Protocol Number: VPED-103

Official Title: A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥ 6 to < 12 Years Who Have Symptomatic Gastroesophageal Reflux Disease

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CLINICAL STUDY PROTOCOL

IND NUMBER: 079212

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A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥ 6 to < 12 Years Who Have Symptomatic Gastroesophageal Reflux Disease

PROTOCOL NO. VPED-103

Sponsor:	Phathom Pharmaceuticals, Inc. 2150 East Lake Cook Road, Suite 800 Buffalo Grove, IL 60089 USA
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Version of Protocol:	Amendment 2
Date of Protocol:	30 August 2023
Previous Date and Version	23 June 2023, Amendment 1

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥ 6 to < 12 Years Who Have Symptomatic Gastroesophageal Reflux Disease
Protocol Number	VPED-103
Protocol Version and Date	Amendment 2 30 August 2023

PROTOCOL ACCEPTED AND APPROVED BY PHATHOM PHARMACEUTICALS:

[redacted] 31-Aug-2023 | 00:17 PDT

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Vice President, Clinical and Patient Safety
Phathom Pharmaceuticals, Inc.

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Clinical Pharmacology Consultant
Phathom Pharmaceuticals, Inc.

Protocol Approval – Principal/Coordinating Investigator

Study Title	A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥ 6 to < 12 Years Who Have Symptomatic Gastroesophageal Reflux Disease
Protocol Number	VPED-103
Protocol Version and Date	Amendment 2 30 August 2023

Protocol accepted and approved by:

Principal/Coordinating Investigator

[redacted]

[redacted]

Signature

31-Aug-2023

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥ 6 to < 12 Years Who Have Symptomatic Gastroesophageal Reflux Disease" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Amendment 2, dated 30 August 2023, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Phathom Pharmaceuticals, Inc. or implement protocol changes without Institutional Review Board/Independent Ethic Committee approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Phathom Pharmaceuticals, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	VPED-103
Title:	A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥ 6 to < 12 Years Who Have Symptomatic Gastroesophageal Reflux Disease
Sponsor:	Phathom Pharmaceuticals, Inc. 2150 East Lake Cook Road, Suite 800 Buffalo Grove, IL 60089 USA
EU Trial Number:	2022-003228-42
Study Phase:	1
Study Sites:	Approximately 20 to 25 sites in the United States and Europe
Indication:	Symptomatic gastroesophageal reflux disease (GERD)
Rationale:	GERD is prevalent globally and represents one of the most common gastrointestinal diseases. Per the Montreal definition, GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. The term GERD covers a spectrum of conditions, including symptomatic non-erosive GERD (sGERD), erosive esophagitis (EE), and Barrett's esophagus. The prevalence of GERD increases with age, from 2.5% of children between 3 and 9 years of age to 8.5% of those between 10 and 17 years of age. Similarly, the overall prevalence of EE increases with age, from 5.5% in infants to 12.4% in children and adolescents. Younger children usually present with extraesophageal manifestations, regurgitation, and epigastric pain, while older children and adolescents typically present with adult-type GERD symptoms of heartburn and regurgitation. Pediatric GERD is a condition that is not always outgrown and can manifest itself as a chronic disease. Vonoprazan belongs to a new class of acid-inhibitory agents called “potassium-competitive acid blockers.” In the United States, vonoprazan in combination with amoxicillin and in combination with amoxicillin and clarithromycin is approved for the treatment of *Helicobacter pylori* infection in adults. Vonoprazan is being developed in adults for the treatment of heartburn in patients with symptomatic non-erosive GERD, healing of all grades of EE and relief of heartburn and maintenance of healing of all grades of EE and relief of heartburn. The pediatric doses for this study were selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD to children ≥ 6 to < 12 years of age.

Objectives:	Primary: • To evaluate the pharmacokinetic profile of vonoprazan (10 or 20 mg once daily [QD]) in children ≥ 6 to < 12 years of age who have symptomatic GERD. Safety: • To evaluate the safety of vonoprazan (10 or 20 mg QD) in children ≥ 6 to < 12 years of age who have symptomatic GERD. Exploratory: • To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg QD) in children ≥ 6 to < 12 years of age who have symptomatic GERD.
Study Population:	Children ≥ 6 to < 12 years of age who have symptomatic GERD, with or without EE.
Study Design and Interventions:	This is a Phase 1, uncontrolled, randomized, open-label, parallel-group, multiple-dose study in children ≥ 6 to < 12 years of age who have symptomatic GERD. Subjects will be screened for up to 28 days. Successfully screened subjects will be randomized to receive 10 or 20 mg of vonoprazan QD for 14 days. Approximately 18 subjects are expected to be enrolled in the study. Blood samples for pharmacokinetic testing will be collected on Days 7 and 14. Select sites will perform gastric pH monitoring in subjects deemed clinically indicated by the principal investigator. Subjects undergoing gastric pH monitoring will be confined to the clinic for testing. Gastric pH will be monitored for 24 hours beginning on Day -1 and on Day 7. The study will include 3 periods: **Screening Period (≤ 4 weeks):** Subjects will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will be randomized and enter the Treatment Period. **Treatment Period (Day 1 to Day 14):** Subjects will be randomized to receive vonoprazan 10 mg or vonoprazan 20 mg QD. **Follow-up Period:** A safety follow-up phone call will occur 2 weeks after the last dose of study drug to assess adverse events (AEs). A subject will be considered to have completed the study if the subject completes the Treatment Period and the safety follow-up phone call. Following the last dose of study drug or early discontinuation, the subject will be transitioned to local standard of care in accordance with each site's prespecified process.

Estimated Study Duration:	The total duration of the study is up to 8 weeks. The Screening Period is up to 4 weeks, Treatment Period is 2 weeks, and safety follow-up phone call is 2 weeks after last study drug administration.
Pharmacokinetic Assessments (Primary Endpoints):	The primary vonoprazan pharmacokinetic endpoints will include the following steady state parameters from data collected on Day 7 and Day 14: • Maximum observed drug concentration at steady state ($C_{max,ss}$) • Area under the plasma concentration-time curve during the dosing interval τ (AUC_{τ}) • Apparent oral clearance (CL/F) • Apparent volume of distribution (V_z/F)
Efficacy and Pharmacodynamic Assessments (Exploratory Endpoints):	Efficacy and pharmacodynamic characteristics will be assessed by the following: • The severity of GERD symptoms at screening and Days 7 and 14 as assessed by the investigator • Mean pH and percentage of time above pH 4, 5, and 6 at Day -1 and Day 7 in the subset of subjects for whom intragastric pH monitoring is performed when clinically indicated per the investigator
Safety Assessments (Safety Endpoints):	Safety will be assessed by the following: • AEs • Laboratory test values (hematology, serum chemistry, urinalysis) • Electrocardiograms • Vital signs
Study Drug, Dosage, and Route of Administration:	Open-label study drug (vonoprazan 10 mg or vonoprazan 20 mg) to be taken orally QD for 14 days (Day 1 through Day 14). All study drug doses are to be taken preferably prior to eating any breakfast or food with approximately 240 mL (8 oz) water between 7 and 10 am each day.
Ethical Considerations:	Clinical studies in adults with GERD have shown a positive benefit-risk for vonoprazan. This study is anticipated to provide benefits to children ≥ 6 to < 12 years of age with symptomatic GERD and risks similar to those observed with vonoprazan in adults. This study is needed to identify doses to be used in future trials in children ≥ 6 to < 12 years of age. The study was designed to minimize the number of blood samples and visits to investigate the pharmacokinetics and safety in this population.

Sample Size:	Approximately 18 subjects will be enrolled with 9 subjects in each dose group. Attempts will be made to enroll subjects across the ≥ 6 to < 12 years age range. Because this is a pharmacokinetic and safety trial with no comparator, there is no power determination affecting the sample size. The sample size of approximately 18 subjects is considered sufficient to assess the pharmacokinetics, safety, and tolerability of vonoprazan in this population. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the pharmacokinetic profile.
Statistical Methods:	Pharmacokinetic Endpoints: Individual pharmacokinetic parameter estimates will be summarized descriptively by vonoprazan dose. Efficacy Endpoint: The severity of GERD symptoms at screening and Days 7 and 14, as assessed by the investigator, will be summarized overall and by vonoprazan dose. Pharmacodynamic Endpoints: Mean pH and the percentage of time above pH 4, 5, and 6 at baseline (Day -1) and Day 7 will be summarized for the subset of subjects for whom intragastric pH monitoring is available. Safety: Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing treatment-emergent AEs will be summarized by MedDRA system organ class and preferred term overall, by severity, and by relationship to study drug for each treatment group. Clinical laboratory tests, electrocardiograms, and vital signs will be summarized with descriptive statistics at each time point by treatment group.
Version and Date of Protocol:	Amendment 2.0 30 August 2023

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{ss}	area under the drug concentration-time curve at steady state
AUC τ	area under the drug concentration-time curve during the dosing interval τ
CFR	Code of Federal Regulations
CL/F	Oral clearance
$C_{max,ss}$	maximum drug concentration at steady state
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
H+, K+-ATPase	hydrogen, potassium–adenosine triphosphatase
H_2RA	histamine-2 receptor antagonist
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
LAR	legally authorized representative
LFT	liver function test

Abbreviation	Definition
LLC	Limited Liability Company
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
PCAB	potassium-competitive acid blocker
popPK	population pharmacokinetic
PPI	proton pump inhibitor
PTE	pretreatment adverse event
QD	once daily
RBC	Red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
sGERD	Symptomatic non-erosive gastroesophageal reflux disease
SoE	schedule of events
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SUSAR	suspected unexpected serious adverse reaction
Takeda	Takeda Pharmaceutical Company Limited
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
V_z/F	Apparent volume of distribution
WBC	White blood cell

Note: Abbreviations used only in tables and figures are defined with the relevant tables and figures.

1 Introduction

Vonoprazan belongs to a new class of acid-inhibitory agents called potassium-competitive acid blockers (PCABs). In the United States, vonoprazan in combination with amoxicillin and in combination with amoxicillin and clarithromycin have been approved for the treatment of *Helicobacter pylori* infection in adults. Vonoprazan is being developed for the treatment of heartburn in patients with symptomatic non-erosive gastroesophageal reflux disease (sGERD), healing of all grades of erosive esophagitis (EE) and relief of heartburn and maintenance of healing of all grades of EE and relief of heartburn.

In countries other than the United States, vonoprazan has been studied in other gastric acid-related diseases such as healing of gastric and duodenal ulcers, and for the prevention of recurrence of gastric or duodenal ulcer during nonsteroidal anti-inflammatory drug or aspirin administration. Vonoprazan has received regulatory approval for adults in Japan, Russia, and other countries in Asia and Latin America for a variety of indications, including the healing of erosive esophagitis and maintenance of healing of erosive esophagitis. Vonoprazan is not currently approved for use in pediatric patients in any country.

Phathom Pharmaceuticals, Inc. licensed the exclusive rights from Takeda Pharmaceutical Company Limited (Takeda) to develop, manufacture, and commercialize vonoprazan in the United States, Europe, and Canada.

1.1 Study Rationale

The purpose of this study is to determine a dose of vonoprazan in children aged ≥ 6 to< 12 years with symptomatic gastroesophageal reflux disease (GERD) that provides an exposure similar to the exposures in adults after administration of vonoprazan 10 or 20 mg once daily (QD). Like proton pump inhibitors, vonoprazan is expected to provide benefit in pediatric patients with GERD.

1.2 Background

1.2.1 Epidemiology, Symptoms, and Current Treatments for GERD

Gastroesophageal reflux disease is prevalent globally and represents one of the most common gastrointestinal diseases. Per the Montreal definition, GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications

[Vakil 2006]. The term GERD covers a spectrum of conditions, including symptomatic non-erosive GERD, EE, and Barrett's esophagus.

The prevalence of GERD increases with age, from 2.5% of children between 3 and 9 years of age to 8.5% of those between 10 and 17 years of age [Nelson 2000]. Similarly, the overall prevalence of EE increases with age, from 5.5% in infants to 12.4% in children and adolescents [Gilger 2008]. Younger children usually present with extraesophageal manifestations, regurgitation, and epigastric pain, while older children and adolescents typically present with adult-type GERD symptoms of heartburn and regurgitation [Cezard 2004, Rosen 2018]. Pediatric GERD is a condition that is not always outgrown and can manifest itself as a chronic disease [Rosen 2018].

Management of GERD includes lifestyle changes (eg, diet, weight loss, sleeping position), over-the-counter antacids, histamine-2 receptor antagonists (H_2RAs), and proton pump inhibitors (PPIs). Proton pump inhibitors are considered superior to H_2RAs for the healing of EE and relief of GERD symptoms and have become the pharmacological mainstay for the treatment of adult and pediatric GERD [Gold 2002, Rosen 2018].

1.2.2 Vonoprazan

The gastric hydrogen, potassium–adenosine triphosphatase (H+, K+-ATPase), also known as the proton pump, is responsible for acid secretion from parietal cells in the stomach. It is inactive in the cytosol but relocates from the cytosol to the secretory membrane of the parietal cells when food is present in the stomach, thereby becoming active and pumping H+ ions out of the cells and into the canaliculi in exchange for K+ ions. It represents an attractive pharmacological target since it is the final step of the acid secretion process.

Two classes of pharmaceuticals, with distinct mechanisms of action for inhibiting the gastric proton pump, have been developed for clinical application: PPIs and PCABs. As a PCAB, vonoprazan has a unique mechanism of action and pharmacokinetics relative to PPIs:

- Acid activation and stability: Conventional PPIs are prodrugs, which are activated by acid and covalently bind to the H+, K+-ATPase; however, activated PPIs are not stable in acidic conditions. In contrast, vonoprazan does not require acid activation, is stable in acidic conditions, and has a more durable effect. Further, vonoprazan is

rapidly protonated in the parietal cell canaliculi, which concentrates the drug proximal to the H+, K+-ATPase [Scarpignato 2019].

- Activity against proton pumps: Vonoprazan inhibits acid secretion by competitively inhibiting the binding of potassium ions to the H+, K+-ATPase. Vonoprazan may selectively concentrate in the parietal cells in both the resting and stimulated states and binds to the active pumps in a noncovalent and reversible manner. In contrast, PPIs covalently bind H+, K+-ATPase only when the pump is active, as an acidic environment is required for the activation and accumulation of PPIs in the parietal cell [Scott 2015].

