56.2	55.7
SD		12.4	7.8	10.0
Min - Max		22 - 65	44 – 74	22 – 74

Concomitant Therapy/Medications

Concomitant medications were defined as any medications received during the period of treatment with pantoprazole. A summary of nonstudy concomitant medications received by ≥10% of patients in any pantoprazole dose group is presented in Table 99.

Table 99: Concomitant Medications Taken by Patients (Study 334)

Generic term	Overall p-Value[a]	----------Treatment--------- Pantoprazole Low (0.6 mg/kg) (n=18)	Pantoprazole High (1.2 mg/kg) (n=23)	Total (n=41)
Salbutamol	0.243	0	3 (13.0)	3 (7.3)
Amitriptyline	0.187	2 (11.1)	0	2 (4.9)
Cetirizine hydrochloride	0.573	2 (11.1)	1 (4.3)	3 (7.3)
Ibuprofen	0.363	1 (5.6)	4 (17.4)	5 (12.2)
Amoxicillin	0.573	2 (11.1)	1 (4.3)	3 (7.3)
MiraLax	1.000	2 (11.1)	3 (13.0)	5 (12.2)
Multivitamins	0.187	2 (11.1)	0	2 (4.9)
Pseudoephedrine hydrochloride	0.187	2 (11.1)	0	2 (4.9)
Acetaminophen	1.000	3 (16.7)	4 (17.4)	7 (17.1)
Montelukast	0.438	2 (11.1)	5 (21.7)	7 (17.1)
Budesonide	0.243	0	3 (13.0)	3 (7.3)

Safety Evaluation

Exposure

There were no significant differences between treatment groups in the percentage of exposure to study drug or the number of days of study medication received. On average, the exposure to the low dose and high doses were 90% and 98%, respectively. Patients in both treatment arms were treated for a median of 28 days with mean of 26.1 and 28.2 days for the low and high doses, respectively.

In the age < six-years/spheroid group, all patients in the high-dose group and 6 of the 7 (86%) patients in the low-dose group had a minimum of 21 days of exposure to pantoprazole treatment. All patients in the high-dose group and 10 of the 11 (91%) patients in the low-dose group in the > six-years age group (tablet) had a minimum of 21 days of exposure to pantoprazole treatment. One medication error occurred for patient 334-002-001026 during the study. The patient accidentally took two doses of the 40-mg tablet, however, no associated AEs were reported.

Adverse Events

A total of 27 of 41 patients overall had TEAEs: 13 of 18 patients in the low-dose group and 14 of 23 patients in the high-dose group. Specific AEs reported as TEAEs for more than one patient were abdominal pain (6 patients); diarrhea (5); accidental injury, upper respiratory infection, and vomiting (4 each); fever, headache, and otitis media (3 each); and nausea and cough increased (2 each); these events were considered mild or moderate in severity.

There were no statistically significant differences between the two dose groups in the numbers of any specific TEAEs. Five patients had six TEAEs which were considered possibly related to pantoprazole by the investigator. These include abdominal pain (2); fever, diarrhea, increased CPK (non PCI), and eructation (1 each). All related TEAEs were considered of mild or moderate severity.

Table 100: Number of patients reporting TEAEs (Study 334)

