CLINICAL PROTOCOL

AN OPEN-LABEL, MULTICENTER STUDY TO EVALUATE THE PHARMACOKINETICS OF SINGLE AND MULTIPLE INTRAVENOUS DOSES OF PANTOPRAZOLE IN TWO AGE COHORTS OF HOSPITALIZED PEDIATRIC SUBJECTS 1 TO 16 YEARS OF AGE WHO ARE CANDIDATES FOR ACID SUPPRESSION THERAPY

Compound:	PF-05208751
Compound Name :	Pantoprazole sodium
US IND (United States Investigational New Drug) Number:	52,132
European Clinical Trial Database (EudraCT) Number:	2014-002182-29
Protocol Number:	B1791089
Phase:	4

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 3	07 November 2018	PK sampling: 9 samples total (4 samples on Day 1 and 5 samples on Day 2) for all age cohorts in order to make the study more feasible. Consequently, pantoprazole concentration data will be analyzed by nonlinear mixed-effects models. Treatment duration is flexible, depending on subject need (4-7 days), to make the study more feasible. Physical examination and safety laboratory assessments have been moved from the day of the last dose to the day *after* the last dose to ensure all evaluations are done after treatment is completed. Assessments of vital signs, adverse events, and concomitant medications have been extended to include the day after the last dose. Formatting and editing throughout.
Amendment 2	29 June 2017	Reduce PPI and H2RA washout periods, as prior use ≥48 and 24 hours prior to Day 1, respectively, is not expected to impact PK or safe use of pantoprazole

Document	Version Date	Summary of Changes and Rationale
		sodium. Remove exclusion criteria for upper GI abnormalities and treatment for GI ulcers, as they are not expected to impact objectives of the study. Update content from Protocol Administrative Change Letters, including the diagnosis of GERD in young children (Section 7.1), collection of PK samples (Section 7.2), and collection of temperature (Section 7.8). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this. Reduce background information that is already addressed in IB. Screening numbers assigned by investigator via IRT – clarified wording. Clarify dose selection rationale. Update text and formatting per protocol template. Make editorial changes and correct typographical errors

Document	Version Date	Summary of Changes and Rationale
		throughout.
Amendment 1	28 October 2014	Changed compound number from PF-00579917 to PF-05208751. Changed protocol number from B2851006 to B1791089. Specified that this is a Post-Authorization Safety Study Removed 1-11 month cohort, as efficacy has not previously been demonstrated in this age group with the oral formulation. Removed subject selection criteria from protocol summary, as this is addressed in the body of the protocol. Updated exclusion criteria to reflect that screening endoscopy is not required (eg, patients with known eosinophilic esophagitis or *H. pylori* infection are excluded, instead of requiring investigators to demonstrate these conditions). Removed Day 1 pregnancy test and specified that Screening pregnancy test must be evaluated in serum within 24 hours before administration of investigational product.

Document	Version Date	Summary of Changes and Rationale
		Removed electrocardiogram and exclusion criterion related to QT prolongation, as there is no evidence of proarrhythmic potential with short-term exposure to pantoprazole. Removed exclusion criterion relating to elevation of AST, as this could unnecessarily exclude patients with transient elevations that do not indicate liver injury. The exclusion of patients with ALT elevations >2 x ULN has been maintained. Added daily vital signs during treatment period. Added instructions for assessing blood pressure and pulse. Changed investigational product dosing in response to FDA request. Moved drug administration instructions to a separate document. Allowing standard-of-care laboratory results to serve as study entry labs, provided they are collected in appropriate time frame. Specifying that PK samples are to be collected from IV line. Updated text under sections

Document	Version Date	Summary of Changes and Rationale
		Administration, Adverse Event Reporting and Communication of Results by Pfizer per protocol template.
Original Protocol	27 March 2014	Not applicable (N/A)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

PROTOCOL SUMMARY

BACKGROUND AND RATIONALE

Pantoprazole sodium is a proton pump inhibitor indicated in adults and pediatric patients 12 years of age and above (5 years of age and above in the US) as oral treatment for the healing and symptomatic relief of erosive esophagitis. Pantoprazole sodium is also indicated as oral treatment for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with gastroesophageal reflux disease (GERD). Pantoprazole sodium is further indicated as long-term oral treatment of pathological hypersecretory conditions in adult patients, including Zollinger-Ellison syndrome. Pantoprazole sodium intravenous (IV) formulation is indicated for short-term treatment (7 to 10 days) of adult patients with GERD and a history of erosive esophagitis. The IV formulation is not indicated for use in children.

The US Food and Drug Administration (FDA) Modernization Act, issued in 1997, stresses the need for improved information about drugs used in the pediatric population.

The rationale for conducting this Post Authorization Safety Study (PASS) is to characterize the pharmacokinetic (PK) of pantoprazole, following single and repeated once daily IV doses of pantoprazole sodium in hospitalized pediatric subjects in age groups of 1 to 16 years who in the judgment of the investigator are candidates for gastric acid suppression therapy. These data will address FDA Post Marketing Requirements issued under the Pediatric Research Equity Act (PREA).

Rationale for dose selection is based on:

- The safety and tolerability of 0.8 mg/kg and 1.6 mg/kg doses of pantoprazole sodium administered IV in children aged 1 to 2 years (3001K1-117) and 2 to 16 years respectively (3001K1-110).

- The efficacy, safety, and tolerability of 0.3 mg/kg to 1.2 mg/kg oral doses of pantoprazole sodium in children aged 1 to 5 years of age (3001B3-328).

- The efficacy of 20 mg and 40 mg oral doses of pantoprazole sodium in children aged 5 to 11 years of age (3001A1-322).

- The efficacy, safety, and tolerability of 20 mg and 40 mg oral doses of pantoprazole sodium in children aged 12 to 16 years of age (3001A1-326 and 3001A3-337).

- The exposures were approximately similar following IV and oral administrations, as the absolute bioavailability of pantoprazole is about 77%.

- According to population PK analysis across the age groups, the body weight was the most influencing covariate to clearance of pantoprazole in pediatric patients. FDA recommended that pediatric doses be based on body weight as well as age to match the adult exposure more closely. The proposed 10 mg dose for pediatric subjects aged 1 to <2 years (body weight 8 to <15 kg), 20 mg dose for 2 to 11 years (body weight >15 to <40 kg), and 40 mg dose for 12 to 16 years old (body weight ≥40 kg) are based on body weight and age of the patients in this study.

- Based on modeling and simulation analysis, the predicted systemic exposures – maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) – in patients aged 1 to <2 years, 2 to 11 years, and 12 to 16 years at the respective doses of 10, 20 and 40 mg were similar to the exposures seen in adults.