- Vonoprazan maintains acid control over 24 hours with QD dosing [Engevik 2020]. Vonoprazan can also be dosed in the presence or absence of food, while most PPIs require dosing before a meal to optimize their acid suppressant effect because activated pumps are at their highest level post-prandially due to activation of pumps by the meal [Shin 2013].

- Extended half-life: The mean plasma half-life is typically 7 to 8 hours after single and multiple QD administration of vonoprazan 20 mg (TAK-438_107). This is significantly longer than the half-life of conventional PPIs (<2 hours) [Shin 2013].

- Metabolism: Vonoprazan is metabolized by a combination of cytochrome P450 (CYP) isoforms including CYP3A4/5, which does not have a high degree of genetic polymorphism as compared with CYP2C19, which is the primary enzyme responsible for the metabolism of PPIs [Shin 2013].

These unique aspects of the vonoprazan mechanism of action and pharmacokinetics relative to PPIs translate into greater magnitude and duration of gastric acid suppression, which are reflected in the pharmacodynamic profile [Jenkins 2015; Sakurai 2015].

The pharmacokinetic and pharmacodynamic profiles of vonoprazan were assessed in multiple studies, including Study TAK-438_107, which showed rapid rise in pH following vonoprazan administration and a dose response for percent time above pH 4. The mean percentage of time above pH 4 on Day 1 for vonoprazan 10 mg, 20 mg, and 40 mg were 43%, 63%, and 86%, respectively, and by Day 7 were 60%, 85%, and 93%, respectively [Jenkins 2015].

Takeda conducted 8 short-term clinical studies in adults with EE (5 studies) and symptomatic non-erosive GERD (3 studies) with treatment durations of 2 to 8 weeks. In addition, Takeda conducted 3 studies of maintenance of healing of EE with treatment durations of 24 to 52 weeks. Vonoprazan is approved in multiple countries outside of the United States for the treatment of adults for reflux (erosive) esophagitis (for healing: vonoprazan 20 mg QD up to 4 weeks or, if insufficient effect, 8 weeks; for maintenance: 10 mg QD or, if insufficient effect, 20 mg QD).

The safety profile of vonoprazan in Phase 3 studies of adults across indications showed no evidence of a dose-related increase in adverse effects with vonoprazan from 5 mg to 40 mg QD. As of 25 December 2022, the global cumulative post-marketing patient exposure to vonoprazan is estimated to be approximately 97 million patients.

Overall, with vonoprazan's pharmacological profile of rapid, potent, and sustained elevations of gastric pH, vonoprazan offers the potential to be a highly effective treatment option for children with symptomatic GERD.

1.3 Justification for Dose

The proposed pediatric doses are selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD in pediatric patients ≥ 6 to < 12 years of age.

The proposed doses are based on simulations using an updated population pharmacokinetic (popPK) model [Facius 2023]. The 2-compartment linear popPK model for vonoprazan was developed with adult pharmacokinetic data from healthy subjects aged 18 to 54 years who participated in 9 studies specifically selected to enable the extrapolation and characterization of the disposition of vonoprazan in pediatric subjects. The final dataset consisted of 354 subjects (205 Asian and 149 Western) with 8010 plasma concentration observations.

As planned, an analysis of interim PK data from the first adolescent subjects aged 12 to 17 years randomized in Study VPED-102 was performed using the updated popPK model. Interim data from VPED-102 was combined with adult data from the updated popPK model to investigate potential differences in the pharmacokinetic properties of vonoprazan between adolescents and adults. Individual predicted area under the drug concentration-time curve at steady state (AUC_{ss}) values for the 8 adolescent subjects with symptomatic GERD included

in the preliminary analysis were within the range expected from healthy adults at their respective doses and no obvious effect of age or body weight was observed. Model assessments indicated the updated popPK model was working well in adolescents and substantiated the usefulness of simulations using the model to select doses for younger pediatric subjects.

For predicting the appropriate doses in pediatric subjects aged ≥ 6 to <12 years, simulations were performed using the updated popPK model for vonoprazan and were summarized by both age and body weight. For reference, all boys and girls aged ≥ 6 to < 12 years who have a body weight between the 5th and 95th percentiles would have a body weight between 15 and 65 kg. Different model assumptions in terms of the allometric weight scaling exponent (as estimated (none) in the adult data or fixed at 0.2) were compared.

The updated model was used to simulate posterior distributions of AUC_{ss} in both adults and pediatric subjects aged ≥6 to <12 years or with a body weight of 15 to 65 kg for a series of pediatric candidate doses. Matching pediatric doses were selected to limit the predicted percentage of pediatric subjects with an exposure exceeding the adult reference exposure (median AUC_{ss}) at 50%.

For children aged ≥ 6 to < 12 years or with a body weight of 15 to 65 kg each of the simulations gave similar exposure predictions, thereby suggesting that the selected doses for these pediatric patients (10 and 20 mg) should result in a majority of exposures that are within the 95% prediction interval in adults for both the 10 and 20 mg targeted doses.

2 Study Objectives and Endpoints

Study objectives with corresponding endpoints are presented in Table 2-1.

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetic profile of vonoprazan (10 or 20 mg QD) in children ≥ 6 to < 12 years of age who have symptomatic GERD.	• $C_{max,ss}$, AUC_{τ}, CL/F, V_z/F from data collected on Days 7 and 14.
Safety	
• To evaluate the safety of vonoprazan (10 or 20 mg QD) in children ≥ 6 to < 12 years of age who have symptomatic GERD.	• Adverse events • Laboratory test values (hematology, serum chemistry, urinalysis*) • Electrocardiograms (ECGs) • Vital signs
Exploratory	
• To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg) in children ≥ 6 to < 12 years of age who have symptomatic GERD.	• The severity of GERD symptoms at baseline and Days 7 and 14, as assessed by the investigator • Mean pH and % time above pH 4, 5, and 6 at baseline and Day 7 in the subset of subjects for whom intragastric pH monitoring is performed when clinically indicated per the investigator.

AUCτ: area under the drug concentration-time curve during the dosing interval τ; CL/F: oral clearance; $C_{max,ss}$: maximum drug concentration at steady-state; ECGs; electrocardiograms; GERD: gastroesophageal reflux disease; QD: once daily; V_z/F: apparent volume of distribution
* Urinalysis is only required if deemed necessary by the investigator.

3 Investigational Plan

3.1 Study Design

This is a Phase 1, randomized, open-label, parallel-group, multiple-dose study in children aged ≥ 6 to < 12 years who have symptomatic GERD. A total of approximately 18 subjects will be enrolled.

Blood samples for pharmacokinetic testing will be collected on Days 7 and 14. Select sites will perform gastric pH monitoring in subjects deemed clinically indicated by the principal investigator. Gastric pH will be monitored for 24 hours beginning on Day -1 and on Day 7.

Following completion of study drug dosing on Day 14 or early discontinuation, the subject will be transitioned to local standard of care for 14 days during the Follow-up Period. Note, standard of care does not include the use of study drug but can include other acid suppressant agents.

A schematic diagram of the overall study design is presented in Figure 3-1.

Figure 3-1 Study Scheme

Screening Period		Treatment Period (14 Days)				Follow-up Period [b] (14 Days)
Up to 4 weeks		→ **Vonoprazan 10 mg QD** (N=9)			→	**Follow-up** (local standard of care)
		→ **Vonoprazan 20 mg QD** (N=9)			→	
Day -1: Placement of probe for 24-hour gastric pH monitoring [a]		**Day 1:** Randomization First dose of study drug taken at the clinic Removal of pH probe [a]	**Day 7:** Placement of probe for 24-hour gastric pH monitoring [a] Dose of study drug taken at the clinic PK blood collection: pre-dose, 0.5 to 1.5 hours and 2.5 to 3.5 hours post-dose Symptom assessment **Day 8:** Removal of pH probe [a]	**Day 14:** Last dose of study drug taken at clinic [b] PK blood collection: pre-dose, 1 to 2 hours and 3 to 4 hours post-dose Symptom assessment		**Day 28:** Phone call

PK: pharmacokinetic; QD: once daily

a At select sites if deemed clinically indicated by the investigator. Subjects who undergo pH monitoring will have monitoring performed on both Day -1 and Day 7 for 24 hours.

b Following completion of study drug dosing or early discontinuation, the subject will be transitioned to local standard of care for 14 days.

The study will include 3 periods (see the schedule of events [SoE] in Section 13.1 for details).

Screening Period (≤ 4 weeks): Subjects will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will be randomized and enter the Treatment Period.

Treatment Period (Day 1 to Day 14): Subjects will be randomized to receive 1 of 2 vonoprazan doses (10 mg QD or 20 mg QD) for 14 days.

Follow-up Period (2 weeks): A safety follow-up visit phone call will occur 2 weeks after the last dose of study drug to assess adverse events (AEs). Following completion of study drug dosing or early discontinuation, the subject will be transitioned to local standard of care for 14 days.

End-of-study definition: A subject will be considered to have completed the study (up to 8 weeks, including 4 weeks of screening, 2 weeks of treatment and 2 weeks of safety follow-up) if the subject completes the Treatment Period and the safety follow-up visit phone call.

3.1.1 Rationale of Study Design

Blinding is not necessary in this study since the primary objective is to evaluate the pharmacokinetic profile of vonoprazan. The pharmacokinetic endpoints are objective and unlikely to be biased by the open-label design.

A parallel-group design with 2 dose levels of vonoprazan (10 and 20 mg QD) was selected to provide unbiased estimates of the vonoprazan pharmacokinetic and safety profile across doses likely to be safe and efficacious in children aged ≥ 6 to < 12 years. Dose justification is provided in Section 1.3. A placebo control group is not considered practical or ethical in children aged ≥ 6 to < 12 years with symptoms of GERD.

Pharmacokinetic studies with PPIs (dexlansoprazole, esomeprazole, lansoprazole, rabeprazole) in pediatric GERD patients were generally less than 7 days [Gunasekaran 2002, Gremse 2002, James 2007, Kukulka 2014, Kukulka 2012, Li 2006, Rosen 2018, Zannikos 2011, Zhao 2006]. Historical PPI data (esomeprazole, lansoprazole, pantoprazole) in pediatric GERD patients have shown benefit in terms of resolution of heartburn and other GERD symptoms within a week of treatment [Gold 2007, Gunasekaran 2002, Tolia 2006].

The pharmacological profile of vonoprazan relative to PPIs suggest that, if effective, the onset of efficacy in pediatric patients would be similar or earlier than with PPIs.

This study will include children aged ≥ 6 to < 12 years who have symptomatic GERD with or without EE. In Study EE-301, which enrolled 1027 adult subjects with endoscopically confirmed EE of Los Angeles Classification Grades A to D, 514 subjects were evaluated for EE healing after receiving vonoprazan 20 mg QD for 2 weeks. Of the 514 subjects, 74.3% had healed EE at Week 2. Based on this data, the proposed 14-day treatment duration will provide clinical benefit to subjects with EE, with a possibility of healing of EE.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

This study will be conducted at approximately 20 to 25 sites in the United States and Europe. Approximately 18 subjects will be enrolled.

4.1.1 Inclusion Criteria

Subjects are eligible for enrollment in the study if they meet all of the following inclusion criteria:

1. The subject is ≥ 6 to < 12 years of age at the time of informed consent signing.
2. The subject has a body weight within the 5th through 95th percentile by age, inclusive, as determined by the National Center for Health Statistics (Section 13.6).
3. The subject must have a diagnosis of GERD prior to randomization and medical history of signs or symptoms of GERD for at least 3 months prior to screening, based on physical examination, current symptoms (eg, heartburn), or diagnostic tests (eg, pH or endoscopy). Notes in the medical records and/or other source documents, such as prior endoscopies, can be used to support the diagnosis and will be recorded in the electronic case report form (eCRF).
4. The subject has at least one moderate GERD symptom based on the GERD Symptom Assessment-Investigator scale performed at screening.
5. The subject must be able to swallow study drug tablet with water.
6. Parent or legal guardian (ie, legally authorized representative [LAR]) is willing and able to complete the informed consent process and subjects are able to comply with study procedures and visit schedule.
7. Female subjects who have experienced menarche must have a negative pregnancy test and will be counseled on pregnancy avoidance (Section 13.2).

4.1.2 Exclusion Criteria

Subjects are not eligible for study participation if they meet any of the following exclusion criteria:

1. The subject has used prescription or non-prescription PPIs or H_2RAs within 7 days prior to randomization or requires use during the Treatment Period.

2. The subject has used sucralfate, or antacids within 1 day prior to randomization or requires their use during the Treatment Period.

3. The subject has received other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth from 30 days prior to Day 1 or requires their use during the course of the study.

4. The subject has received atazanavir sulfate or rilpivirine hydrochloride from 5 days prior to Day 1 or requires their use during the course of the study.

5. The subject has received any investigational compound (including vonoprazan) within 30 days prior to the start of the Screening Period.

6. The subject is an immediate family member or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, child, sibling) or subject may have consented under duress.

7. The subject requires hospitalization or has surgery scheduled during the course of the study or has undergone major surgical procedures within 30 days prior to the Screening Period.

8. The subject has undergone prior gastrointestinal surgeries.

9. The subject has any abnormal laboratory test values that are considered clinically significant in the opinion of the investigator during the Screening Period.

10. The subject has a history of hypersensitivity or allergies to vonoprazan (including the formulation excipients: D-mannitol, microcrystalline cellulose, hydroxypropyl

cellulose, fumaric acid, ascorbic acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 8000, and titanium dioxide, or red or yellow ferric oxide).

11. The subject has used any prescription or over-the-counter medications (including herbal or nutritional supplements), other than those already excluded in criteria 1 to 5 above, within 14 days before the first dose of study drug or throughout the study. That is, unless the medication(s) is permitted by the sponsor following a review of available data which confirms concomitant administration of the medication is unlikely to affect either the safety of the patient or the pharmacokinetics of vonoprazan.