Body System	p-Value	0.6 mg/kg total=18 N (%)	1.2 mg/kg total=23 N (%)	All treated total=41 N (%)
Any AE	0.520	13 (72)	14 (61)	27 (66)
Body as a whole	0.503	7 (39)	6 (26)	13 (32)
Abdominal pain	0.377	4 (22)	2 (9)	6 (15)
Accidental injury	1.000	2 (11)	2 (9)	4 (10)
Fever	1.000	1 (6)	2 (9)	3 (7)
Headache	1.000	1 (6)	2 (9)	3 (7)
Inj site hemmor.	1.000	0	1 (4)	1 (2)
Injection site pain	0.439	1 (6)	0	1 (2)
Pain	1.000	0	1 (4)	1 (2)
CV system	1.000	0	1 (4)	1 (2)
Hypotension	1.000	0	1 (4)	1 (2)
Digestive system	0.291	3 (17)	8 (35)	11 (27)
Diarrhea	1.000	2 (11)	3 (13)	5 (12)
Eructation	1.000	0	1 (4)	1 (2)
Gastroenteritis	1.000	0	1 (4)	1 (2)
Nausea	0.495	0	2 (9)	2 (5)
Vomiting	0.618	1 (6)	3 (13)	4 (10)
Met and Nutrit.	0.618	1 (6)	3 (13)	4 (10)
CPK inc	1.000	0	1 (4)	1 (2)
Hyperlipemia	1.000	0	1 (4)	1 (2)
Hyperuricemia	1.000	0	1 (4)	1 (2)
Hypoglycemia	1.000	0	1 (4)	1 (2)
Thirst	1.000	0	1 (4)	1 (2)
Weight loss	0.439	1 (6)	0	1 (2)
Nervous system	0.439	1 (6)	0	1 (2)
Abn behavior	0.439	1 (6)	0	1 (2)
Resp system	0.267	5 (28)	3 (13)	8 (20)
Cough inc	0.495	0	2 (9)	2 (5)
Rhinitis	0.439	1 (6)	0	1 (2)
Sinus cong	0.439	1 (6)	0	1 (2)
URI	0.303	3 (17)	1 (4)	4 (10)
Skin-appendage	1.000	1 (6)	1 (4)	2 (5)
Contact derm	1.000	0	1 (4)	1 (2)
Mac-pap rash				
Special senses	0.303	3 (17)	1 (4)	4 (10)
Eye disorder	0.439	1 (6)	0	1 (2)
Otitis media	0.573	2 (11)	1 (4)	3 (7)
Urogenital	1.000	0	1 (4)	1 (2)
UTI	1.000	0	1 (4)	1 (2)

In the age < six years/spheroid group, 11 of 17 (65%) patients had one or more TEAEs: 4 of 7 patients in the low-dose group and 7 of 10 patients in the high-dose group. Six specific AEs were reported as TEAEs in two or more patients. The following were reported: diarrhea and vomiting (4); and abdominal pain, accidental injury, nausea, and cough increased (2 each). All of the TEAEs reported in the low-dose group were assessed as mild or moderate in severity by the reporting investigators.

In the age ≥ six years/tablet group, 16 of 24 (67%) patients had one or more TEAEs: 9 of 11 patients in the low-dose group and 7 of 13 patients in the high-dose group. Six specific AEs reported as TEAEs were reported in two or more patients: abdominal pain (4); headache (3); and accidental injury, fever, upper respiratory infection, and otitis media (2 each). All TEAEs reported in the high-dose group were assessed as mild or moderate in severity by the reporting investigators.

The overall incidences of TEAEs were similar between the two age groups (p=1.000). There were no statistically significant differences between the two age groups in the numbers of any specific TEAEs except for two mapping to the COSTART Digestive body system (p=0.029; 8 patients age <6 years/spheroid group versus 3 patients in the age ≥ 6 years/tablet group). This difference is due to the reports of vomiting (p=0.024; 4 patients in the younger age group versus no patients in the older age group). In the lower age group, one patient was in the 0.6 mg/kg treatment and three were in the 1.2 mg/kg treatment group.
Comment: This could be a dose-associated AE to which younger children are more susceptible. However, the numbers are too small to make any firm conclusion.

Serious Adverse Events

There were no SAEs reported during this study.

Safety Related Discontinuations

No patients withdrew because of AEs.

Other Clinically Important Adverse Events

Laboratory assessments:
A total of 6 of 41 patients reported laboratory values of PCIs throughout the study. Of those, four were in the <6 years/spheroid group (increased gastrin, positive urine leukocyte esterase, 2 patients each) and two were in the > 6 years/tablet group (increased gastrin and elevated triglyceride, 1 patient each). Two of the four patients in the younger age group had PCI lab values during active treatment (inc gastrin, positive urinary leukocyte esterase – no AEs were reported), whereas there were no patients in the older age group that had any PCI laboratory test results during treatment.
Comment: Other than the one triglyceride increase, the other abnormal laboratory results do not appear significant. Given the small numbers, other study reports will need to be reviewed for comparison of elevations in triglyceride levels.