OBJECTIVES AND ENDPOINTS

In hospitalized pediatric subjects, age 1 to 16 years who in the judgment of the investigator are candidates for gastric acid suppression therapy, the following are the objectives of this trial:

Primary Objectives

- To characterize the PK of pantoprazole, following single and multiple IV doses of pantoprazole sodium in pediatric subjects aged 1 to less than 2 years old.

- To characterize the PK of pantoprazole, following single and multiple IV doses of pantoprazole sodium in pediatric subjects aged 2 to 16 years old.

Secondary Objectives

- To determine the safety, tolerability, and PK of single and multiple IV doses of pantoprazole sodium in each of the two independent age cohorts.

- To assess the CYP2C19 genotype in pediatric subjects receiving IV pantoprazole sodium, to determine the presence of the gene for the major enzyme responsible for metabolism of pantoprazole.

Endpoints

Primary Endpoints

- PK Parameters: clearance (CL) and volume of distribution (Vd).

Secondary Endpoints

- PK Parameters to be estimated from the population PK model:

  Maximum plasma concentration (C_{max}), area under the plasma concentration-time profile from time zero to the 24 hour time post dose (AUC_{24}), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}) and terminal phase half-life ($T_{1/2}$) of pantoprazole following single and multiple IV doses.

- Safety and tolerability of single- and multiple doses of IV pantoprazole sodium for each of the two age cohorts will be assessed by physical examinations, adverse event (AE) monitoring, clinical laboratory measurements, blood pressure, and pulse rate.

- CYP2C19 genotype to determine the presence of the gene for the major enzyme responsible for metabolism of pantoprazole.

STUDY DESIGN

This is a non-randomized, open-label, multicenter study to characterize the pharmacokinetics of single and multiple IV doses of pantoprazole sodium in hospitalized pediatric subjects in two independent age cohorts of 1 to 16 years who in the judgment of the investigator are candidates for gastric acid suppression therapy. There will be approximately 12 subjects per age cohort (1 to less than 2 years; 2 to 16 years old) and a total of approximately 24 subjects for this two-cohort study.

Eligible subjects will be assigned to the following main age cohorts:

- Cohort 1: 1 to less than 2 years;

- Cohort 2: 2 to 16 years old. In Cohort 2, there will be approximately equal distribution across the age sub-cohorts of 2 to 5 years, 6 to 11 years and 12 to 16 years.

All subjects in each cohort will receive a fixed dose of IV pantoprazole sodium according to weight. The maximum dose per 24 hour period for a subject who weighs at least 40 kg will not exceed 40 mg, irrespective of weight or age. Pantoprazole sodium will be administered IV over 15 minutes through a Y-site or dedicated line (if Y-site is used, IV line must be flushed before and after dose administration) once daily for 4 to 7 days, approximately every 24 hours, preferably in the morning. Guidance will be provided to the investigator site regarding preparation and administration instructions. PK samples will be collected to measure plasma concentrations of pantoprazole on study Day 1 and Day 2. Vital signs, adverse events, and concomitant medications will be evaluated daily during treatment and on the day after the last dose; physical examination and safety laboratory assessments will be performed on the day after the last dose. A follow up post treatment telephone contact will occur approximately 31 days after the last dose.

DATA ANALYSIS/STATISTICAL METHODS

Sample Size Determination

A sample size of 12 subjects in each age cohort is likely to have an 80% chance to achieve 20% Relative Standard Error (RSE) for both clearance (CL) and volume of distribution (Vd). This sample size was estimated using simulations of a previous population PK model of pantoprazole in pediatric patients reported by Knebel et al. (2011).[16] The simulations used the sparse PK sampling scheme specified in Section 7.2.

Population Pharmacokinetic Analysis

Pantoprazole concentration data will be analyzed using a population PK analysis approach (nonlinear mixed-effects models). Prior pediatric PK data may be used to guide and assist the model building and covariate selection. A two-compartment model with IV infusion will be used to describe pantoprazole concentrations, with clearance (CL) and volume of distribution (Vd) of the central compartment being the key population PK parameters in the model. The potential influence of covariates, including age and body weight, on these parameters will be explored during the model building phase of the analysis. Other covariates, including gender and baseline values, may also be explored using graphical approaches.

The final population PK model will also be used to estimate the following PK Parameters: maximum plasma concentration (Cmax), area under the plasma concentration-time profile from time zero to the 24 hour time post dose (AUC24), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUCinf) and terminal phase half-life (T1/2) of pantoprazole following single and multiple IV doses.

A Population Modeling Analysis Plan (PMAP) describing the details of the model building, covariate assessment, model validation and PK parameter estimation will be provided separately.

Analysis of Other Endpoints

Pharmacogenomic Endpoint:

CYP2C19 genotype: buccal cell samples will be collected at pre-dose by using a brush (supplied by the laboratory) and by scraping the inside of the subject's cheek. These samples will be examined to determine the presence of genes for the major (CYP2C19) enzymes responsible for metabolism of pantoprazole.

Safety Analysis

Adverse events, physical examinations, blood pressure, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, blood pressure, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Safety results will be reported separately for each age cohort.

Safety summaries will be produced in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) for safety reporting.

Baseline characteristics (eg, demographics, medical history) will be also summarized using CaPS for reporting.

SCHEDULE OF ACTIVITIES

The Schedule of Activities below provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Protocol Activity	Screening	Treatment Period			Day After Last Dose	Follow- Up 31 (±3) Days After Last Dose
	Day 0 or Day 1 Prior to Treatment	Day 1	Day 2	-Daily During Treatment		
Subject/parent/legal guardian informed consent	X					
Review Inclusion/Exclusion	X					
Medical history[a]	X					
Physical examination[b]	X				X	
Vital Signs[c]	X	X	X	X	X	
Safety Laboratory evaluation[d]	X				X[h]	
Pregnancy test[e]	X				X	
Subject Enrollment		X				
Investigational product administration[f]		X	X	X		
PK blood sample collection[g]		X	X			
Pharmacogenomics (Buccal cell collection for CYP2C19 genotyping)		X				
Drug Accountability		X	X	X		
Prior/Concomitant Medication	X	→	→	→	X	X
Telephone contact						X
Adverse Event Monitoring	X	→	→	→	X	X

a. Medical history includes complete history of all prescription or nonprescription drugs, vitamins, and dietary supplements taken prior to screening procedures, history of drug, alcohol, and tobacco use.

b. Physical exam will include height (cm) (Screening only) and weight (kg).

c. Blood pressure, pulse rate, and temperature (C°). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.

d. Refer to ASSESSMENTS sectionfor a list of laboratory parameters.

e. For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, within 24 hours before investigational product administration. On the day after the last dose a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

f. Refer to the Preparation and Dispensing section of this protocol and IP Manual, which is provided separately.

g. Refer to the Pharmacokinetics section of this protocol for PK collection times.

h. To minimize the amount of blood collected, routine laboratory studies planned within 48 hours after the last dose of investigational product may be used as the final study evaluation safety laboratory values, provided the information specified in the protocol is obtained.