12. The subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or other food products that may be CYP3A4 inhibitors (eg, vegetables from the mustard green family [kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard] and charbroiled meats) within 7 days (or 5 half-lives) before the first dose of study drug or throughout the study.

13. The subject has positive results at screening for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus (HCV) infection at screening.

14. The subject has severe renal impairment (estimated glomerular filtration rate < 30 mL/min).

15. The subject has moderate to severe hepatic impairment (Child-Pugh Class B and Child-Pugh Class C).

16. The subject has any of the following abnormal laboratory test values at the start of the Screening Period:

    a. Creatinine levels: >1 mg/dL (>88 µmol/L).

    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × the upper limit of normal (ULN) or total bilirubin >2 × ULN (except subjects with Gilbert Syndrome).

17. In the opinion of the investigator, the subject is not suitable for entry into the study.

4.1.3 Screen Failures

Screen failures are defined as subjects whose LAR signed the informed consent form (ICF) to participate in the clinical study but are not subsequently entered in the Treatment Period of the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, pretreatment adverse events (PTEs), AEs, and any serious adverse events (SAEs).

Subjects may be allowed to be rescreened upon discussion with and approval by the medical monitor.

4.2 Withdrawal of Subjects From Study Drug and/or the Study

The duration of the study is defined for each subject as the date signed written informed consent is provided through the last follow-up visit phone call performed 2 weeks after completing the last dose of study drug in the Treatment Period.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects or LARs may withdraw from the study at any time (eg, Treatment Period, Follow-up Period) and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. The primary reason for discontinuation or withdrawal of the subject from the study drug or the study should be recorded in the eCRF. For screen failure subjects, refer to Section 4.1.3.

A subject may be withdrawn from the study for any of the following reasons:

1. Adverse event or SAE: The subject has experienced a PTE, AE, or SAE that requires early termination because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the PTE, AE, or SAE.
   Note: If a subject is discontinued from study participation due to a PTE, AE, or SAE, the event will be followed until it is fully resolved or stable.

2. Liver function test (LFT) abnormalities: Appropriate clinical follow-up (including repeat laboratory tests) is to be done until a subject's laboratory profile has returned to

normal/baseline status. See Section 13.2 to monitor LFT abnormalities and for the criteria of liver function abnormalities for temporary and permanent discontinuation of study drug.

3. Significant protocol deviation: The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented (3 documented telephone contact attempts and 1 certified letter, at a minimum) within 6 weeks of the most recent planned visit.

5. Voluntary withdrawal: The subject or the LAR wishes to withdraw from the study. The reason for the withdrawal, if provided, should be recorded in the eCRF.
Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).

6. Study termination: The sponsor, Institutional Review Board (IRB)/Independent Ethics Committees (IECs), or regulatory agency terminates the study.

7. Pregnancy: The subject is found to be pregnant. Note: If the subject is found to be pregnant, the subject must be withdrawn immediately from the treatment. See Section 6.3.2 for further instructions on pregnancy.

8. Lack of efficacy: The investigator has determined that the subject is not benefiting from investigational treatment and continued participation would pose an unacceptable risk to the subject.

9. Other: The subject is discontinued from the study for any reason other than those listed above. The specific reason(s) for subject discontinuation will be recorded in the eCRF where appropriate.

4.2.2 Handling of Withdrawals

Subjects or LARs are free to withdraw from the study drug or the study at any time upon request.

Subject participation in the study may be stopped at any time at the discretion of the investigator.

Following completion of study drug dosing or early discontinuation, the subject will be transitioned to local standard of care in accordance with each site's prespecified process.

Subjects who discontinue study drug or active participation in the study will no longer receive study drug. When a subject withdraws from the study drug or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will undergo all end-of-study assessments. Subjects who fail to return for final assessments will be contacted by the site to make every attempt to comply with the protocol.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified follow-up procedures to assess safety.

See the SoE in Section 13.1 for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 4.2.1.

4.2.3 Lost to Follow-up

A subject will be considered lost to follow-up if the LAR signed the ICF, the subject fails to return for scheduled visits during the Treatment Period or Follow-up Period, and the LAR is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the LAR and reschedule the missed visit as soon as possible, counsel the subject and LAR on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject and LAR wish to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the LAR (where possible, 3 telephone calls and, if necessary, a certified letter [or local equivalent methods] to the subject's last known mailing address within 6 weeks of most recent planned visit). These contact attempts should be documented in the subject's source document.

- Should the LAR continue to be unreachable, the subject will be considered to have withdrawn from the study due to being lost to follow-up.

4.2.4 Replacements

At the discretion of the sponsor, subjects may be replaced to achieve the target of approximately 18 subjects with expected usable pharmacokinetic sample collections.

5 Study Drugs

5.1 Method of Assigning Subjects to Treatment Groups

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to 1 of the following 2 groups during the Treatment Period:

- Vonoprazan 10 mg QD for 14 days
- Vonoprazan 20 mg QD for 14 days

An interactive response technology (IRT) system will be used to administer the randomization schedule. Biostatistics will generate the randomization schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IRT, which will link sequential subject randomization numbers to treatment codes. The randomization will also use an appropriate block size, which will not be revealed.

5.2 Treatments Administered

Subjects will be administered study drug orally at the clinic on Day 1 and on Days 7 and 14, after the pre-dose pharmacokinetic sample, with approximately 240 mL (8 oz) of water in the morning between 7 and 10 am preferably prior to eating any breakfast or food. If necessary, a dosing cup can be used to facilitate administration. Study drug will be dispensed to the parent/LAR for study drug to be administered to the subject at home. Clinic staff will provide the parent/LAR a Study Drug Reminder Card and instruct the parent/LAR to record the date and time of every dose taken at home and to bring this card back to the next clinic visit.

On Days 2 to 6 and 8 to 13, the parent/LAR will be instructed to give the subject study drug orally with approximately 240 mL (8 oz) of water each morning between 7 and 10 am preferably prior to eating any breakfast or food. Any missed doses should also be recorded by the parent/LAR and communicated to clinic staff immediately. All dosing information including missed doses will be recorded on the Study Drug Reminder Card and in the eCRF.

On Days 7 and 14 subjects may have a meal/snack 30 to 60 minutes after study drug dosing.

Following completion of study drug dosing on Day 14 or early discontinuation, the subject will be transitioned to local standard of care for 14 days. Note, the local standard of care does not include study drug but can include other acid suppressant agents.

5.3 Identity of Investigational Product

Vonoprazan study medication will be supplied as 10 mg and 20 mg tablets. [redacted] manufactures the vonoprazan fumarate drug substance. [redacted] manufactures the vonoprazan tablets.

Vonoprazan tablets contain vonoprazan free base (MW 345.39) and the following inactive excipients: D-Mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, ascorbic acid, croscarmellose sodium, magnesium stearate, hypromellose, polyethylene glycol 8000, titanium dioxide, and red or yellow ferric oxide.

Study drug will be packaged for shipment to the investigational site.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Vonoprazan tablets will be packaged and shipped by [redacted].

Study supplies must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature (20°C to 25°C [68°F to 77°F]; excursions are allowed between 15°C and 30°C [59°F to 86°F]) until they are used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed.

Sites should refer to the pharmacy manual for detailed information regarding packaging and labeling and for reporting temperature excursions.

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected

dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

Sites should refer to the pharmacy manual and follow the accountability process described for this clinical study.

5.5 Overdose Management

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

Cases of overdose without manifested signs or symptoms are not considered AEs. Adverse events associated with an overdose will be documented on the AE eCRF(s) according to Section 6.3.1.3.1. The SAEs associated with overdose should be reported according to the procedure outlined in Section 6.3.1.3.2.

5.5.1 Treatment of Overdose

Vonoprazan is not removed from circulation by hemodialysis. In the event of drug overdose, the subject should be treated symptomatically.

5.6 Blinding

This is an open-label study.

5.7 Study Compliance

5.7.1 Treatment Compliance

Compliance with study drug is to be assessed as specified in the SoE (Section 13.1). Compliance with study drug dosing will be assessed by clinic staff reviewing the Study Drug Reminder Card returned at each visit, direct questioning and counting any returned tablets, which will be documented in the source documents and eCRF.

The date and time of each dose taken (in clinic or at home) must be recorded on the Study Drug Reminder Card, source documents and eCRF. If a subject misses any dose for any

reason, the sponsor must be notified immediately, and the date of the missed dose(s) and reason must be recorded in the eCRF.

If a subject misses a scheduled visit or exhibits poor compliance, as assessed by tablet counts, the sponsor should be notified immediately to determine appropriate mitigation. Actions may include subjects provided with specific dosing instructions to continue study drug or discontinuation from the study. The LARs and subjects should be counseled at each visit on the importance of good compliance regarding the dosing regimen and scheduled study visits.

5.8 Prior and Concomitant Therapy

Any medication including H_2RAs and PPIs or vaccines (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of screening (or has received within 30 days before the time of screening) or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The LARs and subjects are to be instructed that the subject should not take any medications, including over-the-counter medications, without first consulting the investigator or subinvestigators. However, single-use medications for endoscopic examination and topical medications, including liniments, ophthalmic drops, nasal drops, ear drops, inhaled drugs, adhesive skin patches, and gargle (mouthwash) will be allowed, whether or not they are excluded or restricted.

The medical monitor should be contacted if there are any questions regarding prior or concomitant therapy.

5.8.1 Excluded Medications

A list of excluded medications is provided in Table 5-1.

Table 5-1 Excluded Medications and Treatments

Excluded Medications and Treatments	Beginning of Exclusion	End of Exclusion
Other investigational drugs or drugs administered due to participation in another clinical trial	30 days prior to start of Screening Period	Follow-up phone call
Antacids and sucralfate	Day -1 (day before first dose of study drug)	Day 14 (end of study drug dosing)
H_2RAs	7 days prior to Day 1	Day 14 (end of study drug dosing)
PPIs	7 days prior to Day 1	Day 14 (end of study drug dosing)
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	14 days prior to Day 1	Day 14 (end of study drug dosing)
CYP3A4 substrates with a narrow therapeutic index	14 days prior to Day 1	Day 14 (end of study drug dosing)
CYP2C19 substrates clopidogrel, citalopram, cilostazol	14 days prior to Day 1	Day 14 (end of study drug dosing)
Other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth	30 days prior to Day 1	Follow-up phone call
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	Follow-up phone call

CYP: cytochrome P450 isoenzyme; H_2RA: histamine-2 receptor antagonist; PPI: proton pump inhibitor

6 Study Assessments and Procedures

Prior to undergoing any protocol-specific procedures or assessments, all LARs of potential subjects must sign and date the ICF. Participating subjects will provide assent as applicable. Subjects and LARs will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject and LAR. The investigator or designee will also sign and date the ICF.

Study procedures and their timing are summarized in the SoE (Section 13.1). Adherence to the study design requirements, including those specified in the SoE, is essential and required for study conduct. All safety concerns should be discussed with the principal investigator and medical monitor immediately to determine if any active intervention is needed, including action taken with study drug. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1 Pharmacokinetic and Pharmacodynamic Assessments

6.1.1 Pharmacokinetic Assessments

Parents/LARs will ensure that the subject arrives at the clinic in the morning on Days 7 and 14 for pharmacokinetic sampling. Subjects should not eat or take the vonoprazan study drug before arriving at the clinic. The Day 7 and 14 dose of study drug will be given in the clinic.

Blood samples for pharmacokinetic analysis of vonoprazan in plasma will be collected on Days 7 and 14. On Day 7, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 0.5 to 1.5 hours post-dose and one between 2.5 to 3.5 hours post-dose. On Day 14, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 1 to 2 hours post-dose and one between 3 to 4 hours post-dose. The exact date and time of each pharmacokinetic sample must be recorded in subject source document and eCRF.

If a subject terminates early, an attempt should be made to collect one blood sample if it can be collected within 24 hours following the last dose of study drug. The exact date and time of the early termination sample must be recorded.

Blood samples will be collected into sodium heparin vacutainer collection tubes and processed into plasma. Details of collection, processing, storage and shipping will be contained in the Clinical Laboratory Manual.

Bioanalytical Methods

Plasma concentrations of vonoprazan will be measured at Labcorp Early Development Laboratories Inc. (Madison, WI) using a validated liquid chromatrography/mass spectrometry method with an analytical range of 0.5 to 100 ng/mL and will be used for the calculation of the plasma vonoprazan pharmacokinetic parameters.

Depending on pace of enrollment, pharmacokinetic samples from a subset or subsets of subjects may be analyzed prior to the completion of enrollment. In any case, all of the pharmacokinetic samples collected from a given subject will be analyzed in the same bioanalytical batch.

Pharmacokinetic Parameters

Plasma pharmacokinetic parameters shown in Table 6-1 will be estimated using a non-linear mixed effects model and will be determined from the concentration-time data for all evaluable subjects. The primary vonoprazan pharmacokinetic endpoints will include the following steady state parameters: $C_{max,ss}$, AUC_{τ}, CL/F and V_z/F. Actual sampling times, rather than scheduled or nominal sampling times, will be used in all computations using sampling time. Additional pharmacokinetic parameters may be estimated as appropriate.

Table 6-1 Pharmacokinetic Parameters to be Estimated using Vonoprazan Plasma Concentration Data

Parameter	Definition
$C_{max,ss}$	Maximum observed plasma concentration at steady state
$C_{max,ss}$/Dose	Dose-normalized $C_{max,ss}$ ($C_{max,ss}$ divided by the administered dose in mg)
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve during the dosing interval τ, where τ is the length of the dosing interval in hours, calculated using the linear trapezoidal rule
$AUC_{\tau,ss}$/Dose	Dose-normalized $AUC_{\tau,ss}$ ($AUC_{\tau,ss}$ divided by the administered dose in mg)
λ_z	Terminal elimination rate constant, calculated as the negative slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase
CL/F	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/ $AUC_{\tau,ss}$
V_z/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (CL/F)/ λ_z

6.1.2 Pharmacodynamic Assessments

Select sites may participate in a sub-study collecting gastric pH when deemed clinically necessary by the principal investigator. In the pharmacodynamic sub-study, gastric pH will be measured and recorded continuously for a 24-hour period on Day -1 and Day 7 as outlined in the SoE **(**Section 13.1**)** using a suitable pH probe and ambulatory pH recording system**.** All instruments will be calibrated prior to and following use. Gastric pH will be sampled and recorded every 5 seconds. The 24-hour continuous pH recording session for Day -1 will commence 24-hours prior to the first dose of study drug. The 24-hour continuous pH recording session for Day 7 will commence 30 to 60 minutes prior to the next dose of study drug. The reason for pH assessments, start time, stop time and any interruptions will be recorded in the source document and the eCRF. To minimize the discomfort of probe insertion, administration of a topical anesthetic (lidocaine) will be permitted per the institutional process. Details of collection, processing, storage and shipping will be contained in the Gastric pH Monitoring Plan.