Vital Signs:
Patients had vital sign measurements at multiple time points during their first and second PK assessments. Six patients, two in the younger age group and four in the older age group had PCI readings for individual parameters (respiratory rate, systolic blood pressure, and diastolic blood pressure) at isolated time points.
Comment: No patients had sustained abnormal readings involving multiple parameters that might be indicative of a treatment effect of clinical concern.

ECG:
There were 13 of 41 patients had PCI ECG abnormalities at some point during the study. Twelve of these patients had PCI prolonged (>84 ms) QRS intervals and one had PCI short QRS intervals; one of the patients with a prolonged QRS also had a PCI prolonged PR interval. Of the 12 patients with a PCI prolonged QRS interval, 9 had a PCI prolonged QRS interval at screening. In three patients the QRS interval of PCI was prolonged only after treatment with pantoprazole (two of these patients the QRS was borderline PCI prolonged [82 ms and 83 ms] at baseline).
Comment: As the majority of the PCI ECG abnormalities were seen as baseline, there is likely no causal association between QRS prolongation and treatment with pantoprazole.

One patient (334-017-001241) had an ECG finding that was reported to show a clinically significant abnormality. This patient's screening ECG finding was assessed as normal on overall evaluation, whereas the final study ECG finding was reported as showing right ventricular hypertrophy that was considered to be a clinically significant abnormality on an overall evaluation. A follow-up echocardiogram, performed 50 days later, showed no evidence of right ventricular hypertrophy. The patient had no history of cardiac problems and had no abnormalities on physical examination either at screening or at the final evaluation, the day the abnormal ECG was recorded.
Comment: Given the results of the negative echo, it is difficult to interpret the significance of the abnormal ECG reading at the final study visit.

Growth Parameters

The mean weight increased slightly in both groups (0.55 kg in the low-dose treatment group and 0.35 kg in the high-dose treatment group) from baseline to final visit but the increases were not statistically significant; the between group comparison of the mean change in weight was not statistically significant. Mean height increased from baseline to the final visit in both treatment groups. The mean height increased by 1.2 cm in the low-dose treatment group (p=0.060) and by 1.3 cm in the high-dose treatment group (p=0.004); the between-group comparison of the mean change in height was not statistically significant. There were no significant changes from baseline within each dose or significant differences between dose groups in z-scores for weight, height, weight-for-height (ages 1-5), or BMI (ages 2-11) indicating that the growth seen in these patients was as expected for children of their ages.

Table 101: Comparisons to Baseline for Wt (kg) and Ht (cm) – LOW dose (Study 334)

		Age 1 to < 6 years		Age 6 to 11 years	
		Baseline	Final visit	Baseline	Final visit
Weight (kg)	N	7	7	11	11
	Mean (SD) [min, max]	17.9 (3.8) [11.9, 23.4]	18.0 (3.7) [12.6, 22.8]	33.6 (10.8) [20.4, 57.1]	34.5 (11.2) [20.4, 56.3]
	Mean change		0.11		0.84
Height (cm)	N	7	7	11	11
	Mean (SD) [min, max]	104.4 (13.5) [76.8, 116]	107.2 (13.4) [79.8, 116]	134.3 (14.0) [110, 157]	134.3 (14.6) [107, 157]
	Mean change From baseline		2.86		0.09

Table 102: Comparisons to Baseline for Wt (kg) and Ht (cm) – HIGH dose (Study 334)