1. INTRODUCTION

1.1. Indication

Pantoprazole sodium is a proton pump inhibitor indicated in adults and pediatric patients 12 years of age and above (5 years of age and above in the US) as oral treatment for the healing and symptomatic relief of erosive esophagitis. Pantoprazole sodium is also indicated as oral treatment for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD. Pantoprazole sodium is further indicated as long-term oral treatment of pathological hypersecretory conditions in adult patients, including Zollinger-Ellison syndrome. Pantoprazole sodium IV formulation is indicated for short-term treatment (7 to 10 days) of adult patients with GERD and a history of erosive esophagitis. The IV formulation is not indicated for use in children. Pantoprazole sodium is approved for marketing in more than 90 countries and registered clinical indications vary among countries.

1.2. Background and Rationale

The North American Society for Pediatric Gastroenterology Hepatology and Nutrition (NASPGHAN) has acknowledged that gastroesophageal reflux, defined as the regurgitation of gastric contents into the esophagus, and gastroesophageal reflux disease (GERD), defined as symptoms or complications of this regurgitation, are common pediatric problems.[1] Gastroesophageal reflux disease is a common clinical disorder in children that can cause esophagitis and lead to or predispose a child to other medical problems such as malnutrition or respiratory disease. Symptoms of GERD in children differ depending on their age and on the extent of the exposure of the esophageal epithelium to refluxed gastric contents. Clinical manifestations can include spitting-up/regurgitation, vomiting, poor weight gain, dysphagia, abdominal or substernal pain, esophagitis, and respiratory disorders. The symptoms of GERD can cause significant distress to children.[2,3] The prevalence of GERD in children is unknown, but is thought to be increasing.[4,5] Incidence is age-dependent and varies from 5% to 35%. In children diagnosed with GERD between the ages of 3.5 and 16 years, it is estimated that less than 50% will have spontaneous resolution of symptoms and that many will require continued medical or surgical management.[6,7] In contrast, many infants develop GERD in the first few months of life but few infants and younger children will require long-term medical intervention because GERD generally resolves spontaneously by 12 to 14 months of age. Diagnostic testing, such as barium contrast (upper gastrointestinal series) radiographic studies and radionuclide scintiscanning tests are commonly used to diagnose GERD in children. Esophageal pH monitoring is used to measure the presence of abnormal acid reflux. Esophagogastroduodenoscopy (EGD) with biopsy is used to determine the presence and severity of esophagitis, strictures, and Barrett's esophagus, as well as to exclude other disorders (eg, Crohn's disease and eosinophilic or infectious esophagitis).

Treatment options for children and adolescents with GERD include dietary changes, lifestyle modifications, and antacids for symptom relief. When these conservative measures are unsuccessful, other pharmacologic treatments are used to relieve symptoms and promote healing of esophagitis.

Proton pump inhibitors (PPIs) and histamine2-receptor antagonists (H2RAs) are used to relieve symptoms and promote healing of esophagitis, although prescribing information for the pediatric population is limited.[8,9] Antireflux surgery may be of benefit in selected children with chronic-relapsing GERD.

Pantoprazole sodium was synthesized and developed by Altana Pharma (formerly Byk Gulden Pharmaceuticals), Konstanz, Germany. Pantoprazole sodium 20 mg is approved for marketing in more than 95 countries, the 40 mg tablet in more than 100 countries, and the 40 mg powder for injection solution is approved in more than 90 countries. Pfizer holds the marketing authorization for pantoprazole sodium in the US under the brand name Protonix, whilst Takeda has marketing authorization rights in territories outside the US.

Pantoprazole sodium is a PPI that suppresses the final step in gastric acid production by covalently binding to the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H^+, K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

Pantoprazole sodium is commercially available as delayed-release granules for oral suspension and as delayed-release 20 mg or 40 mg oral tablets. It is also available as a 40 mg powder for injection solution for intravenous administration.

1.2.1. Clinical Pharmacology

1.2.1.1. Pharmacokinetics

In adults, pantoprazole peak serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following IV administration of pantoprazole sodium, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In CYP2C19 extensive metabolizers with normal liver function receiving a 40 mg IV dose of pantoprazole sodium by constant rate over 15 minutes, the peak concentration (C_{max}) is 5.52 ±1.42 μg/mL and the total area under the plasma concentration versus time curve (AUC) is 5.4 ±1.5 μg•hr/mL. The total clearance is 7.6-14.0 L/hr.

The absolute bioavailability of oral pantoprazole is about 77%. The exposures were approximately similar following IV and oral administrations.[11,12]

1.2.1.1.1. Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

1.2.1.1.2. Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (eg, 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values from 3.5 to 10.0 hours, they still have minimal accumulation (≤23%) with once daily dosing.

1.2.1.1.3. Excretion

After administration of a single intravenous dose of 14C-labeled pantoprazole sodium to healthy, extensive CYP2C19 metabolizers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

1.2.2. Pediatric Pharmacokinetics

Following single intravenous doses of pantoprazole sodium administered over 15 minutes as a single dose of 0.8 mg/kg or 1.6 mg/kg to 19 hospitalized subjects aged 2 to 16 years (study 3001K1-110), the pharmacokinetics of pantoprazole were similar in the age groups 2 to 4 years, 5 to 10 years, and 11 to 16 years. The mean C_{max} and AUC values increased with dose from 0.8 mg/kg to 1.6 mg/kg. No trends toward a change with age were observed in the dose-independent pharmacokinetic (PK) parameters (ie, clearance, CL and volume of distribution at steady state, V_{ss}) normalized by body weight in pediatric subjects aged 2 to 16 years. The values of CL and $T_{1/2}$ (ie, mean half life: 1.2 hours) of IV pantoprazole sodium in these pediatric subjects were similar to those previously observed with IV pantoprazole sodium (40 mg) in healthy adult subjects.

In a different study (3001K1-117), the PK, safety, and tolerability of pantoprazole following administration of a single IV dose of 0.8 mg/kg or 1.6 mg/kg to hospitalized pediatric subjects at least 1 year but less than 2 years of age were assessed. The study 3001K1-117 was conducted in 2 patients at each dose level. The C_{max} and AUC of pantoprazole increased proportionally with dose from 0.8 mg/kg to 1.6 mg/kg doses. The t½ value of pantoprazole in children 1 to 2 years of age were similar to that observed in 2 to 16-year olds (ie, mean of 1.2 hours). Children younger than 2 years required the higher dose (1.6 mg/kg) to achieve exposure similar to that seen in older children (2-16 years) with the lower dose (0.8 mg/kg).