6.2 Efficacy Assessments

6.2.1 GERD Symptom Assessment-Investigator

The GERD Symptom Assessment-Investigator scale evaluates 4 symptoms of GERD: heartburn, vomiting, acid regurgitation, and trouble eating. The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit, Day 7 and Day 14 will be assessed. The severity for each symptom will be recorded as either none, mild, moderate, severe or very severe. At screening, the subject will be eligible for inclusion in the study if the subject has at least one moderate GERD symptom. Symptom and severity definitions are presented in Section 13.4.1.

6.3 Safety Assessments

6.3.1 Pretreatment Events and Adverse Events

6.3.1.1 Definitions

6.3.1.1.1 Definitions of Pretreatment Adverse Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject whose informed consent to participate in a study has been signed, which has occurred prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

6.3.1.1.2 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its causal relationship to study drug. An AE can therefore be an unfavorable sign or symptom, or a disease temporally associated with the use of study drug.

A treatment-emergent adverse event (TEAE) is defined as any event that occurs after the first dose of study drug or any event at baseline that worsens in either intensity or frequency after the first dose of study drug.

6.3.1.1.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence at any dose for which the following occurs:

1. Results in DEATH.
2. Is LIFE-THREATENING. The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above
    - May include any event or symptoms described in the medically significant AE list (Table 6-2)
    - Exposes the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization

Table 6-2 Medically Significant Adverse Event List

Term
Acute respiratory failure / acute respiratory distress syndrome
Torsade de pointes / ventricular fibrillation / ventricular tachycardia
Malignant hypertension
Convulsive seizure
Agranulocytosis
Aplastic anemia
Toxic epidermal necrolysis/Stevens-Johnson syndrome
Hepatic necrosis
Acute liver failure
Anaphylactic shock
Acute renal failure
Pulmonary hypertension
Pulmonary fibrosis
Confirmed or suspected endotoxin shock
Confirmed or suspected transmission of infectious agent by a medicinal product
Neuroleptic malignant syndrome / malignant hyperthermia
Spontaneous abortion / stillbirth and fetal death

The PTEs that fulfill one or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Section 6.3.1.3.2 and Section 6.3.1.3.3).

If a subject is noted to ALT or AST value >3 × the ULN and a total bilirubin value >2 × ULN, for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 6.3.1.3.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history or concurrent medical conditions. Follow-up laboratory tests, as described in Section 6.3.3, must also be performed. In addition, if the LFT increases are SAEs, a Liver Function Test Increase Form must be completed and transmitted (see Section 13.2).

6.3.1.1.4 Adverse Events of Special Interest

An AE of special interest is a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or nonserious (eg, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

Adverse events of special interest include any event listed in Table 6-3.

Table 6-3 Adverse Events of Special Interest List

Term
Hepatotoxicity
Severe cutaneous adverse reactions, including hypersensitivity
Clostridium difficile infections and pseudomembranous colitis
Hypersensitivity reactions (anaphylaxis)
Acute interstitial nephritis/tubulointerstitial nephritis
Bone fracture
Hematologic abnormalities

For additional details on liver function monitoring, see Section 13.2.

6.3.1.1.5 Additional Points to Consider for PTEs and AEs

An untoward finding generally may involve the following:

- Indicates a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitates therapeutic intervention.
- Requires an invasive diagnostic procedure.
- Requires discontinuation or a change in dose of study drug or a concomitant medication.
- Is considered unfavorable by the investigator for any reason.

- Is caused by a study procedure (eg, a bruise after blood collection); these events should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

- Each event is required to be recorded to represent a single diagnosis or disorder using standard medical terminology rather than individual symptoms. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (eg, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of a pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Abnormal findings identified at baseline evaluations and screening assessments (eg, laboratory tests, ECG, endoscopy, or X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug).

Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").

- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study drug, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

- At each required study visit, all AEs that have occurred since the previous visit or AEs that have changed in severity since the previous visit must be recorded in the AE record of the eCRF.

Changes in severity of AEs/serious PTEs:

- If the subject experiences a change in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned procedures:

- Preplanned procedures that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned procedure should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

6.3.1.2 Documenting Adverse Events

6.3.1.2.1 Assessment of Severity

The severity or intensity of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.3.1.2.2 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of study drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the study drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

6.3.1.2.3 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as not related.

6.3.1.2.4 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or physician.

6.3.1.2.5 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae, or the subject died.

6.3.1.2.6 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are considered intermittent. All other events are considered continuous.

6.3.1.2.7 Action Concerning Study Drug

- Drug withdrawn: A study drug is stopped due to the particular AE.
- Dose not changed: The particular AE did not require stopping a study drug.
- Unknown: Only to be used if it has not been possible to determine what action has been taken.
- Not applicable: A study drug was stopped for a reason other than the particular AE, eg, the study has been terminated, the subject died, or dosing with the study drug was already stopped before the onset of the AE.
- Dose interrupted: The dose was interrupted/held due to the particular AE.

6.3.1.2.8 Outcome

- Recovered/resolved: Subject returned to baseline status with respect to the AE/PTE.
- Recovering/resolving: The intensity is lowered by one or more stages: the diagnosis or signs/symptoms have lessened/improved; the abnormal laboratory value improved but has not returned to the normal range or to baseline; or the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving."
- Not recovered/not resolved: There is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period has worsened from when it started; is an irreversible congenital anomaly; or the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved."
- Resolved with sequelae: Subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: The AEs/PTEs are considered the cause of death.
- Unknown: The course of the AE/PTE cannot be followed up due to a hospital change or residence change at the end of the subject's participation in the study.

6.3.1.3 Time Period and Frequency for Collecting AE and SAE Information

6.3.1.3.1 Collection and Reporting of Adverse Events

Collection of PTEs will commence from the time the informed consent to participate in the study has been signed and will continue until the subject is first administered study drug or until screen failure. For subjects who discontinue the study prior to study drug administration, PTEs are collected until the subject discontinues study participation. Collection of AEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection will continue until the follow-up visit or withdrawal from the study.

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not be followed up for the purposes of the protocol. All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed.

All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term
- Start and stop date
- Severity
- Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs)
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
- Action concerning study drug (not applicable for PTEs)
- Outcome of event
- Seriousness

6.3.1.3.2 Collection and Reporting of Serious Adverse Events

When an SAE occurs through the AE collection period, it should be reported according to the following procedure:

An SAE eCRF must be completed and submitted via Medidata Rave immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

If the Medidata Rave system is not functioning for any reason, a paper SAE case report form must be completed (in English), signed by the investigator, and faxed to the contact listed below.

The SAE form should be transmitted within 24 hours to [redacted] Pharmacovigilance.

[redacted] 24-Hour Safety Contact Information

SAE Hotline: [redacted]

SAE Fax: [redacted] or [redacted]

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Investigators are not obligated to actively seek information regarding new AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor. Reporting of serious PTEs will follow the procedure described for SAEs.

6.3.1.3.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should update the SAE eCRF and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be provided, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

6.3.1.3.4 Safety Reporting to Investigators, IRB/IECs, and Regulatory Authorities

The sponsor designee (contract research organization) will be delegated the responsibility for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and the IRB/IEC, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities (eg, EudraVigilance Database, FDA Adverse Event Reporting System) as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required. The sponsor designee will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products.

6.3.1.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor/sponsor designee of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study drug under clinical investigation are met.

The sponsor/sponsor designee has a legal responsibility to notify regulatory agencies about the safety of a study drug under clinical investigation. The sponsor/sponsor designee will comply with regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSARs according to regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate, according to local requirements.

If there is an increase in unexpected SAEs or if there is a change in the frequency and character of expected SAEs based on the known safety profile of vonoprazan, further evaluation will be conducted to characterize these events and any impact on benefit/risk. Health authorities will be consulted to agree upon the appropriate action to be taken regarding the conduct of the study, including no change to the protocol, revision of the safety monitoring plan, suspension of enrollment, or discontinuation of the study.

6.3.2 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug (vonoprazan active) should be immediately discontinued. If the pregnancy occurs during administration of active study drug, eg, after Visit 2 or within 2 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 6.3.1.3.2. If the subject (and LAR, if legally applicable) agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of the treatment the subject received. All pregnancies will be reported using the pregnancy form and will be followed up to final outcome. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

6.3.3 Laboratory Analyses

See Table 6-4 for the list of clinical laboratory tests to be performed and the SoE (Section 13.1) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Abnormal laboratory findings that are expected with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

- All laboratory tests with abnormal values considered clinically significant during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

    - All protocol-required laboratory assessments, as defined in Table 6-4, must be conducted in accordance with the laboratory manual and the SoE.

        - If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the unscheduled laboratory eCRF.

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be provided in the laboratory manual.

All study-required laboratory assessments will be performed by a central laboratory.

Table 6-4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices: MCV, MCH • Percent reticulocytes • WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils	
Clinical chemistry [a]	• Blood urea nitrogen • Creatinine • Total and direct bilirubin • ALT/SGPT • AST/SGOT • Alkaline phosphatase	• Total protein • Potassium • Sodium • Calcium • Glucose [b] • GGT
Routine urinalysis [c]	• Specific gravity, appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)	
Other screening tests	• Serology (HIV antibody, HBsAg, HCV antibody, HCV viral load RNA [qualitative]), hCG pregnancy test [d]	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; hCG: human chorionic gonadotropin; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; RBC: red blood cell; RNA: ribonucleic acid; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; WBC: white blood cell

a See Section 13.3 for the appropriate guidance on reporting of abnormal liver function tests. For liver function test monitoring, see Section 13.3.1. For temporary and permanent discontinuation of study drugs due to abnormal liver function tests, see Section 13.3.2 and Section 13.3.3, respectively.

b Glucose will be obtained at Visit 1 and at any unscheduled visit.

c At the discretion of the investigator.

d Only female subjects who have experienced menarche will have urine hCG; if the urine hCG test is positive confirm with serum hCG.

Investigators must document their review of each laboratory safety report.

6.3.4 Physical Examinations

Refer to the SoE (Section 13.1) for the timing and frequency for full and brief physical examinations, as well as height and body weight.

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, neurological systems and Tanner staging (Section 13.5). Height and body weight will also be measured and recorded. The subject should be dressed in light clothing and without shoes when the body weight is being measured.

A brief physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, and gastrointestinal systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.3.5 Vital Signs

Refer to the SoE (Section 13.1) for the timing and frequency of vital sign assessments.

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.

6.3.6 Electrocardiograms

Refer to the SoE (Section 13.1) for the timing and frequency of ECG assessments.

A single, standard 12-lead ECG recording will be made after the subject has been in the supine position for at least 5 minutes. ECGs will be read and interpreted centrally by a pediatric cardiologist for eligibility during Screening and on Day 14. A single repeat measurement is permitted during screening period for eligibility determination. Assessments will include whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant).

6.4 Safety Monitoring Committee

Based on the well-characterized safety profile in adults, a Safety Monitoring Committee is not planned for this study. The sponsor and investigators will review safety and tolerability data throughout the study.

7 Statistical and Analytical Plan

This section describes the statistical and analytical methods to be used for the study.

7.1 Sample Size Calculations

Approximately 18 subjects are expected to be enrolled with 9 subjects in each dose group. Attempts will be made to enroll subjects across the ≥ 6 to < 12 years age range. Because this is a pharmacokinetic and safety trial with no comparator, there is no power determination affecting the sample size. The sample size of approximately 18 subjects is considered sufficient to assess the pharmacokinetics, safety, and tolerability of vonoprazan in this population. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the PK profile.

7.2 Analysis Sets

The pharmacokinetic population will include subjects who receive at least 1 dose of study drug and have sufficient concentration data to support accurate estimation of at least 1 pharmacokinetic parameter.

The pharmacodynamic population will include subjects who receive at least 1 dose of study drug and have sufficient pH data to support calculation of pharmacodynamic parameters.

The safety population will include all subjects who receive at least 1 dose of study drug.

7.3 Statistical Analysis Methodology

7.3.1 Pharmacokinetic Analyses

The individual pharmacokinetic parameter estimates in Table 6-1 will be summarized descriptively by vonoprazan dose.

The following pharmacokinetic parameters will be considered the primary endpoints for the study: $C_{max,ss}$, AUC_{τ}, CL/F, V_z/F.

7.3.2 Pharmacodynamic Analyses

Mean pH and the percentage of time above pH 4, 5, and 6 at baseline (Day -1) and Day 7 will be summarized for the subset of subjects for whom intragastric pH monitoring is available.

7.3.3 Efficacy Analyses

The severity of GERD symptoms at baseline and Days 7 and 14, as assessed by the investigator, will be summarized overall and by vonoprazan dose.

7.3.4 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized by treatment and overall.

Actual values and changes from baseline for clinical laboratory test results and vital sign measurements will be summarized at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results.

7.3.5 Interim Analyses

No formal interim analyses will be performed in this study.

However, a popPK analysis of interim data from a subset of subjects may be conducted prior to completion of enrollment to assess whether plasma exposure in pediatric subjects aged ≥ 6 to < 12 years is within the range observed in adults receiving the same dose.

8 Data Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents and Regulation 536/2014 of the European Parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management [DHHS 2018]. The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and ECG strips.