		Age 1 to < 6 years		Age 6 to 11 years	
		Baseline	Final Visit	Baseline	Final visit
Weight (kg)	N	10	10	13	13
	Mean (SD) [min, max]	15.0 (5.2) [8.9, 25.5]	15.2 (5.2) [9.8, 25.9]	37.2 (11.1) [24.4, 60]	37.7 (11.2) [25.3, 62.6]
	Mean change		0.2		0.5
Height (cm)	N	10	10	13	13
	Mean (SD) [min, max]	93.4 (14.2) [68.9, 116.8]	95.2 (12.7) [76.7, 116.8]	136.3 (6.2) [129, 147.6]	137.2 (6.1) [130, 148.9]
	Mean change From baseline		1.81		0.9

CONCLUSIONS

PK Results:

- PK parameters were more variable in the 1 to 5 years age group compared to 6 to 11 years.
- Cmax and AUC increased with increasing doses of pantoprazole.
- Exposures observed with the 1.2 mg/kg dose in children 6 to 11 years were similar to that in adults with 40 mg dose.
- Exposures observed with the 1.2 mg/kg dose in children 1 to 5 years were less than that in adults.

Safety Results:

- The TEAE reported by the highest number of patients was abdominal pain.
- The incidence of TEAEs in the digestive system and the incidence of vomiting were significantly higher among children ages < six-years than in children ages ≥ six-years. Of note, vomiting related to GERD is also more common in younger children.
- Among patients ages ≥ six-years, the overall incidence of respiratory system TEAEs was higher in the low-dose group than in the high-dose group. These represented a variety of common diseases in childhood, reflecting no pattern or dose relationship.
- No deaths, SAEs, or withdrawal due to TEAE occurred during the course of this study.

No new safety signals were detected during this study.

9.4.8 Study 3001A3-337-US: Ages 12 to 16 years - PK and safety

A. General Design and Objective

Study 3001A3-337-US (Study 337) is a multicenter, randomized, open-label, single- and multiple-dose PK study in adolescents aged 12 through 16 years with GERD. There were two dose groups (20-mg and 40-mg tablets), with each subject receiving 5 to 11 doses of pantoprazole. Patients were randomly assigned in a 1:1 fashion to the 20- or 40-mg treatment groups. Single-dose PK analysis was performed after the first dose of pantoprazole. Multiple-dose PK values were assessed on day 8 (± 3 days) of pantoprazole administration after the last of at least five consecutive doses. Because patients were to be provided with a 14-day supply of pantoprazole, if a patient missed a dose, that patient could restart accumulating a run of five consecutive doses. Safety evaluations were performed on an ongoing basis by review of adverse events (AEs) and clinically important laboratory test results as described in the PWR.

The primary objective of the study was to characterize the PK profile of single and repeated oral doses of pantoprazole in adolescents aged 12 through 16 years with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically-proven GERD. The secondary objective of the study was to assess safety and tolerability of pantoprazole in adolescents aged 12 through 16 years with a clinical diagnosis of GERD.

B. Background

This study was conducted in response to the Study 5 requirement of the PROTONIX PWR for PROTONIX (pantoprazole sodium) Delayed-Release Tablets (NDA 20-987) and PROTONIX IV (pantoprazole sodium) for Injection (NDA 20-988) that was issued by FDA on Dec 31, 2001. The PWR Study 5 requires PK data for patients 12 to 16 years of age with a clinical diagnosis of suspected, symptomatic, or endoscopically-proven GERD.

C. Inclusion

1. Male or nonpregnant, nonlactating, female patients aged 12 through 16 years.
2. Had a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically-proven GERD. A GERD diagnosis was defined by one or more of the following:
    a. Clinical symptoms consistent with GERD.
    b. A diagnosis of erosive esophagitis by endoscopy.
    c. Esophageal biopsy with histopathology consistent with reflux esophagitis.
    d. Abnormal pH-metry consistent with reflux esophagitis.
    e. Other objective testing consistent with GERD.
3. Male and female patients who were sexually active must have agreed to use an acceptable method of contraception. Acceptable methods included oral contraceptives, injectable or implantable contraceptives, intrauterine devices, and spermicide with condoms.