The observed C_{max} values of pantoprazole following a 0.8 mg/kg IV dose were 4,846 and 5,613 ng/mL in 1-2 year-olds in study 3001K1-117, which is comparable to that observed (C_{max} of 5,520 ng/mL) in adults after 40 mg IV dose.[10,11] The observed exposure (AUC) values of pantoprazole following a 0.8 mg/kg IV dose were 2,224 and 1762 ng.hr/mL in the two pediatric patients (ie, less than two years old) in study 3001K1-117, and the mean

exposures in the adults were 5,400 ng.hr/mL and 4,000 ng·hr/mL with a range of 1,400 – 13,300 ng·hr/mL following IV and oral administrations of 40 mg pantoprazole sodium, respectively.[11,12] Although the exposures in the less than 2 years old pediatrics fall in the lower end of the exposure range (1,400 – 13,300 ng·hr/mL) observed in the adults, the individual AUC values in two pediatrics appear lower than those mean exposures in adults.

1.2.2.1. Similar PK Between Single- and Multiple-Dose

Following single-dose IV administration in pediatrics, the elimination half-life of pantoprazole is approximately one hour. Pantoprazole does not accumulate and its PK is unaltered with multiple daily dosing (Ref. PROTONIX® for intravenous use United States Package Insert (USPI) – Revised: 10/2016). Following single-dose IV dosing in pediatrics aged 1 to 16 years old, plasma concentrations of pantoprazole were close to the lower limit of quantification (ie, 10 ng/mL) of the bioanalytical assay at 12 hours post dose, providing further evidence that there will be no accumulation with multiple-day dosing (ref. studies 3001K1-117 and 3001K1-110, and New Drug Application (NDA) 22-020 FDA Review of Clinical Pharmacology). In conclusion, these data provide further evidence to indicate that the PK profile of pantoprazole following a single IV dose on Day 1 is expected to be similar to the multiple dose PK profile on Day 7 after once-daily dosing in pediatric subjects.

In addition, a PK modeling and simulation analysis was performed for pediatric subjects aged 1 to <2 years (body weight 8 to <15 kg), 2 to 11 years (body weight >15 to <40 kg), and 12 to 16 years old (body weight ≥40 kg) at the respective doses of 10, 20 and 40 mg pantoprazole proposed for this study protocol. The simulation results showed similar concentration–time profiles between Day 1 and Day 7 following once-daily IV administrations. The simulation results also confirmed that there was no accumulation of pantoprazole following the once-daily dosing of 10, 20 and 40 mg IV pantoprazole for 7 days.

1.2.3. Pharmacogenomics

CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (eg, approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 3.5 to 10.0 hours in adults, they still have minimal accumulation (≤23%) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed.

Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers.

1.2.4. Safety

1.2.4.1. Adults

The safety and tolerability of pantoprazole sodium has been assessed in more than 250 clinical studies and through post-marketing surveillance that has occurred since the product was first approved in 1996.

Approximately 5% of adult patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADR with the IV formulation in adults was injection site thrombophlebitis. Diarrhea and headache occurred in approximately 1% of patients.

1.2.4.2. Pediatric Patients

Safety of oral pantoprazole sodium in the treatment of erosive esophagitis associated with GERD was evaluated in pediatric patients aged 1 year through 16 years in 3 clinical trials. Safety trials involved pediatric patients with erosive esophagitis; however, as erosive esophagitis is uncommon in the pediatric population, 249 pediatric patients with endoscopically-proven or symptomatic GERD were also evaluated. The most commonly reported (>4%) adverse reactions included upper respiratory infection (URI), headache, fever, diarrhea, vomiting, rash, and abdominal pain.

The safety of IV pantoprazole sodium was investigated as a single dose of 0.8 mg/kg or 1.6 mg/kg randomly administered to 19 hospitalized patients aged 2 to 16 years (3001K1-110). Intravenous pantoprazole sodium at both doses was well tolerated with treatment emergent adverse events (TEAEs) reported for 3 patients in the 11 to 16 years age group and no patients in the other age groups. All TEAEs were mild in severity and considered to be unrelated to pantoprazole sodium.

1.2.5. Benefit Risk Assessment

The safety and effectiveness of oral pantoprazole sodium for the short-term treatment (up to eight weeks) of erosive esophagitis associated with GERD has been established in pediatric patients 1 year through 16 years of age. In adults, both the IV (short term therapy only) and oral formulations of pantoprazole sodium have been found to be safe and effective in management and prevention of relapse in reflux esophagitis. Pantoprazole sodium is well tolerated and has demonstrated an acceptable safety profile in adult patients when administered by either the oral or IV routes. Oral pantoprazole sodium has also demonstrated an acceptable safety profile in pediatric patients from 1 month to 16 years of age and the IV formulation was well tolerated after a single dose.

The vast majority of adverse drug reactions with oral and IV pantoprazole sodium are mild and/or resolve upon treatment discontinuation. Based on the efficacy and safety profile of oral pantoprazole sodium in children aged 1 to 16 years of age and single dose pediatric safety data, the benefit-risk profile of multiple dose IV pantoprazole sodium use in pediatric patients participating in this study is anticipated to be positive.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Brochure.[10]

1.3. Study Rationale

The US Food and Drug Administration (FDA) Modernization Act, issued in 1997, stresses the need for improved information about drugs used in the pediatric population.

The rationale for conducting this post authorization safety study (PASS) is; to characterize the PK of pantoprazole, following single and repeated once daily IV doses of pantoprazole sodium in hospitalized pediatric subjects in age group of 1 to 16 years who in the judgment of the investigator are candidates for gastric acid suppression therapy. These data will address FDA Post Marketing Requirements (PMRs) issued under PREA.

This protocol is composed of two independent age cohorts (1 to less than 2 years and 2 to 16 years), which will be operationalized under a single protocol for logistical efficiency. While each cohort will have the same primary objective, they will be powered independently of each other and will be analyzed separately; data/results will not be combined or pooled across the two age cohorts.

1.3.1. Dose Selection Rationale

Rationale for dose selection is based on:

- The safety and tolerability of 0.8 mg/kg and 1.6 mg/kg IV doses of pantoprazole sodium in children aged 1 to 2 years (3001K1-117) and 2 to 16 years respectively (3001K1-110).

- The efficacy, safety, and tolerability of 0.3 mg/kg to 1.2 mg/kg oral doses of pantoprazole sodium in children aged 1 to 5 years of age (3001B3-328).

- The efficacy of 20 mg and 40 mg oral doses of pantoprazole sodium in children aged 5 to 11 years of age (3001A1-322).

- The efficacy, safety, and tolerability of 20 mg and 40 mg oral doses of pantoprazole sodium in children aged 12 to 16 years of age (3001A1-326 and 3001A3-337).

- The exposures were approximately similar following IV and oral administrations, as the absolute bioavailability of pantoprazole is about 77%.