Investigative site personnel will enter subject data into electronic data capture. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures to ensure the integrity of the data, eg, correcting errors and inconsistencies in the data. Adverse event terms will be coded using the MedDRA, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After the database lock, each study site will receive a file containing all of their site-specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a file of all of the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate file for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Institutional Review Board or Independent Ethics Committee

Federal regulations, national regulations, and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject and/or LAR must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline, E6: Good Clinical Practice (GCP), will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairperson or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

All potential serious breaches must be reported to the sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol which is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

9.3 Subject Information and Consent

A written informed consent in compliance with regulatory authority regulations shall be obtained from each subject’s LAR before entering the subject in the study or performing any unusual or nonroutine procedure that involves risk to the subject. Participating subjects will

provide assent as applicable. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent and assent materials should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent and assent materials will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF or assent form is revised during the course of the study, the LAR for each active participating subject and the active participating subject (if applicable) must sign the revised form as applicable.

Before recruitment and enrollment, each LAR and prospective subject (if applicable) will be given a full explanation of the study and be allowed to read the approved ICF and assent form (if applicable). Once the investigator is assured that the LAR and subject (if applicable) understand the implications of participating in the study, the LAR will be asked to give consent for the subject to participate in the study by signing the ICF. If applicable, the subject will be asked to give assent by signing the assent form.

The investigator shall retain the signed original form(s) and give a copy of the signed original form(s) to the LAR and subject (if applicable).

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

The Investigator will also be responsible for providing oversight of the conduct of the study or site, including oversight of all personnel involved in the study, and adherence to all applicable laws and regulations as set forth in the Clinical Trial Agreement.

Personnel involved in conducting this study will be qualified by education, training and experience prior to performing their respective tasks.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the sponsor, its designee, the United States Food and Drug Administration (FDA) or any regulatory authority(ies), or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 Code of Federal Regulations (CFR) 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor [redacted] is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor [redacted] is financially responsible for further treatment of the subject's disease.

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to the following:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 for United States sites and equivalent form for non-US sites
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572 equivalent form for non-US sites
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent and assent (if applicable), samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject and LAR
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6. The investigator will conduct all aspects of this study in accordance with all

national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 and all applicable guidelines and regulations.

10.6 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs to the sponsor and/or IRB/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

10.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it

will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

11.1 Monitoring

11.1.1 External Data Monitoring Committee

An external data monitoring committee will not be used for this study. This is a Phase 1 study with 14 days dosing and adverse events will be evaluated on an ongoing basis. Additionally, vonoprazan has a well characterized safety profile in adults.

11.1.2 Monitoring of the Study

The clinical monitor, acting as the main line of communication between the sponsor (or designee) and the investigator and as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and may lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the investigative site staff, the clinical monitor, and/or the contract research organization throughout the course of the study. Principal investigators will be notified in writing by the monitor of any deviations discovered during a monitoring visit. The IRB/IEC should be notified of all protocol deviations they consider reportable in a timely manner.

11.3 Study Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes follow-up visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

The sponsor will submit to clinical trial registries a summary of the results of the clinical trial and where applicable a summary that is understandable to a layperson, and the clinical study report health authorities, within 6 months after the end of the study. The investigator is encouraged to share the summary results with the LARs and study subjects, as appropriate.

12 Reference List

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13 Appendices

13.1 Appendix 1: Schedule of Events

	Screening Period		Treatment Period					Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day -1 [a]**	**Day 1**	**Phone Call Day 6**	**Day 7**	**Day 8 [a]**	**Phone Call Day 13**	**ET/ Day 14**	**Phone Call Day 28**	**Unscheduled Visit [b]**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Informed consent [c]	X									
Inclusion/exclusion criteria	X	X	X							
Demographic and medical history	X									
Physical examination [d]	X				X			X		X
Vital signs [e]	X		X		X			X		X
Weight and height [f]	X				X			X		
Prior/Concomitant medications	X	X	X		X	X		X	X	X
Concurrent medical conditions	X									
Hepatitis B and C; HIV [g]	X									
Clinical laboratory tests [h]	X				X			X		X
Pregnancy test [i]	X		X		X			X		
Guidance on avoidance of pregnancy [i]	X		X		X			X		
12-lead electrocardiogram [j]	X							X		
GERD Symptom Assessment-Investigator	X				X			X		
Randomization [k]			X							
Dispense study drug [l]			X		X					
Study drug administration (at clinic) [l]			X		X			X		
Gastric pH monitoring [a]		X	X		X	X				
PK blood sample collection **Day 7**: pre-dose, 0.5 to 1.5 hour and 2.5 to 3.5 hours post dose. **Day 14:** pre-dose, 1 to 2 hours and 3 to 4 hours post dose. [m]					X			X		
Drug return/accountability					X			X		
Telephone call to subject				X			X		X	
AE/pretreatment event assessment [n]	X	X	X		X			X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; HIV: human immunodeficiency virus, PK: pharmacokinetic; PTE: pretreatment event

a For subjects participating in the pharmacodynamic substudy, Visit 2 (Day -1) and Visit 6 (Day 8) are only required for subjects undergoing gastric pH monitoring if clinically indicated at select sites. pH monitoring will be conducted on Day -1 for 24 hours and on Day 7 for 24 hours. pH probes would be placed on Days -1 and 7 and removed on Days 1 and 8.

b At an unscheduled visit, the following procedures are to be completed with additional procedures at the investigator's discretion: a brief physical examination, vital sign measurements, concomitant medication assessment, AE assessment, and clinical laboratory tests. If the visit results in premature termination, then all procedures outlined for the final visit should be performed.

c Informed consent will be signed by the subject's legally authorized representative prior to any activity in the study. Subject assent (if applicable) may be obtained as required per site guidelines.

d A complete physical examination will be performed at screening (at minimum, assessment of skin, cardiovascular, respiratory, gastrointestinal, neurological systems and Tanner staging). A brief physical examination will be performed at other visits (at minimum, assessment of skin, cardiovascular, respiratory, and gastrointestinal systems). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

e Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.

f Height collected only at screening.

g Hepatitis B surface antigen, hepatitis C virus antibody, and HIV type 1 and 2 antibodies.

h Clinical laboratory testing will include hematology, serum chemistry, and urinalysis (if deemed necessary by the PI). Blood draws should follow vital signs or electrocardiograms.

i Only female-born subjects who have reached menarche, will require guidance on avoidance of pregnancy and urine or serum hCG; if urine hCG is positive, confirm with serum hCG.

j Single 12-lead electrocardiogram recordings will be made after the subject has been in the supine position for at least 5 minutes at screening. A pediatric cardiologist will interpret the ECG for eligibility and any abnormality. A single repeat measurement is permitted at screening for eligibility determination after the read by a pediatric cardiologist. Assessments should include comments on whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant). An ECG will be collected at the final visit and interpreted by a pediatric cardiologist.

k Subject will be randomized to study treatment after all eligibility criteria have been met.

l Study drug will be administered in the clinic on Days 1, 7, and 14. Study drug should be taken every day between 7 and 10 am preferably prior to eating any breakfast or food. Study drug for at home administration will be dispensed on Day 1 (to be taken on Days 2 to 6) and Day 7 (to be taken on Days 8 to 13). At home, parents/caregivers will administer study drug to subjects. Clinic staff will review instructions with parents/LARs for administering study drug at home and completing the Study Drug Reminder Card. Phone call reminders may be conducted as required.

m Blood samples for PK analysis of vonoprazan in plasma will be collected on Days 7 and 14. On Day 7 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 0.5 to 1.5 hours post-dose and one between 2.5 to 3.5 hours post-dose. On Day 14 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 1 to 2 hours post-dose and one between 3 to 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded in the source and eCRF.
If a subject terminates early, an attempt should be made to collect one blood sample if it can be collected within 24 hours following the last dose of study drug. The exact date and time of the early termination sample must be recorded.

n Collection of pretreatment events will start after the informed consent form has been signed. Adverse events will be assessed from time of informed consent signing until the follow-up visit and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

13.2 Appendix 2: Contraceptive Guidance

Contraception Guidance:

From signing of informed consent, throughout the duration of the study, and for 2 weeks after the last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

> *Females NOT of childbearing potential are defined as those who are premenarchal, have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with a follicle-stimulating hormone level >40 International units per liter or at least 5 years since last regular menses, confirmed before any study drug is implemented).
>
> **Sterilized males should be at least 1-year post vasectomy and should have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

Note: If the childbearing potential of a subject changes after start of the study (eg, a premenarchal female subject experiences menarche) or the risk of pregnancy changes (eg, a female subject who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if the female subject must begin a highly effective method of contraception or a male participant must use a condom.

Birth Control: Birth control methods considered acceptable for this study include:

Barrier methods (each time that you have intercourse):

- Male condom PLUS spermicide
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide

Intrauterine Devices

- Copper T PLUS condom or spermicide
- Progesterone T PLUS condom or spermicide

Hormonal Contraceptives

- Implants
- Hormone shot/injection
- Combined pill
- Minipill
- Patch
- Vaginal ring PLUS male condom and spermicide

During the course of the study, serum human chorionic gonadotropin (hCG) will be performed at screening and regular urine hCG pregnancy tests will be performed only for women of childbearing potential. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Section 13.1). Female subjects must have a negative urine hCG pregnancy test on Day -1 prior to study drug dispensation.

13.3 Appendix 3: Liver Function Tests

13.3.1 Liver Function Test Monitoring

Liver function will be carefully monitored throughout the study. Additional monitoring may be necessary and is recommended for subjects with abnormal LFTs.

If subjects with normal baseline ALT or AST levels experience ALT or AST >3 × ULN and a 2-fold increase above baseline, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase (GGT), and international normalized ratio [INR]) should be repeated within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

If subjects with normal baseline ALT or AST levels experience ALT or AST >8 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be repeated within a maximum of 48 hours after the abnormality was found.

13.3.2 Considerations for Temporary Discontinuation of Study Drug

If the ALT or AST levels remain elevated >3 × ULN in subjects with normal baseline ALT or AST levels and a 2-fold increase above baseline **OR** if the ALT or AST levels remain elevated >5 × ULN in subjects with elevated baseline ALT or AST levels on 2 consecutive occasions, the investigator must contact the medical monitor to discuss additional testing, recommended monitoring, possible temporary discontinuation of study drug, and possible alternative etiologies.

13.3.3 Permanent Discontinuation of Study Drug

If any of the circumstances occur as mentioned in Table 13-1 at any time during treatment, the study drug should be permanently discontinued:

Table 13-1 Abnormal Liver Function Criteria for Permanent Discontinuation of Study Drug

Subject Baseline Aminotransferases	Criteria for Discontinuation of Study Drug
Normal ALT or AST at baseline (all subjects)	• ALT or AST >8 × ULN • ALT or AST >5 × ULN and persists for more than 2 weeks • ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value in conjunction with elevated total bilirubin >2 × ULN **or** INR >1.5 • ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; ULN: upper limit of normal

In each of these instances, appropriate clinical follow-up should be instituted (including repeat laboratory tests) until a satisfactory conclusion (ie, until the AE resolves, the laboratory value returns to baseline, or the condition becomes stable).

If a subject meets the liver safety criteria and must be discontinued from study drug, the subject will continue to be followed per the protocol schedule until the study is completed. If the subject refuses to return for the study visits, telephone visits may be conducted; however, this is not preferred or recommended. The reason for discontinuation of study drug should be listed as an LFT abnormality.

If any of the above circumstances occur at any time during the study, the abnormality should be documented as an SAE, and a Liver Function Test Increase Form completed and sent to:

Pharmacovigilance
[redacted]

24-Hour Safety Contact Information
SAE Hotline: [redacted]
SAE Fax: [redacted] or [redacted]

13.3.4 Re-initiation of Study Drug

If the study drug is discontinued due to any of the scenarios provided above, study drug must not be re-initiated without consultation with the medical monitor.

13.4 Appendix 4: Questionnaires

13.4.1 GERD Symptom Assessment-Investigator

The following 4 symptoms of GERD will be evaluated, as defined below when asked of children 9 to 12 years of age.

Symptom	Definition
Heartburn	Hurting or burning in the stomach, chest or throat
Vomiting	Something coming out of your mouth (throw-up)
Acid regurgitation	Food come up from your stomach to your mouth
Trouble eating	Ate less than usual, did not want to eat, did not want to eat certain foods because of hurting or burning

The following 4 symptoms of GERD will be evaluated, as defined below when asked of parents of children 6 to 8 years of age if the child reported or they observed any of the following behaviors.

Symptom	Definition
Heartburn	Hurting or burning in the stomach, chest or throat such as holding his/her stomach/chest/throat, lying in curled up position, crying, acting fussy, or other behaviors
Vomiting	Something coming out of the mouth
Acid regurgitation	Partially digested food or stomach contents coming up in their mouth
Trouble eating	Refused to eat anything, ate less than usual, refused to eat certain foods because of hurting or burning or stomach contents coming up in their mouth

The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit will be assessed, as detailed below.