D. Exclusion

Similar to Study 331 with additional exclusion of pregnant females (See Secion 9.4.5).

E. Treatment

Patients received either a 20 mg or 40 mg daily dose of pantoprazole, with each patient to receive 5 to 11 doses.

Concomitant Medications

Patients were to continue their usual medical therapies according to standard clinical practice. Medications used to treat nongastrointestinal conditions were allowed, provided that no dose adjustment was likely to be necessary during the study. Patients were permitted to receive acid suppressant therapy during the two-week posttreatment period if clinically indicated.

Prohibited Medications

Patients were to discontinue any use of PPIs, H2RAs, prokinetic agents, anticholinergics, and bismuth preparations at least 24 hours before first administration of pantoprazole, and were not to use any of these drugs throughout the treatment period. Antacids were prohibited within the four hours before and after pantoprazole administration. Treatment requiring chronic use of warfarin, carbamazepine, or phenytoin for any disorder was prohibited. Special diets or herbal or alternative medication that might affect the metabolism of pantoprazole were not to be used without prior approval of the WR medical monitor. In addition, grapefruit and grapefruit-containing products were prohibited from 48 hours before study day 1 through the collection of the last PK sample.

F. Safety Considerations/Monitoring

See the study flow chart from the Applicant for details of the visits.

Table 103: Study Schedule (Study 337)

Study Phase	Screening[a]			---------- Treatment Period ----------				F/U Telephone Call	Early Withdrawal
							Final Visit		
Study Day	-7±4	-1	1	1	2-3	4	8±3	25±3	
Study Hour			-2	0					
Visit	X	X	X	X			X		X
Informed consent	X								
Medical history	X								
Physical examination[b,c]	X	X					X		X
Vital signs	X	X	X	X			X		X
ECG (12-lead)	X						X		X
Laboratory evaluation[d]	X						X		X
Urine drug screen	X								
Serum pregnancy test	X								
Urine pregnancy test[e]		X	X				X		X
Buccal cell collection[f]	X	X	X				X		
Randomization			X						
Dispense pantoprazole				X					
Pantoprazole administration in the office[g]				X			X		
Pantoprazole administration at home[h]					X	X			
Telephone contact[h]						X		X	
Provide daily diary				X					
Collect daily diary							X		X
PK blood sample collection[i,j]			X	X			X		
Concomitant medication recording	X	X	X	X			X	X	X
Adverse event recording	X	X	X	X----------X				X	X

G. Data Analysis

Descriptive statistics were calculated for the PK parameters for each dose group. Safety data (vital sign measurements, ECG readings, and routine laboratory test results) were summarized by descriptive statistics and were analyzed using an ANCOVA with predose data as the baseline covariate and treatment as a factor.

H. Results

Disposition of Patients
Twenty-three patients were enrolled in the study. One patient was a screen failure because of elevated BP at the screening examination (337-001-000502). Twenty-two patients were randomly assigned to treatment and received at least one dose of pantoprazole; 11 patients were randomly assigned to the 20-mg dose group and 11 patients were randomly assigned to the 40-mg dose group.

Discontinuations
One patient (337-005- 000622) was withdrawn from the study because of a loss of venous access. No patients withdrew from the study due to AEs.

One patient (337-005-000622) reported the use of a prohibited medication, tegaserod

maleate, before and during treatment. There were no other patients for whom the use of prohibited medications was reported during the period of treatment. None of the patients took carbamazepine, digoxin, phenytoin, or theophylline.

Demographics

The study population consisted of 10 male and 12 female adolescents, aged 12 to 16 years (mean age 14.4 years), with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically-proven GERD.