- According to population PK analysis across the age groups, the body weight was the most influencing covariate to clearance of pantoprazole in pediatric patients. FDA recommended that pediatric doses be based on body weight as well as age to match the adult exposure more closely. The proposed 10 mg dose for pediatric subjects aged 1 to <2 years (body weight 8 to <15 kg), 20 mg dose for 2 to 11 years (body weight >15 to <40 kg), and 40 mg dose for 12 to 16 years old (body weight ≥40 kg) are based on body weight and age of the patients in this study.

- Based on modeling and simulation analysis, the predicted systemic exposures (C_{max} and AUC) in patients aged 1 to < 2 years, 2 to 11 years, and 12 to 16 years at the respective doses of 10, 20 and 40 mg were similar to the exposures seen in adults.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

In hospitalized pediatric subjects aged 1 to 16 years who in the judgment of the investigator are candidates for gastric acid suppression therapy, the following are the objectives of this trial:

2.1.1. Primary Objectives

- To characterize the PK of pantoprazole, following single and multiple IV doses of pantoprazole sodium in pediatric subjects aged 1 to less than 2 years old.

- To characterize the PK of pantoprazole, following single and multiple IV doses of pantoprazole sodium in pediatric subjects aged 2 to 16 years old.

2.1.2. Secondary Objectives

- To determine the safety, tolerability, and PK of single and multiple IV doses of pantoprazole sodium in each of the two independent age cohorts.

- To assess the CYP2C19 genotype in pediatric subjects receiving IV pantoprazole sodium, to determine the presence of the gene for the major enzyme responsible for metabolism of pantoprazole.

2.2. Endpoints

2.2.1. Primary Endpoints

- PK Parameters: clearance (CL) and volume of distribution (Vd).

2.2.2. Secondary Endpoints

- PK Parameters to be estimated from the population PK model:

  Maximum plasma concentration (Cmax), area under the plasma concentration-time profile from time zero to the 24 hour time post dose (AUC24), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUCinf) and terminal phase half-life (T1/2) of pantoprazole following single and multiple IV doses.

- Safety and tolerability of single- and multiple doses of IV pantoprazole sodium for each of the two age cohorts will be assessed by physical examinations, adverse event (AE) monitoring, clinical laboratory measurements, blood pressure, and pulse rate.

- CYP2C19 genotype to determine the presence of the gene for the major enzyme responsible for metabolism of pantoprazole.

3. STUDY DESIGN

This is a non-randomized, open-label, multicenter study to characterize the pharmacokinetics of single and multiple IV doses of pantoprazole sodium in hospitalized pediatric subjects in two independent age cohorts of 1 to 16 years who in the judgment of the investigator are candidates for gastric acid suppression therapy. There will be approximately 12 subjects per age cohort (1 to less than 2 years and 2 to 16 years old) and a total of approximately 24 subjects for this two-cohort study.

Eligible subjects will be assigned to the following main age cohorts:

- Cohort 1: 1 to less than 2 years,
- Cohort 2: 2 to 16 years old. In Cohort 2, there will be approximately equal distribution across the age sub-cohorts of 2 to 5 years, 6 to 11 years and 12 to 16 years.

All subjects in each cohort will receive fixed dose IV pantoprazole sodium according to weight. The maximum dose per 24 hour period for a subject who weighs at least 40 kg will not exceed 40 mg, irrespective of weight or age. Pantoprazole sodium will be administered IV over 15 minutes through a Y-site or dedicated line (if Y-site is used, IV line must be flushed before and after dose administration) once daily for 4 to 7 days, approximately every 24 hours, preferably in the morning. Guidance will be provided to the investigator site regarding administration instructions. PK samples will be collected to measure plasma concentrations of pantoprazole on study Day 1 and Day 2. Vital signs, adverse events, and concomitant medications will be evaluated daily during treatment and on the day after the last dose; physical examination and safety laboratory assessments will be performed on the day after the last dose. A follow up, post treatment telephone contact will occur approximately 31 days after the last dose.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in this study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the parent/legal guardian has been informed of all pertinent aspects of the study.

2. Evidence of a personally signed and dated assent, indicating that the subject understands the nature of all pertinent aspects of the study, and is willing to participate in the study activities, if applicable, as consistent with the subject's age and ability to provide assent.

3. The subject (to degree appropriate for age) and parent or legal guardian are able to understand and comply with protocol requirements, instructions and protocol-stated restrictions and are likely to complete the study as planned.

4. Subjects aged 1 to 16 years who in the judgment of the investigator are candidates for gastric acid suppression therapy (ie, those with a presumptive diagnosis of GERD, a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD) and whom the investigator judges would need to receive IV PPI therapy for at least 4 days. See Section 7.1.

5. Physical examination and clinical laboratory evaluations within normal limits unless the investigator documents that the deviations are not clinically significant or are directly related to the reason for gastric acid suppression therapy or to the subject's underlying disease process.

6. Body weight >5th percentile for subject's age.

7. Y-site or dedicated IV line for administration of pantoprazole sodium.

8. Expected survival for at least 30 days.

9. The subject (to degree appropriate for age) and parent or legal guardian are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

10. Fertile male subjects and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

    a. If subject is a female of childbearing potential, she must agree to use adequate contraception and must have a negative serum pregnancy test within 24 hours prior to administration of investigational product.

    Female subjects of non-childbearing potential must meet at least one of the following criteria:

    a. Premenarchal: The investigator (or other appropriate staff) must discuss the subject's premenarchal status with the subject or parent/caregiver at office visits and during telephone contacts, as subjects who achieve menarche during the study would no longer be considered "female subjects of nonchildbearing potential" and must comply with the protocol requirements applicable to women of childbearing potential;

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

c. Have medically confirmed ovarian failure; or

d. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

   All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.

2. Participation in other studies involving investigational drug(s) within 30 days or 5 half-lives prior to study entry and/or during study participation.

3. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4. Pregnant females; breastfeeding females; fertile male subjects and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product.

5. Serum creatine kinase levels >3x upper limit of normal.

6. Known history of human immunodeficiency virus (HIV) or clinical manifestations of acquired immune deficiency syndrome (AIDS).

7. Known hypersensitivity to proton pump inhibitors (PPIs), including pantoprazole sodium or to any substituted benzimidazole or to any of the excipients.

8. History of treatment with any PPI (eg, omeprazole, esomeprazole, lansoprazole, rabeprazole, or pantoprazole sodium) within 2 days (ie, 48 hours) before investigational product dosing on Day 1.

9. Use of Histamine 2 Receptor Blockers (H2RAs) (eg, cimetidine, famotidine, ranitidine or nizatidine), sucralfate, misoprostol, or prokinetic agents (eg, cisapride, urecholine, erythromycin or metoclopramide), and bismuth preparations within 1 day (ie, 24 hours) before investigational product dosing on Day 1, whether prescription or over the counter.