Severity	**Definition**
None	No symptom
Mild	Symptom did not last long and was easily tolerated
Moderate	Symptom caused discomfort and/or interrupted usual activities (including sleep)
Severe	Symptom caused great interference with usual activities and may have been incapacitating (including sleep)
Very severe	Symptom caused intense and constant discomfort and/or marked interference with usual activities (including sleep)

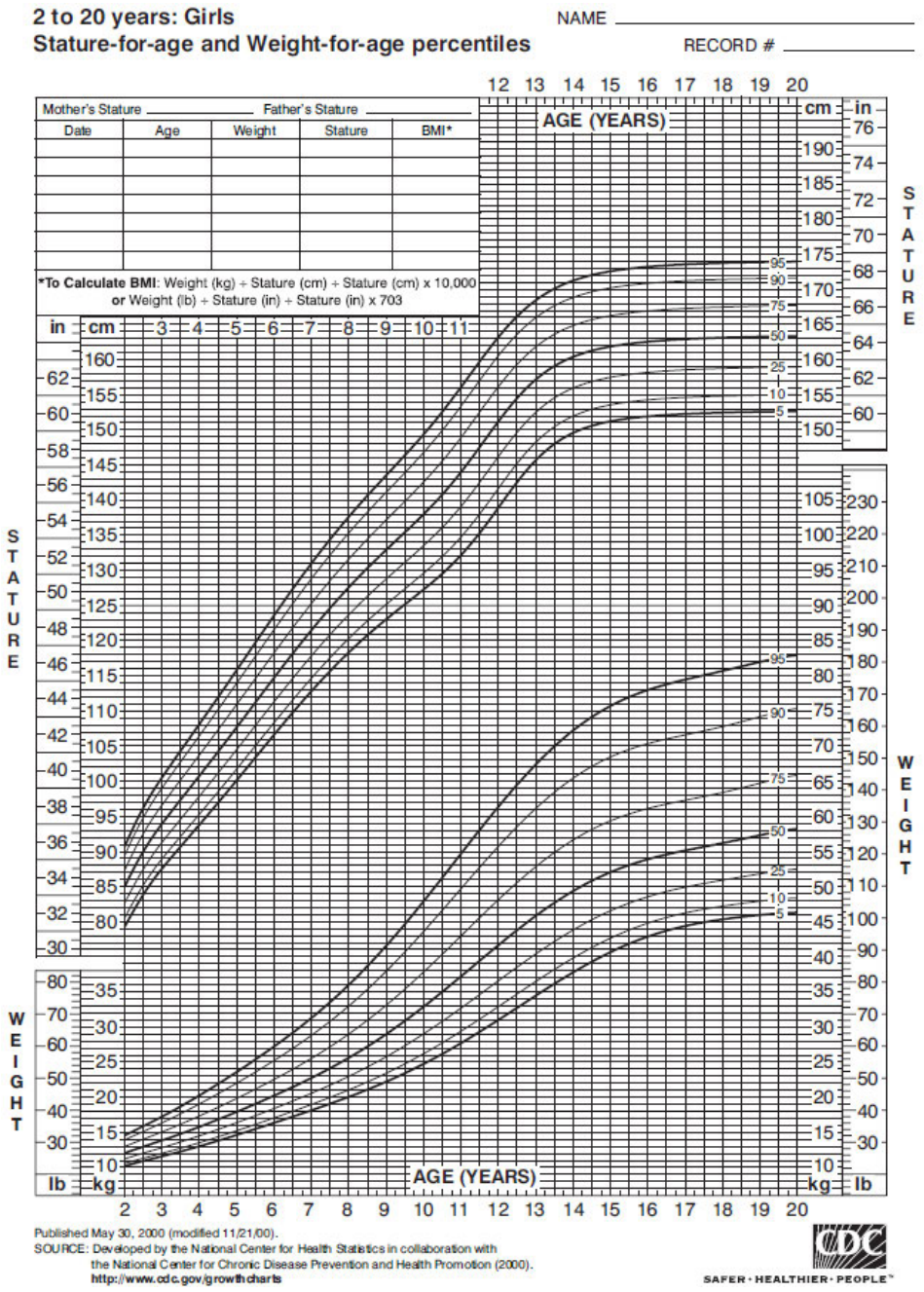
13.5 Appendix 5: Tanner Staging

Tanner Staging will be reported based on the following criteria:

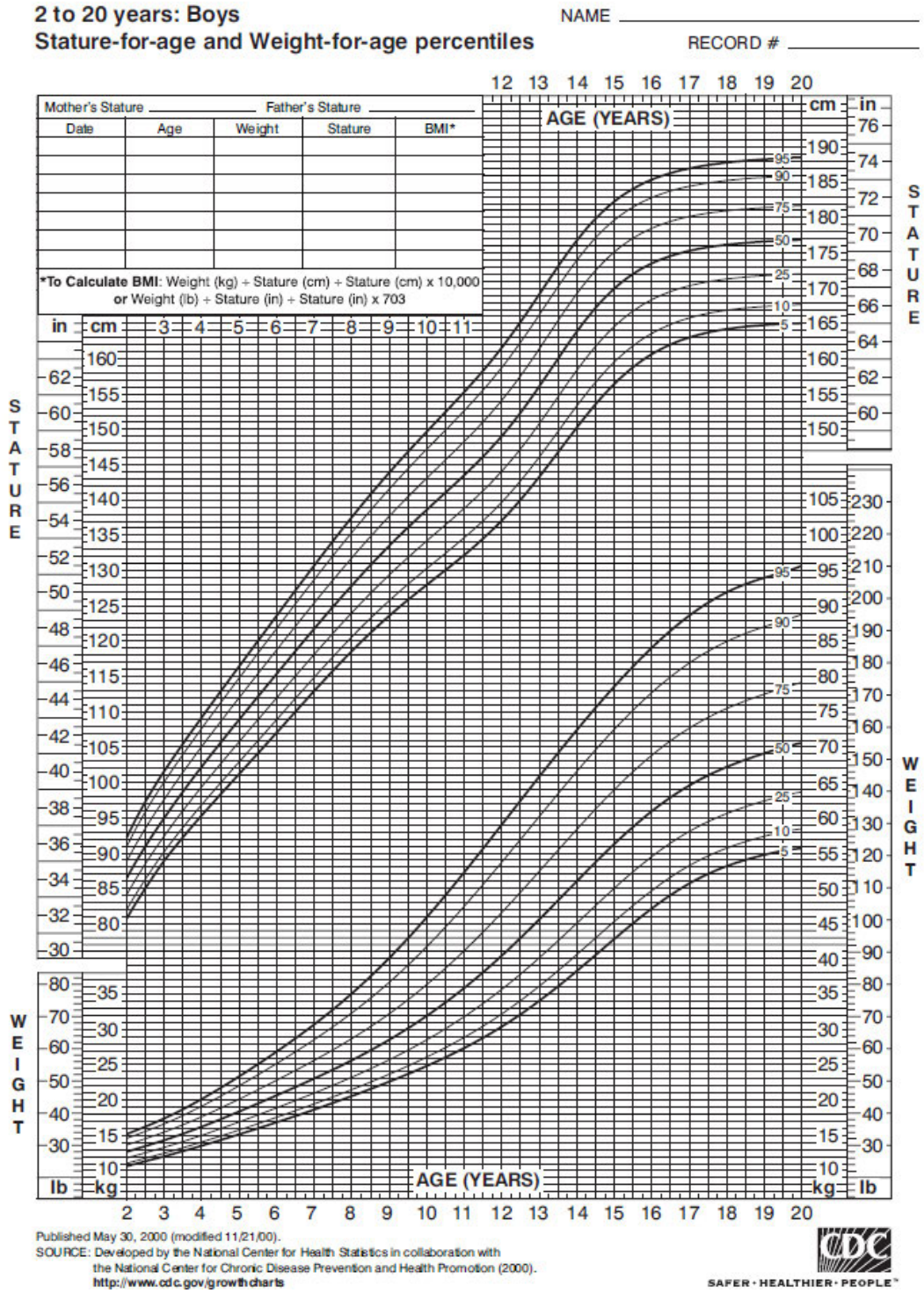
Boys – Development of external genitalia
Stage 1: Prepubertal
Stage 2: Enlargement of testes and scrotum; scrotal skin reddens and changes in texture
Stage 3: Enlargement of penis (length at first); further growth of testes
Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker
Stage 5: Adult genitalia
Girls – Breast development
Stage 1: Prepubertal
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
Stage 3: Further enlargement of breast and areola; no separation of their contour
Stage 4: Areola and papilla form a secondary mound above level of breast
Stage 5: Mature stage: Projection of papilla only, related to recession of areola
Boys and girls – Pubic hair
Stage 1: Prepubertal (the pubic area may have vellus hair, similar to that of forearms)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3: Darker, coarser, and more curled hair, spreading sparsely over junction of pubes
Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5: Adult in type and quantity, with horizontal upper border

13.6 Appendix 6: National Center for Health Statistics Clinical Body Weight Charts with 5th and 95th Percentiles

13.6.1 Girls



13.6.2 Boys


2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
SAFER · HEALTHIER · PEOPLE™

13.7 Appendix 7: Protocol Amendments

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the study protocol are shown in red and deletions are shown in strike-through text. Corrections of obvious typing errors or omissions are not highlighted.

Globally "with body weight ≥ 30 kg" was removed and is not highlighted below unless other information changed within the section.

13.7.1 Protocol Amendment 1

Synopsis (EU Trial Number)

2022-003228-42

Synopsis (Study Sites)

Approximately 20 to 25 sites in the United States and Europe

Synopsis (Study Design and Interventions)

This is a Phase 1, uncontrolled, randomized, open-label, parallel-group, multiple-dose study in children ≥ 6 to < 12 years of age ~~with a body weight ≥ 30 kg~~ who have symptomatic GERD. Subjects will be screened for up to 28 days. Successfully screened subjects will be randomized to receive 10 or 20 mg of vonoprazan QD for 14 days. Approximately ~~A total of~~ 18 subjects are expected to be enrolled in the study.

Blood samples for pharmacokinetic testing will be collected on Days 7 and 14. Select sites will perform gastric pH monitoring in subjects deemed clinically indicated by the principal investigator.

Subjects undergoing gastric pH monitoring will be confined to the clinic for testing. Gastric pH will be monitored for 24 hours beginning on Day -1 and on Day 7.

The study will include 3 periods:

Screening Period (≤ 4 weeks): Subjects will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will be randomized and enter the Treatment Period.

Treatment Period (Day 1 to Day 14): Subjects will be randomized to receive vonoprazan 10 mg or vonoprazan 20 mg QD.

Follow-up Period: A safety follow-up phone call will occur 2 weeks after the last dose of study drug to assess adverse events (AEs).

A subject will be considered to have completed the study if the subject completes the Treatment Period and the safety follow-up phone call.

Following the last dose of study drug or early discontinuation, the subject will be transitioned to local standard of care in accordance with each site's prespecified process.

Synopsis (Pharmacokinetic Assessments (Primary Endpoints))

The primary vonoprazan pharmacokinetic endpoints will include the following steady state parameters from data collected on Day 7 and Day 14:

- Maximum observed drug concentration at steady state ($C_{max,ss}$)
- Area under the plasma concentration-time curve during the dosing interval τ (AUC_{τ})
- Apparent oral clearance (CL/F)
- Apparent volume of distribution (V_z/F)

Synopsis (Study Drug, Dosage, and Route of Administration)

Open-label study drug (vonoprazan 10 mg or vonoprazan 20 mg) to be taken orally QD for 14 days (Day 1 through Day 14). All study drug doses are to be taken ~~on an empty stomach~~ preferably prior to eating any breakfast or food with approximately 240 mL (8 oz) water between 7 and 10 am each day.

Synopsis (Ethical Considerations)

Clinical studies in adults with GERD have shown a positive benefit-risk for vonoprazan. This study is anticipated to provide benefits to children ≥ 6 to < 12 years of age with symptomatic GERD and risks similar to those observed with vonoprazan in adults. This study is needed to identify doses to be used in future trials in children ≥ 6 to < 12 years of age.

The study was designed to minimize the number of blood samples and visits to investigate the pharmacokinetics and safety in this population.

Synopsis (Sample Size)

Approximately 18 subjects will be enrolled with 9 subjects in each dose group. Attempts will be made to enroll subjects across the ≥ 6 to < 12 years age range. Because this is a pharmacokinetic and safety trial with no comparator, there is no power determination affecting the sample size. The sample size of approximately 18 subjects is considered sufficient to assess the pharmacokinetics, safety, and tolerability of vonoprazan in this population. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the ~~PK~~ pharmacokinetic profile

Synopsis (Statistical Methods)

Pharmacokinetic Endpoints:

Individual pharmacokinetic parameter estimates will be summarized descriptively by vonoprazan dose.

Efficacy ~~and Pharmacodynamic~~ Endpoints~~:~~

The severity of GERD symptoms at screening and Days 7 and 14, as assessed by the investigator, will be summarized overall and by vonoprazan dose.

Pharmacodynamic Endpoints:

Mean pH and the percentage of time above pH 4, 5, and 6 at baseline (Day -1) and Day 7 will be summarized for the subset of subjects for whom intragastric pH monitoring is available.

Safety:

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing treatment-emergent AEs will be summarized by MedDRA system organ class and preferred term overall, by severity, and by relationship to study drug for each treatment group.

Clinical laboratory tests, electrocardiograms, and vital signs will be summarized with descriptive statistics at each time point by treatment group.

Introduction (Section 1.0)

Vonoprazan belongs to a new class of acid-inhibitory agents called potassium-competitive acid blockers (PCABs). In the United States, vonoprazan in combination with amoxicillin and in combination with amoxicillin and clarithromycin have been approved for the treatment of *Helicobacter pylori* infection in adults. Vonoprazan is being developed for the treatment of heartburn in patients with symptomatic non-erosive gastroesophageal reflux disease (sGERD), healing of all grades of erosive esophagitis (EE) and relief of heartburn and maintenance of healing of all grades of EE and relief of heartburn.

In countries other than the United States, vonoprazan has been studied in other gastric acid-related diseases such as healing of gastric and duodenal ulcers, and for the prevention of recurrence of gastric or duodenal ulcer during nonsteroidal anti-inflammatory drug or aspirin administration. Vonoprazan has received regulatory approval for adults in Japan, Russia, and other countries in Asia and Latin America for a variety of indications, including the healing of erosive esophagitis and maintenance of healing of erosive esophagitis. Vonoprazan is not currently approved for use in pediatric patients in any country.

Phathom Pharmaceuticals, Inc. licensed the exclusive rights from Takeda Pharmaceutical Company Limited (Takeda) to develop, manufacture, and commercialize vonoprazan in the United States, Europe, and Canada.

Study Rationale (Section 1.1)

The purpose of this study is to determine a dose of vonoprazan in children aged ≥ 6 to < 12 years ~~with body weight ≥ 30 kg~~ with symptomatic gastroesophageal reflux disease (GERD) that provides an exposure similar to the exposures in adults after administration of vonoprazan 10 or 20 mg once daily (QD). Like proton pump inhibitors, vonoprazan is expected to provide benefit in pediatric patients with GERD.

Vonoprazan (Section 1.2.2)

The gastric hydrogen, potassium–adenosine triphosphatase (H+, K+-ATPase), also known as the proton pump, is responsible for acid secretion from parietal cells in the stomach. It is inactive in the cytosol but relocates from the cytosol to the secretory membrane of the parietal cells when food is present in the stomach, thereby becoming active and pumping H+ ions out of the cells and into the canaliculi in exchange for K+ ions. It represents an attractive pharmacological target since it is the final step of the acid secretion process.