Table 104: Demographics of the Safety Population (Study 337)

Characteristic	P-Value	Panto 20mg (n = 11)	Panto 40 mg (n = 11)	Total (n = 22)
Age (Year)	0.509			
Mean		14.6	14.2	14.4
SD		1.63	1.5	1.6
Min - Max		12 - 16	12 – 16	12 – 16
Sex, N (%)	1.000			
Female		6 (55%)	6 (55%)	12 (55%)
Male		5 (45%)	5 (45%)	10 (45%)
Race, N (%)	1.000			
Black		3 (27%)	3 (27%)	6 (27%)
Other		0	1 (9%)	1 (5%)
White		8 (72%)	7 (63%)	15 (68%)
Ethnicity, N (%)	1.000			
Hispanic		0	1 (9%)	1 (5%)
Non-Hispanic		11 (100%)	10 (91%)	21 (95%)
Baseline Ht (cm)				
Mean	0.342	163.94	159.95	161.95
SD		10.53	8.55	9.58
Min – Max		147.5 – 178.8	149.0 – 176.2	147.5 – 178.8
Baseline wt (kg)				
Mean	0.642	70.53	75.66	73.10
SD		21.27	29.09	25.01
Min - Max		46.4 – 107.5	47.5 – 126.6	46.4 – 126.6
Study Duration	0.300			
Mean		35.91	31.91	33.91
SD		9.5	8.1	8.8
Min – Max		24 - 53	20 - 43	20 - 53

GERD Indications at Screening

All patients entered the study with clinical signs and symptoms of GERD, including four patients with a diagnosis of EE by endoscopy, four patients with a diagnosis of reflux esophagitis established by biopsy, four patients with abnormal pH-metry that was consistent with reflux esophagitis, and four patients with other objective testing consistent with GERD.

Concomitant Therapy/Medications

The following table from the Applicant lists the concomitant medications used commonly by the participants.

Table 105: Nonstudy Concomitant Medications Used (Study 337)

ATC classification[a] Generic term	Overall p-Value[b]	Treatment: Pantoprazole 20 mg n = 11	Treatment: Pantoprazole 40 mg n = 11	Total n = 22
Salbutamol	1.000	2 (18.2)	1 (9.1)	3 (13.6)
Aripiprazole	0.476	0	2 (18.2)	2 (9.1)
Heparin[c]	0.214	0	3 (27.3)	3 (13.6)
Hydroxyzine hydrochloride	0.476	2 (18.2)	0	2 (9.1)
Polyethylene glycol 3350	1.000	2 (18.2)	3 (27.3)	5 (22.7)
Paracetamol	0.586	3 (27.3)	1 (9.1)	4 (18.2)
Montelukast sodium	1.000	3 (27.3)	2 (18.2)	5 (22.7)

Safety Evaluation

Adverse Events
A total of six patients had TEAEs, two (18%) patients in the 20-mg dose group and four (36%) patients in the 40-mg dose group. The only TEAE reported in more than one patient was abdominal pain, which was reported for two (18.2%) patients in the higher 40-mg dose group; these events were considered mild in severity and not related to pantoprazole.

One 14-year-old male patient in the 40-mg dose group (337-008-000711) had nausea and fever which were considered mild in severity and related to pantoprazole. The nausea and the fever resolved after one day and 11 days, respectively. Patient 337-003-00561, a 16-year-old female patient in the 20-mg dose group, developed reflux symptoms on the final day of the study, 24 hours after her last dose of pantoprazole. The symptoms were considered mild in severity and not related to pantoprazole.

Comment: There is no statistically significant difference between the two dose groups in the incidence of any reported TEAE or in the reported TEAEs overall. The numbers of patients involved are too small to make any definitive safety conclusion.

Table 106: Summary of Patients Reporting TEAEs (Study 337)

Body system Adverse event	Overall P-value	Pantoprazole 20 mg n=11	Pantoprazole 40 mg n=11	Total n=22
Any adverse event	0.635	2 (18%)	4 (36)	6 (27)
Body as a whole	0.090	0	4 (36)	4 (18)
Abdominal pain	0.476	0	2 (18)	2 (9)
Fever	1.000	0	1 (9)	1 (5)
Headache	1.000	0	1 (9)	1 (5)
Digestive system	1.000	1 (9)	2 (18)	3 (14)
Diarrhea	1.000	0	1 (9)	1 (5)
GERD	1.000	1 (9)	0	1 (5)
Nausea	1.000	0	1 (9)	1 (5)
Nervous system	1.000	1 (9)	0	1 (5)
Insomnia	1.000	1 (9)	0	1 (5)
Special senses	1.000	0	1 (9)	1 (5)
Otitis externa	1.000	0	1 (9)	1 (5)

Serious Adverse Events

There were no deaths nor SAEs reported during this study.