10. Any disorder requiring chronic (every day) use of warfarin, carbamazepine, or phenytoin, methotrexate, atazanavir or nelfinavir, clopidogrel, and potent inhibitors and inducers of CYP2C19.

11. Chronic (daily) use of glucocorticoids (eg, prednisone, prednisolone, dexamethasone). Steroid inhalers and topical steroids may be used.

12. Active malignancy of any type, or history of a malignancy (Subject with a history of malignancies that have been surgically removed or eradicated by irradiation or chemotherapy and who have no evidence of recurrence for at least 5 years before Screening are acceptable).

13. Alanine aminotransferase (ALT) or Blood urea nitrogen (BUN) >2.0 Upper limit of normal (ULN) or estimated creatinine >1.5 X ULN for age or any other laboratory abnormality considered by the Investigator to be clinically significant within 14 days before Screening.

14. In the Investigator's opinion, a chronic condition (eg, diabetes, epilepsy), which is either not stable or well controlled and may interfere with the conduct of the study.

15. History of sensitivity to heparin or heparin-induced thrombocytopenia.

4.3. Life Style Guidelines

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted transdermal) provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigator product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or

packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is IV pantoprazole sodium.

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject or affect the order in which subjects are enrolled.

Upon completion of screening assessments, if the subject is found to be eligible for the study, they will be entered into the interactive response technology (IRT) system. The IRT will assign a subject identification (ID).

5.2. Subject Compliance

All doses of investigational product will be administered by the appropriately designated and qualified study staff at the investigator site. Study treatment will be administered under the supervision of investigator site personnel and verified.

5.3. Investigational Product Supplies

Pantoprazole sodium for injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole sodium per vial.

5.3.1. Dosage Form and Packaging

Pantoprazole sodium for injection 40 mg will be supplied by Pfizer, Inc. as single use vial for IV administration in a single subject and will be labeled according to local regulations.

5.3.2. Preparation and Dispensing

See the Investigational Product (IP) Manual for instructions on how to prepare the investigational product for administration.

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the investigator site staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

Lyophilized powder for solution for injection will be provided by Pfizer and will be reconstituted according to the directions in IP Manual. The IP Manual will be provided to sites in advance and will contain instructions for reconstitution, and administration, shelf life, storage conditions, and other necessary information for the proper handling and management of the investigational product. Sites are required to comply with the IP Manual.

5.4. Administration

The pantoprazole sodium dose is fixed according to subject weight. See the Investigational Product Dosing Table below. The maximum dose per 24 hour period for a subject who weighs at least 40 kg will not exceed 40 mg, irrespective of weight or age. Pantoprazole sodium will be administered intravenously through a Y-site or dedicated line (if Y-site is used, IV line must be flushed before and after dose administration) once daily for 4 to 7 days, approximately every 24 hours, preferably in the morning. The IP Manual will be provided to the investigator site and include pantoprazole sodium administration instructions.

Investigational Product Dosing

IV Dose of Pantoprazole Sodium	
Subject Weight	**Total Daily Dose**
Less than 15 kg	10 mg
At least 15 kg to less than 40 kg	20 mg
At least 40 kg	40 mg

Pantoprazole sodium IV for Injection should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit. When administered via a Y-site, immediately stop use if precipitation or discoloration occurs.

5.5. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. See the IP Manual for storage conditions of the product once reconstituted.

Any storage conditions stated in the Single Reference Safety Document (SRSD) (eg, Investigator Brochure (IB)) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer. Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

5.6. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Subjects will continue their usual medical therapies according to standard clinical practice. Continuous treatment with theophylline derivatives or digoxin should be closely monitored throughout the study to assure that proper serum levels of these drugs are maintained.

Medications used to treat non-gastrointestinal (GI) conditions are allowed (with the exception of prohibited treatment). The use of any concomitant treatment (eg, the treatment of an adverse event) must be recorded on the case report form (CRF).

Concurrent treatment with any of the following medications (whether prescription or over the counter) during the treatment period of this study is prohibited:

1. Other PPIs (eg, omeprazole, esomeprazole, lansoprazole, or rabeprazole).

2. Prokinetic agents (eg, cisapride, urecholine, erythromycin, domperidone, bethanechol, or metoclopramide).

3. H2RAs (eg, cimetidine, famotidine, ranitidine, or nizatidine).

4. Antacids or other drugs that affect luminal pH or pH dependent drugs.

5. Bismuth-containing agents (eg, Pepto-Bismol®).

6. Anticholinergics (eg, scopolamine, belladonna, or Donnatal®).

7. Chronic (daily) use of glucocorticoids (eg, prednisone, prednisolone, dexamethasone). Steroid inhalers and topical steroids may be used.

8. Chronic (daily) use of carbamazepine, phenytoin, methotrexate, atazanavir or nelfinavir, clopidogrel, and potent inhibitors and inducers of CYP2C19.

9. Prostaglandins (eg, 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 investigational product.

6. STUDY PROCEDURES

The subjects will be hospitalized due to their primary medical condition or the need for a surgical procedure.

6.1. Screening

Subjects will be screened on Day 0 or on Day 1 prior to investigational product administration to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent and assent (depending on subject age and ability to provide assent) from each subject/parent/legal guardian in accordance with section Subject Information and Consent. The following procedures will be obtained:

- Obtain written parent/legal guardian informed consent, assent as appropriate.
- Review Inclusion/Exclusion criteria.
- Complete medical history, including documentation of diagnosis of GERD (Section 7.1), all prescription or nonprescription drugs, vitamins, and dietary supplements taken prior to screening procedures.
- Obtain history of drug, alcohol and tobacco use.
- Conduct physical examination, including height and weight.

- Obtain vital signs (blood pressure, pulse rate, and temperature). If a pulse rate abnormality is detected, electrocardiogram (ECG) or rhythm strip should be obtained to document this.

- Collect blood and urine specimens for the following:

  - Safety laboratory tests (to minimize the amount of blood collected, laboratory studies performed within 1 week before investigational administration may serve as screening safety laboratory values provided the information specified in the protocol is obtained). See Section 7.5.

  - Pregnancy test for female subjects of childbearing potential.

- Assess symptoms/adverse events.

- Review prior or concomitant medications.

Laboratory results for standard care may serve as study entry labs (eg, safety laboratory tests and vital signs), provided they are collected within the protocol-specified timeframe.

6.2. Treatment Period

For the treatment period described below, where multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- Blood pressure/pulse rate: obtain prior to blood specimen collections on Day 1 and Day 2. Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.

- Pharmacokinetic blood specimens: obtain at scheduled PK collection times on Day 1 and Day 2.

Other Procedures

- All other procedures should be obtained as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

6.2.1. Study Day 1

Subjects will be enrolled into the study provided that they meet all the inclusion/exclusion criteria.