Two classes of pharmaceuticals, with distinct mechanisms of action for inhibiting the gastric proton pump, have been developed for clinical application: PPIs and PCABs. As a PCAB, vonoprazan has a unique mechanism of action and pharmacokinetics relative to PPIs:

- Acid activation and stability: Conventional PPIs are prodrugs, which are activated by acid and covalently bind to the H+, K+-ATPase; however, activated PPIs are not stable in acidic conditions. In contrast, vonoprazan does not require acid activation, is stable in acidic conditions, and has a more durable effect. Further, vonoprazan is rapidly protonated in the parietal cell canaliculi, which concentrates the drug proximal to the H+, K+-ATPase [Scarpignato 2019].

- Activity against proton pumps: Vonoprazan inhibits acid secretion by competitively inhibiting the binding of potassium ions to the H+, K+-ATPase. Vonoprazan may selectively concentrate in the parietal cells in both the resting and stimulated states and binds to the active pumps in a noncovalent and reversible manner. In contrast, PPIs covalently bind H+, K+-ATPase only when the pump is active, as an acidic environment is required for the activation and accumulation of PPIs in the parietal cell [Scott 2015].

- Vonoprazan maintains acid control over 24 hours with QD dosing [Engevik 2020]. Vonoprazan can also be dosed in the presence or absence of food, while most PPIs require dosing before a meal to optimize their acid suppressant effect because activated pumps are at their highest level post-prandially due to activation of pumps by the meal [Shin 2013].

- Extended half-life: The mean plasma half-life is typically 7 to 8 hours after single and multiple QD administration of vonoprazan 20 mg (TAK-438_107). This is significantly longer than the half-life of conventional PPIs (<2 hours) [Shin 2013].

- Metabolism: Vonoprazan is metabolized by a combination of cytochrome P450 (CYP) isoforms including CYP3A4/5, which does not have a high degree of genetic polymorphism as compared with CYP2C19, which is the primary enzyme responsible for the metabolism of PPIs [Shin 2013].

These unique aspects of the vonoprazan mechanism of action and pharmacokinetics relative to PPIs translate into greater magnitude and duration of gastric acid suppression, which are reflected in the pharmacodynamic profile [Jenkins 2015; Sakurai 2015].

The pharmacokinetic and pharmacodynamic profiles of vonoprazan were assessed in multiple studies, including Study TAK-438_107, which showed rapid rise in pH following vonoprazan administration and a dose response for percent time above pH 4. The mean percentage of time above pH 4 on Day 1 for vonoprazan 10 mg, 20 mg, and 40 mg were 43%, 63%, and 86%, respectively, and by Day 7 were 60%, 85%, and 93%, respectively [Jenkins 2015].

Takeda conducted 8 short-term clinical studies in adults with EE (5 studies) and symptomatic non-erosive GERD (3 studies) with treatment durations of 2 to 8 weeks. In addition, Takeda conducted 3 studies of maintenance of healing of EE with treatment durations of 24 to 52 weeks. Vonoprazan is approved in multiple countries outside of the United States for the treatment of adults for reflux (erosive) esophagitis (for healing: vonoprazan 20 mg QD up to 4 weeks or, if insufficient effect, 8 weeks; for maintenance: 10 mg QD or, if insufficient effect, 20 mg QD).

The safety profile of vonoprazan in Phase 3 studies of adults across indications showed no evidence of a dose-related increase in adverse effects with vonoprazan from 5 mg to 40 mg

QD. As of 25 December ~~2021~~2022, the global cumulative post-marketing patient exposure to vonoprazan is estimated to be approximately ~~70~~97 million patients.

Overall, with vonoprazan's pharmacological profile of rapid, potent, and sustained elevations of gastric pH, vonoprazan offers the potential to be a highly effective treatment option for children with symptomatic GERD.

Justification for Dose (Section 1.3)

The proposed pediatric doses are selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD in ~~children aged~~ pediatric patients ≥ 6 to < 12 years of age ~~with body weight of ≥ 30 kg~~.

The proposed doses are based on simulations using ~~a~~an updated population pharmacokinetic (popPK) model [Facius 2023]. The 2-compartment linear popPK model for vonoprazan was developed with adult pharmacokinetic data from ~~13~~ healthy subjects aged 18 to 54 years who participated in 9 studies ~~in healthy volunteers, 1 study in EE patients~~specifically selected to enable the extrapolation and ~~1 study in GERD patients.~~characterization of the disposition of vonoprazan in pediatric subjects. The final dataset consisted of ~~1,179~~354 subjects (~~769~~205 Asian and ~~410~~149 Western) with 8010 plasma concentration observations.

As planned, an analysis of interim PK data from the first adolescent subjects aged 12 to 17 years randomized in Study VPED-102 was performed using the updated popPK model. Interim data from VPED-102 was combined with adult data from the updated popPK model to investigate potential differences in the pharmacokinetic properties of vonoprazan between adolescents and adults. Individual predicted AUC_{ss} values for the 8 adolescent subjects with symptomatic GERD included in the preliminary analysis were within the range expected from healthy adults at their respective doses and no obvious effect of age was observed. Model assessments indicated the updated popPK model was working well in adolescents and substantiated the usefulness of ~~For the pediatric dose~~ simulations using the popPK model to select doses for ~~vonoprazan was updated to incorporate body size and maturation correction factors,~~younger pediatric subjects.

For predicting the appropriate ~~to predict~~doses in pediatric subjects aged ≥ 6 to <12 years, simulations were performed using the updated popPK model for vonoprazan ~~exposure in~~

~~infants, children, and adolescents (PopPK Simulation Memo).~~and were summarized by both age and body weight. For reference, all boys and girls aged ≥ 6 to < 12 years who have a body weight between the 5th and 95th percentiles would have a body weight between 15 and 65 kg. Different model assumptions in terms of ~~(i)~~ the allometric weight scaling exponent (as estimated (none) in the adult data or fixed at 0.~~75) and (ii) if or if not to correct for enzyme maturation in infants~~2) were compared.

The ~~resulting models were~~updated model was used to simulate posterior distributions of area under the drug concentration-time curve at steady state (AUC_{ss}) in both adults and ~~pediatrics~~ pediatric subjects aged ≥6 to <12 years or with a body weight of 15 to 65 kg for a series of pediatric candidate doses. Matching pediatric doses were selected to limit the predicted percentage of ~~pediatrics~~pediatric subjects with an exposure exceeding the adult reference exposure (median AUC_{ss}) at 50 ~~to 60~~%.

For children aged ≥ 6 to < 12 years or with a body weight ~~≥ 30~~of 15 to 65 kg~~,~~ each of the ~~four models~~simulations gave similar exposure predictions, thereby suggesting that the selected doses for these pediatric patients (10 and 20 mg) should result in a majority of exposures that are within the 95% prediction interval in adults for both the 10 and 20 mg targeted doses.

Study Objectives and Endpoints (Section 2)

Study objectives with corresponding endpoints are presented in Table 2-1.

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the pharmacokinetic profile of vonoprazan (10 or 20 mg QD) in children ≥ 6 to < 12 years of age ~~with body weight of ≥ 30 kg~~ who have symptomatic GERD.	• $C_{max,ss}$, AUC_{τ}, CL/F, V_z/F from data collected on Days 7 and 14.
Safety	
• To evaluate the safety of vonoprazan (10 or 20 mg QD) in children ≥ 6 to < 12 years of age ~~with body weight of ≥ 30 kg~~ who have symptomatic GERD.	• Adverse events • Laboratory test values (hematology, serum chemistry, urinalysis*) • Electrocardiograms (ECGs) • Vital signs
Exploratory	

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
• To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg) in children ≥ 6 to < 12 years of age ~~with body weight of ≥ 30 kg~~ who have symptomatic GERD.	• The severity of GERD symptoms at baseline and Days 7 and 14, as assessed by the investigator • Mean pH and % time above pH 4, 5, and 6 at baseline and Day 7 in the subset of subjects for whom intragastric pH monitoring is performed when clinically indicated per the investigator.

AUCτ: area under the drug concentration-time curve during the dosing interval τ; CL/F: oral clearance; $C_{max,ss}$: maximum drug concentration at steady-state; ECGs; electrocardiograms; GERD: gastroesophageal reflux disease; QD: once daily; V_z/F: apparent volume of distribution
* Urinalysis is only required if deemed necessary by the investigator.

Study Design (Section 3.1)

This is a Phase 1, ~~uncontrolled,~~ randomized, open-label, parallel-group, multiple-dose study in children aged ≥ 6 to < 12 years ~~with body weight of ≥ 30 kg~~ who have symptomatic GERD. A total of approximately 18 subjects will be enrolled.

Blood samples for pharmacokinetic testing will be collected on Days 7 and 14. Select sites will perform gastric pH monitoring in subjects deemed clinically indicated by the principal investigator. Gastric pH will be monitored for 24 hours beginning on Day -1 and on Day 7.

Following completion of study drug dosing on Day 14 or early discontinuation, the subject will be transitioned to local standard of care for 14 days during the Follow-up Period. Note, standard of care does not include the use of study drug but can include other acid suppressant agents.

A schematic diagram of the overall study design is presented in Figure 3.1.

Figure 3-1 Study Scheme

<table>
<tr><th>Screening Period</th><th></th><th colspan="3">Treatment Period (14 Days)</th><th></th><th>Follow-up Period [b] (14 Days)</th></tr>
<tr><td rowspan="2">Up to 4 weeks</td><td rowspan="2"></td><td>→</td><td colspan="2">Vonoprazan 10 mg QD
(N=9)</td><td rowspan="2">→
→</td><td rowspan="2">Follow-up
(local standard of care)</td></tr>
<tr><td>→</td><td colspan="2">Vonoprazan 20 mg QD
(N=9)</td></tr>
<tr><td>Day -1:
Placement of probe for 24-hour gastric pH monitoring [a]</td><td></td><td>Day 1:
Randomization
First dose of study drug taken at the clinic
Removal of pH probe [a]</td><td>Day 7:
Placement of probe for 24-hour gastric pH monitoring [a]
Dose of study drug taken at the clinic
PK blood collection: pre-dose, 0.5 to ~~2~~1.5 hours and 2.5 to 3.5 ~~4~~-hours post-dose
Symptom assessment

Day 8:
Removal of pH probe [a]</td><td>Day 14:
Last dose of study drug taken at clinic [b]
PK blood collection: pre-dose, ~~0.5~~1 to 2 hours and ~~2.5~~3 to 4 hours post-dose
Symptom assessment</td><td></td><td>Day 28:
Phone call</td></tr>
</table>

PK: pharmacokinetic; QD: once daily

a At select sites if deemed clinically indicated by the investigator. Subjects who undergo pH monitoring will have monitoring performed on both Day -1 and Day 7 for 24 hours.

b Following completion of study drug dosing or early discontinuation, the subject will be transitioned to local standard of care for 14 days.

The study will include 3 periods (see the schedule of events [SoE] in Section 13.1 for details).

Screening Period (≤ 4 weeks): Subjects will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will be randomized and enter the Treatment Period.

Treatment Period (Day 1 to Day 14): Subjects will be randomized to receive 1 of 2 vonoprazan doses (10 mg QD or 20 mg QD) for 14 days.

Follow-up Period (2 weeks): A safety follow-up visit phone call will occur 2 weeks after the last dose of study drug to assess adverse events (AEs). Following completion of study drug dosing or early discontinuation, the subject will be transitioned to local standard of care for 14 days.

End-of-study definition: A subject will be considered to have completed the study (up to 8 weeks, including 4 weeks of screening, 2 weeks of treatment and 2 weeks of safety follow-up) if the subject completes the Treatment Period and the safety follow-up visit phone call.

Selection of Study Population (Section 4.1)

This study will be conducted at approximately 20 to 25 sites in the United States and Europe. Approximately 18 subjects will be enrolled.

Inclusion Criteria (Section 4.1.1)

Subjects are eligible for enrollment in the study if they meet all of the following inclusion criteria:

1. The subject is ≥ 6 to < 12 years of age ~~with body weight of ≥ 30 kg~~ at the time of informed consent signing.
2. The subject has a body weight within the 5th through 95th percentile by age, inclusive, as determined by the National Center for Health Statistics (Section 13.6).

3. The subject must have a diagnosis of GERD prior to randomization and medical history of signs or symptoms of GERD for at least 3 months prior to screening, based on physical examination, current symptoms (eg, heartburn), or diagnostic tests (eg, pH or endoscopy). Notes in the medical records and/or other source documents, such as prior endoscopies, can be used to support the diagnosis and will be recorded in the electronic case report form (eCRF).

4. The subject has at least one moderate GERD symptom based on the GERD Symptom Assessment-Investigator scale performed at screening.

5. The subject must be able to swallow study drug tablet with water.

6. Parent or legal guardian (ie, legally authorized representative [LAR]) is willing and able to complete the informed consent process and subjects are able to comply with study procedures and visit schedule.

7. Female subjects who have experienced menarche must have a negative pregnancy test and will be counseled on pregnancy avoidance (Section 13.2).

Exclusion Criteria (Section 4.1.2)

Subjects are not eligible for study participation if they meet any of the following exclusion criteria:

1. The subject has used prescription or non-prescription PPIs or H_2RAs within 7 days prior to randomization or requires use during the Treatment Period.

2. The subject has used sucralfate, or antacids within 1 day prior to randomization or requires their use during the Treatment Period.

3. The subject has received other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth from 30 days prior to Day 1 or requires their use during the course of the study.

4. The subject has received atazanavir sulfate or ~~rilpivarine~~ rilpivirine hydrochloride from 5 days prior to Day 1 or requires their use during the course of the study.

5. The subject has received any investigational compound (including vonoprazan) within 30 days prior to the start of the Screening Period.

6. The subject is an immediate family member or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, child, sibling) or subject may have consented under duress.

7. The subject requires hospitalization or has surgery scheduled during the course of the study or has undergone major surgical procedures within 30 days prior to the Screening Period.

8. The subject has undergone prior gastrointestinal surgeries.

9. The subject has any abnormal laboratory test values that are considered clinically significant ~~at~~in the ~~start~~opinion of the investigator during the Screening Period.

10. The subject has a history of hypersensitivity or allergies to vonoprazan (including the formulation excipients: D-mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, ascorbic acid, croscarmellose sodium, magnesium stearate, ~~hypermellose~~ hypromellose, macrogol 8000, and titanium dioxide, or red or yellow ferric oxide).