Other Clinically Important Adverse Events

Laboratory evaluations: A total of six (27%) patients, including one (9%) in the 20-mg dose group and five (46%) in the 40-mg dose group, were identified as having PCI values in clinical laboratory values. Four of these six patients had PCI values at screening, and only two patients had PCI values which were treatment emergent (+urine albumin, +urine hemoglobin), neither was determined to be of clinical significance.

Table 107: PCI Abnormality Incidences (Study 337)

	---------- Treatment ----------		
Category Test/units Data analysis interval	Pantoprazole 20 mg N (%)	Pantoprazole 40 mg N (%)	Total N (%)
Total	1/11 (9.1)	5/11 (45.5)	6/22 (27.3)
Blood chemistry			
Total bilirubin µmol/L			
All	0/11	1/11 (9.1)	1/22 (4.5)
Screening	0/11	1/11 (9.1)	1/22 (4.5)
CPK mU/mL			
All	0/11	1/11 (9.1)	1/22 (4.5)
Screening	0/11	1/11 (9.1)	1/22 (4.5)
Urinalysis			
Urine protein albumin			
All	0/11	2/11 (18.2)	2/22 (9.1)
Screening	0/11	1/11 (9.1)	1/22 (4.5)
Treatment	0/10	1/11 (9.1)	1/21 (4.8)
Urine leukocyte esterase			
All	1/11 (9.1)	1/11 (9.1)	2/22 (9.1)
Screening	0/11	1/11 (9.1)	1/22 (4.5)
Treatment	1/10 (10.0)	0/11	1/21 (4.8)
Urine hemoglobin blood			
All	0/11	1/11 (9.1)	1/22 (4.5)
Screening	0/11	1/11 (9.1)	1/22 (4.5)

Vital Signs: There were no vital sign PCI abnormalities during the treatment period.

Growth Parameters: The mean change in height from screening to the final evaluation within the dose groups was 0.4 cm and 1.1 cm for the 20- and 40-mg dose groups, respectively. These changes were not statistically significant in either dose group. There were no statistically significant differences between dose groups. The mean change in weight from screening to the final evaluation within the dose groups was 0.80 kg (± 0.21) and 0.36 kg (± 0.20) for the 20- and 40-mg dose groups, respectively.

ECG: A total of three patients (14%) had ECG PCI findings, two patients in the 20-mg treatment group and one patient in the 40-mg treatment group. In all three patients the PCI findings occurred on the screening ECG which all normalized by end of treatment, thus none are thought to be treatment related.

CONCLUSIONS

Pharmacokinetics:

- The plasma concentrations and the PK parameters, Cmax and AUC, increased with increasing doses of pantoprazole.
- PK parameters in patients ages 12 to 16 years who received the 20 and 40 mg dose were similar to those in adults.
- There was no appreciable accumulation of pantoprazole after multiple dose administration.

Safety:

- Ten (46%) patients reported AEs, of those, six (27%) events were considered treatment emergent.
- The only TEAE reported by more than one patient was abdominal pain (2, 18%).
- No patients were withdrawn from the study because of safety-related AEs.
- No SAEs or deaths occurred during the course of this study.

No new safety signals were detected during this study.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20987	SUPPL 36		PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
NDA 20987	SUPPL 37		PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
NDA 22020	SUPPL 1		PROTONIX DELAYED RELEASE GRANULES
NDA 22020	SUPPL 2		PROTONIX DELAYED RELEASE GRANULES

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/s/

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08/10/2009

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08/10/2009