On study Day 1, the following procedures will be performed according to the Schedule of Activity (SOA), preferably in the morning, to allow adequate time for collection of PK samples:

- Vital signs (blood pressure, pulse rate, and temperature). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.
- Buccal cells will be collected pre-dose for pharmacogenomic analysis.
- The actual time at which the IV pantoprazole sodium infusion begins will be documented as hour 0 of the study. At 0 hour, the subject will begin receiving pantoprazole sodium. The IV infusion will continue for 15 minutes.
- PK blood sample collection, times specified in Section 7.2.
- Assess adverse events.
- Review concomitant medications.
- Drug accountability.

6.2.2. Study Day 2

The following activities will be completed on Study Day 2:

- Pantoprazole sodium IV infusion.
- Vital signs (blood pressure, pulse rate, and temperature). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.
- PK sample collection. Times are specified in Section 7.2.
- Assess adverse events.
- Review concomitant medications.
- Drug accountability.

6.2.3. Daily During Treatment

Doses should be given approximately 24 hours apart. The following activities will be completed daily during treatment:

- Pantoprazole sodium IV infusion.

- Vital signs (blood pressure, pulse rate, and temperature). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.
- Assess adverse events.
- Review concomitant medications.
- Drug accountability.

6.3. -Day After Last Dose

The following activities will be completed on the day after the last dose:

- Physical examination including weight.
- Vital sign (blood pressure, pulse rate, and temperature). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.
- Collect blood and urine specimens for the following:
  - Safety laboratory evaluation (Section 7.5). To minimize the amount of blood collected, routine laboratory studies planned within 48 hours after the last dose of investigational product may be used as the final study evaluation safety laboratory values provided the information specified in the protocol is obtained.
  - Pregnancy test for female subjects of childbearing potential.
- Assess adverse events.
- Review concomitant medications.

6.4. Follow-Up Telephone Call

A follow-up telephone call will occur approximately 31 days (± 3 days) after the last dose of investigational product was taken. All outstanding unresolved adverse events and serious adverse events will be followed-up at this time. The follow-up telephone call should be noted and documented in the subject's primary source records. If the subject had no new or ongoing adverse events or serious adverse events during this time, this should also be noted and added to the subject's primary source records. Any serious adverse events should be reported to Pfizer within 24 hours. Concomitant medications will also be reviewed.

6.5. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request and/or parent/legal guardian, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject and/or parent/legal guardian to comply with the protocol required schedule of study visits or procedures at a given investigator site.

If a subject does not complete a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for the final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws, the following procedures will be completed:

- Physical examination including weight.
- Vital signs (blood pressure, pulse rate, and temperature). Every effort should be made to collect blood pressure at approximately the same time each day. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.
- Safety laboratory evaluation.
- Assess adverse events.
- Review prior or concomitant medications.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventative actions which s/he has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely fashion.

7.1. Diagnosis of GERD

"In infants and toddlers, there is no symptom or symptom complex that is diagnostic of GERD or predicts response".[1] Therefore it would be expected that younger children who are enrolled in this study would have had an objective diagnosis of GERD, as described in the American Academy of Pediatrics' Gastroesophageal Reflux Management Guidance for the Pediatrician.

"Diagnostic tests must be used in a thoughtful and serial manner to document the presence of reflux of gastric contents in the esophagus, to detect complications, to establish a causal relationship between reflux and symptoms, to evaluate the efficacy of therapies, and to exclude other conditions. The diagnostic methods most commonly used to evaluate pediatric patients with GERD symptoms are upper gastrointestinal (GI) tract contrast radiography, esophageal pH and/or impedance monitoring, and upper endoscopy with esophageal biopsy".[13] These or other medically appropriate, objective methods should be employed in young children for whom symptoms would not be diagnostic.

7.2. Pharmacokinetics

Blood samples (0.5 mL) for pharmacokinetic analysis of pantoprazole will be collected at times specified below. Pharmacokinetic blood samples (0.5 mL at each time point listed below) can be collected either by direct venipuncture or from an intravenous catheter. The samples must not be collected from a catheter that is connected to the study drug infusion line. The samples must be collected at a different access site that is not downstream from the site of drug administration. Additional details are found in the laboratory manual.

- Day 1: Venous blood samples (0.5 mL) will be collected to measure plasma concentrations of pantoprazole at 0.25 (the 0.25 hour sample is to be taken at the end of the 15-minute infusion), 1 to 2, 3 to 4, and 5 to 6 hours after the start of the infusion.

- Day 2: Venous blood samples (0.5 mL) will be immediately collected predose and at 0.25 (the 0.25 hour sample is to be taken at the end of the 15-minute infusion), 1 to 2, 3 to 4, and 5 to 6 hours after the start of the infusion.

  Total blood sampling volume for PK analysis is approximately 4.5 mL for an individual subject.

If the actual PK sample collection times differ from the nominal times relative to dosing, the number of samples collected must remain the same. All efforts will be made to obtain the pharmacokinetic samples within the specified windows relative to dosing. However, samples obtained within ± 15 minutes of the nominal time from dosing (ie, for the 1 to 2, 3 to 4, and 5 to 6 hour post-dose samples) will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and data collection tool (eg, CRF/DCT). The 0.25 hour (the 0.25 hour sample is to be taken at the end of the 15-minute infusion) sample must be taken at the exact nominal time relative to dosing.

Samples will be collected, processed, stored, and shipped according to the instructions provided by the sponsor to the investigator site under separate cover prior to study start.

As part of evaluation of the investigational product, samples may be used for evaluation of the bioanalytical method. These data will be used for internal exploratory purposes and will not be included in the clinical report. Samples collected for this purpose will be retained in accordance to local regulations and if not used within this timeframe, will be destroyed.

7.2.1. Shipment of Pharmacokinetic Samples

The shipment address and bioanalytical assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.2.2. Bioanalytical Methodology

The plasma samples will be analyzed for pantoprazole using a validated analytical method in compliance with Pfizer standard operating procedures.

7.3. Pharmacogenomics

CYP2C19 genotype: buccal cell samples will be collected at pre-dose by using a brush (supplied by the laboratory) and by scraping the inside of the subject's cheek. These samples will be examined to determine the presence of genes for the major (CYP2C19) enzyme responsible for metabolism of pantoprazole.

The detailed instructions for sample collection, processing, storage, and shipment will be provided by the sponsor.

The buccal samples will be analyzed in compliance with Pfizer standard operating procedures.

7.3.1. Shipment of Pharmacogenomic Samples

The shipment address and assay lab contact information will be provided to the investigator site prior to initiation of the study.

7.4. Physical Examination

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner, as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

The following parameters will be assessed and the results recorded as part of the complete physical examination:

- Height and Weight (kg) -height only at screening.
    - Note: It is recommended that length be used for subjects younger than 2 years of age.

7.5. Safety Laboratory

The following safety laboratory tests below will be performed at times defined in the Treatment Period section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns (Table 1). To minimize the amount of blood collected, routine laboratory studies planned within 48 hours after the last dose of investigational product may be used as the final study evaluation safety laboratory values, provided the information specified in the protocol is obtained.

Table 1. Safety Labs

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit Red blood cell count with indices (MCV, MCH, and MCHC) White blood cell count with differential Platelet count	Sodium Potassium Chloride Bicarbonate or CO2 Glucose Bun or Urea Creatinine Uric acid Magnesium Total bilirubin Total protein Serum albumin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Creatine kinase (CK) Alkaline phosphatase (ALP)	pH Specific gravity Protein/albumin Glucose/sugar Ketones/acetone Blood/ hemoglobin Nitrites Leukocyte esterase Bilirubin	Serum gastrin level (fasting if possible) Serum or urine pregnancy test [a]

a. For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, within 24 hours before investigational product administration. On the day after the last dose, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.

7.6. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening, within 24 hours before investigational product administration. A negative pregnancy result is required before the subject may receive the investigational product. On the day after the last dose, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of Institutional Review Boards/Independent Ethics Committees (IRB/IECs) or if required by local regulations.

In the case of a positive confirmed pregnancy, the subject will be withdrawn from investigational product but may remain in the study.

7.7. Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be measured at times relative to blood specimen collection specified in Section 6 of this protocol. Every effort should be made to collect blood pressure at approximately the same time each day. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data. If a pulse rate abnormality is detected, ECG or rhythm strip should be obtained to document this.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Blood pressure should not be taken from the arm with an intravenous infusion. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for 30 seconds . When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

7.8. Temperature

No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

"Each part of the body has a unique temperature based on perfusion, hemodynamic circumstances, and thermal conditions"[14] and because institutional standards for measurement of temperature may vary, this protocol will not restrict the accepted routes of temperature measurement. The route selected for each patient should be used consistently.

Investigators are therefore recommended "to evaluate temperature sites available and select the temperature measurement site depending on the patient's age and level of physiologic stability".[14] Furthermore, "an optimal thermometer should provide ease of application within a brief period, accurate temperature measurement, safety, tolerability by the patient, and no potential risks".[15]

7.9. Blood Volume

The total PK blood sampling volume for individual subjects in this study is approximately 4.5 mL. If the actual PK sample collection times differ from the nominal times relative to dosing, the number of samples collected must remain the same. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 30 consecutive days.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least one dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF which is a specific version of the AE page and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminostransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

Concurrent with

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least 1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT (liver function test) abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live–born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent/legal guardian. In addition, each study subject/parent/legal guardian will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for population pharmacokinetic analysis of the data collected in this study is described in Section 9.3 and in Section 11, and will be included in the Clinical Study Report and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

A sample size of 12 subjects in each age cohort is likely to have an 80% chance to achieve 20% Relative Standard Error (RSE) for both clearance (CL) and volume of distribution (Vd). This sample size was estimated using simulations of a previous population PK model of pantoprazole in pediatric patients reported by Knebel et al. (2011).[16] The simulations used the sparse PK sampling scheme specified in Section 7.2.

9.2. Efficacy Analysis

There is no efficacy analysis for this study.

9.3. Population Pharmacokinetic Analysis

Pantoprazole concentration data will be analyzed using a population PK analysis approach (nonlinear mixed-effects models). Prior pediatric PK data may be used to guide and assist the model building and covariate selection. A two-compartment model with IV infusion will be used to describe pantoprazole concentrations, with clearance (CL) and volume of distribution (Vd) of the central compartment being the key population PK parameters in the model. The potential influence of covariates, including age and body weight, on these parameters will be explored during the model building phase of the analysis. Other covariates, including gender and baseline values, may also be explored using graphical approaches.

The final population PK model will also be used to estimate the following PK Parameters: maximum plasma concentration (C_{max}), area under the plasma concentration-time profile from time zero to the 24 hour time post dose (AUC_{24}), area under the plasma concentration-time profile from time zero extrapolated to infinite time (AUC_{inf}) and terminal phase half-life ($T_{1/2}$) of pantoprazole following single and multiple IV doses.

A Population Modeling Analysis Plan (PMAP) describing the details of the model building, covariate assessment, model validation and PK parameter estimation will be provided separately.

9.4. Analysis of Other Endpoints

Pharmacogenomic Endpoint:

- CYP2C19 genotype: buccal cell samples will be collected at pre-dose by using a brush (supplied by the laboratory) and by scraping the inside of the subject's cheek. These samples will be examined to determine the presence of genes for the major (CYP2C19) enzymes responsible for metabolism of pantoprazole.

9.5. Safety Analysis

Adverse events, physical examinations, blood pressure, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, blood pressure, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Safety results will be reported separately for each age cohort.

Safety summaries will be produced in accordance with Clinical Data Interchange Standards Consortium (CDISC) and Pfizer Standards (CaPS) for safety reporting.

Baseline characteristics (eg, demographics, medical history) will be also summarized using CaPS for reporting.

9.6. Interim Analysis

There will be no interim analysis for this study.

9.7. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for GCP (ICH 1996), and the Declaration of Helsinki.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, address, birth date and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent/assent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent document used during the informed consent process must be reviewed and approved by Pfizer, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her parent(s) or legal guardian are fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from the subject's parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as Database Lock.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of pantoprazole sodium at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 5 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed

publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

Investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	AUC from 0 to 24 hours
AUC_{inf}	AUC extrapolated to infinite time
BUN	blood urea nitrogen
CaPS	CDISC and Pfizer Standards
CDISC	Clinical Data Interchange Standards Consortium
CK	creatine kinase
CL	clearance
C_{max}	maximum plasma concentration
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
CYP	cytochrome P450
DCT	data collection tool
DNA	deoxyribonucleic acid
DU	dispensable unit
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDAAA	Food and Drug Administration Amendments Act (United States)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
H2RA	histamine2-receptor antagonist
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application

Abbreviation	Term
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
N/A	not applicable
NASPGHAN	North American Society for Pediatric Gatroenterology, Hepatology, and Nutrition
NDA	New Drug Application
PASS	post-authorization safety study
PK	pharmacokinetics
PMAP	Population Modeling Analysis Plan
PMR	post-marketing requirement
PPI	proton pump inhibitor
PREA	Pediatric Research Equity Act
PT	prothrombin time
RSE	relative standard error
SAE	serious adverse event
SAP	statistical analysis plan
SOA	schedule of activities
SRSD	single reference safety document
T½	half-life
TEAE	treatment emergent adverse event
ULN	upper limit of normal
URI	upper respiratory infection
US	United States
USPI	United States package insert
V_d	volume of distribution
V_{ss}	steady state volume of distribution