11. The subject has used any prescription or over-the-counter medications (including ~~CYP3A4 inducers), including~~ herbal or nutritional supplements), other than those already excluded in criteria 1 to 5 above, within 14 days ~~(or 5 half-lives)~~ before the first dose of study drug or throughout the study. ~~NOTE: Acid suppressive therapies are considered separately under exclusion criteria 1 and 2.~~That is, unless the medication(s) is permitted by the sponsor following a review of available data which confirms concomitant administration of the medication is unlikely to affect either the safety of the patient or the pharmacokinetics of vonoprazan.

12. The subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or other food products that may be CYP3A4 inhibitors (eg, vegetables from the mustard green family [kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard] and charbroiled meats) within 7 days (or 5 half-lives) before the first dose of study drug or throughout the study.

13. The subject has positive results at screening for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus (HCV) infection at screening.

14. The subject has severe renal impairment (estimated glomerular filtration rate < 30 mL/min).

15. The subject has moderate to severe hepatic impairment (Child-Pugh Class B and Child-Pugh Class C).

16. The subject has any of the following abnormal laboratory test values at the start of the Screening Period:

    a. Creatinine levels: >2 mg/dL (>177 µmol/L).

    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × the upper limit of normal (ULN) or total bilirubin >2 × ULN (except subjects with Gilbert Syndrome).

17. In the opinion of the investigator, the subject is not suitable for entry into the study.

Replacements (Section 4.2.4)

~~Discontinued or withdrawn subjects will not be replaced.~~

At the discretion of the sponsor, subjects may be replaced to achieve the target of approximately 18 subjects with expected usable pharmacokinetic sample collections.

Treatments Administered (Section 5.2)

Subjects will be administered study drug orally at the clinic on Day 1 and on Days 7 and 14, after the pre-dose pharmacokinetic sample, with approximately 240 mL (8 oz) of water in the morning between 7 and 10 am preferably prior to eating any breakfast or food. If necessary, a dosing cup can be used to facilitate administration. Study drug will be dispensed to the parent/LAR for study drug to be administered to the subject at home. Clinic staff will provide the parent/LAR a Study Drug Reminder Card and instruct the parent/LAR to record the date and time of every dose taken at home and to bring this card back to the next clinic visit.

On Days 2 to 6 and 8 to 13, the parent/LAR ~~Parents/caregivers~~ will be instructed to ~~have~~give the subject ~~take randomized~~ study drug orally with approximately 240 mL (8 oz) of water each morning between 7 and 10 am ~~on an empty stomach with approximately 240 mL (8 oz) water. Subjects will take study drug at the clinic on Days 1, 7, and 14; otherwise, study drug will be taken on an outpatient basis.~~preferably prior to eating any breakfast or food. Any missed doses should also be ~~noted~~recorded by the ~~parents/caregivers~~parent/LAR and communicated to clinic staff ~~to record~~immediately. All dosing information including missed doses will be recorded on the Study Drug Reminder Card and in the eCRF.

~~For the Days 6 and 13 dose, parents/caregivers will note the time it was taken by the subject. Clinic staff will record this information in the eCRF.~~

~~Water is permitted as desired, except for 1 hour before and 1 hour after administration (other than what is permitted for study drug dosing). Subjects will be provided a~~ On Days 7 and 14 subjects may have a meal/snack 30 ~~-~~to 60 minutes after study drug dosing ~~per the clinic's~~.

Following completion of study drug dosing on Day 14 or early discontinuation, the subject will be transitioned to local standard ~~procedures~~ of care for 14 days. Note, the local standard of care does not include study drug but can include other acid suppressant agents.

Identity of Investigational Product (Section 5.3)

Vonoprazan study medication will be supplied as 10 mg and 20 mg tablets. [redacted] manufactures the vonoprazan fumarate drug substance. [redacted] manufactures the vonoprazan tablets.

Vonoprazan tablets contain vonoprazan free base (MW 345.39) and the following inactive excipients: D-Mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, ascorbic acid, croscarmellose sodium, magnesium stearate, hypromellose, polyethylene glycol 8000, titanium dioxide, and red or yellow ferric oxide.

Study drug will be packaged ~~in bottles~~ for shipment to the investigational site.

Study Drug Packaging and Storage (Section 5.4.1)

Vonoprazan tablets will be packaged ~~in bottles~~ and shipped by [redacted].

Study supplies must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature (20°C to 25°C [68°F to 77°F]; excursions are allowed between 15°C and 30°C [59°F to 86°F]) until they are used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label and remain in the original container until dispensed.

Sites should refer to the pharmacy manual for detailed information regarding packaging and labeling and for reporting temperature excursions.

Treatment Compliance (Section 5.7.1)

Compliance with study drug is to be assessed as specified in the SoE (Section 13.1). Compliance with study drug dosing will be assessed by clinic staff reviewing the Study Drug Reminder Card returned at each visit, direct questioning and counting any returned ~~capsules~~tablets, which will be documented in the source documents and eCRF.

~~A record of the number of study drug tablets dispensed to and taken by each subject must be maintained and reconciled with study drug and compliance records. Study drug start and stop dates will also be recorded in the eCRF.~~

~~If the subjects exhibit~~The date and time of each dose taken (in clinic or at home) must be recorded on the Study Drug Reminder Card, source documents and eCRF. If a subject misses any dose for any reason, the sponsor must be notified immediately, and the date of the missed dose(s) and reason must be recorded in the eCRF.

If a subject misses a scheduled visit or exhibits poor compliance, as assessed by ~~capsule~~tablet counts, the sponsor should be notified immediately to determine appropriate mitigation. Actions may include subjects provided with specific dosing instructions to continue study drug or discontinuation from the study. The LARs and subjects should be counseled at each visit on the importance of good compliance ~~with~~regarding the ~~study~~ dosing regimen and scheduled study visits.

Prior and Concomitant Therapy (Section 5.8)

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of screening (or has received within 30 days before the time of screening) or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The LARs and subjects are to be instructed that the subject should not take any medications, including over-the-counter medications, without first consulting the investigator or subinvestigators. However, single-use medications for endoscopic examination and topical medications, including liniments, ophthalmic drops, nasal drops, ear drops, inhaled drugs, adhesive skin patches, and gargle (mouthwash) will be allowed, whether or not they are excluded or restricted.

~~Prior use of H_2RAs or PPIs should be documented. The dose and duration and whether or not symptoms were relieved by the medication will be collected.~~

The medical monitor should be contacted if there are any questions regarding prior or concomitant therapy.

Excluded Medications (Section 5.8.1)

A list of excluded medications is provided in Table 5-1

Table 5-1 Excluded Medications and Treatments

Excluded Medications and Treatments	Beginning of Exclusion	End of Exclusion
Other investigational drugs or drugs administered due to participation in another clinical trial	30 days prior to start of Screening Period	Follow-up phone call
Antacids and sucralfate	Day -1 (day before first dose of study drug)	Day 14 (end of study drug dosing)
H_2RAs	7 days prior to Day -1	Day 14 (end of study drug dosing)
PPIs	7 days prior to Day -1	Day 14 (end of study drug dosing)
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	14 days prior to Day 1	~~End of treatment~~ Day 14 (end of study drug dosing)
CYP3A4 substrates with a narrow therapeutic index	14 days prior to Day 1	~~End of treatment~~ Day 14 (end of study drug dosing)
CYP2C19 substrates clopidogrel, citalopram, cilostazol	14 days prior to Day 1	~~End of treatment~~ Day 14 (end of study drug dosing)
Other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth	30 days prior to Day 1	Follow-up phone call
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	Follow-up phone call

CYP: cytochrome P450 isoenzyme; H_2RA: histamine-2 receptor antagonist; PPI: proton pump inhibitor

Pharmacokinetic Assessments (Section 6.1.1)

~~Parents/caregivers will be asked to note the exact time the subject took their study drug dose on Days 6 and 13. Clinic staff will record this information in the eCRF.~~

~~Parents/caregivers~~Parents/LARs will ensure that the subject arrives at the clinic in the morning on Days 7 and 14 for pharmacokinetic sampling. Subjects should not eat or take the vonoprazan study ~~medication~~drug before arriving ~~to~~at the clinic. ~~Subjects~~The Day 7 and 14 dose of study drug will be~~ released from~~ given in the clinic ~~after pharmacokinetic sampling and study procedures are completed~~.

Blood samples for pharmacokinetic analysis of vonoprazan in plasma will be collected on Days 7 and 14. ~~On each of this days~~On Day 7, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 0.5 to 1.5 hours post-dose and one between 2.5 to 3.5 hours post-dose. On Day 14, one pre-dose sample will be collected prior to the morning administration of vonoprazan~~. Two~~ along with two additional samples~~ will be~~ collected after drug administration: one between ~~0.5 and~~1 to 2 hours post-dose and one between ~~2.5 and~~ 3 to 4 hours post-dose. The exact date and time of each pharmacokinetic sample must be recorded in subject source document and eCRF.

If a subject terminates early, an attempt should be ~~recorded.~~made to collect one blood sample if it can be collected within 24 hours following the last dose of study drug. The exact date and time of the early termination sample must be recorded.

~~Samples~~Blood samples will be collected into ~~appropriate blood~~sodium heparin vacutainer collection tubes~~, as specified by the bioanalytical laboratory~~ and processed into plasma. Details of collection, processing, storage and shipping will be contained in the Clinical Laboratory Manual.

Bioanalytical Methods

Plasma concentrations of vonoprazan will be measured at Labcorp Early Development Laboratories Inc. (Madison, WI) using a validated liquid chromatrography/mass spectrometry method with an analytical range of ~~1~~0.5 to 100 ~~µg~~ng/mL and will be used for the calculation of the plasma vonoprazan pharmacokinetic parameters.

Depending on pace of enrollment, pharmacokinetic samples from a subset or subsets of subjects may be analyzed prior to the completion of enrollment. In any case, all of the pharmacokinetic samples collected from a given subject will be analyzed in the same bioanalytical batch.

Pharmacokinetic Parameters

Plasma pharmacokinetic parameters shown in Table 6-1 will be estimated using a non-linear mixed effects model and will be determined from the concentration-time data for all evaluable subjects. The primary vonoprazan pharmacokinetic endpoints will include the following steady state parameters: $C_{max,ss}$, AUC_{τ}, CL/F and V_z/F. Actual sampling times, rather than scheduled or nominal sampling times, will be used in all computations using sampling time. Additional pharmacokinetic parameters may be estimated as appropriate.

Table 6-1 Pharmacokinetic Parameters to be Estimated using Vonoprazan Plasma Concentration Data

Parameter	Definition
$C_{max,ss}$	Maximum observed plasma concentration at steady state
$C_{max,ss}$/Dose	Dose-normalized $C_{max,ss}$ ($C_{max,ss}$ divided by the administered dose in mg)
$AUC_{\tau,ss}$	Area under the plasma concentration-time curve during the dosing interval τ, where τ is the length of the dosing interval in hours, calculated using the linear trapezoidal rule
$AUC_{\tau,ss}$/Dose	Dose-normalized $AUC_{\tau,ss}$ ($AUC_{\tau,ss}$ divided by the administered dose in mg)
λ_z	Terminal elimination rate constant, calculated as the negative slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase
CL/F	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/ $AUC_{\tau,ss}$
V_z/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (CL/F)/ λ_z

Pharmacodynamic Assessments (Section 6.1.2)

~~If~~Select sites may participate in a sub-study collecting gastric pH when deemed clinically ~~indicated~~necessary by the principal investigator. In the pharmacodynamic sub-study, gastric pH will be measured and recorded continuously for a 24-hour period on ~~scheduled days~~Day -1 and Day 7 as outlined in the SoE **(**Section 13.1**)** using a suitable pH probe and ambulatory pH recording system**.** All instruments will be calibrated prior to and following use. Gastric pH will be sampled and recorded every 5 seconds. The 24-hour continuous pH recording session for Day -1 will commence 24-hours prior to the first dose of study drug. The 24-hour continuous pH recording session for Day 7 will commence 30 to 60 minutes prior to ~~treatment administration~~ the next dose of study drug. The reason for pH assessments, start

time, stop time and any interruptions will be recorded in the source document and the ~~case report form (CRF)~~ eCRF. To minimize the discomfort of probe insertion, administration of a topical anesthetic (lidocaine) will be permitted~~. After each 24-hour period,~~ per the ~~flashcard~~institutional process. Details of collection, processing, storage and shipping will be ~~removed from~~contained in the ~~recorder and the~~ Gastric pH ~~data will be transferred to the computer.~~Monitoring Plan.

Gerd Symptom Assessment-Investigator (Section 6.2.1)

The GERD Symptom Assessment-Investigator scale evaluates 4 symptoms of GERD: heartburn, vomiting, acid regurgitation, and trouble eating. The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit, Day 7 and Day 14 will be assessed. The severity for each symptom will be recorded as either none, mild, moderate, severe or very severe. At screening, the subject will be eligible for inclusion in the study if the subject has at least one moderate GERD symptom. Symptom and severity definitions are presented in Section 13.4.1.

Adverse Events of Special Interest (Section 6.3.1.1.4)

An AE of special interest is a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or nonserious (eg, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

Adverse events of special interest include any event listed in Table 6-~~2~~3.

Table 6-~~2~~3 Adverse Events of Special Interest List

Term
Hepatotoxicity
Severe cutaneous adverse reactions, including hypersensitivity
Clostridium difficile infections and pseudomembranous colitis
Hypersensitivity reactions (anaphylaxis)
Acute interstitial nephritis/tubulointerstitial nephritis
Bone fracture
Hematologic abnormalities

For additional details on liver function monitoring, see Section 13.2.

Safety Reporting to Investigators, IRB/IECs, and Regulatory Authorities (Section 6.3.1.3.4)

The sponsor designee (contract research organization) will be delegated the responsibility for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and the IRB/IEC, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities (eg, EudraVigilance Database, FDA Adverse Event Reporting System) as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required. The sponsor designee will also prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products.

Laboratory Analyses (Section 6.3.3)

See Table 6-4 for the list of clinical laboratory tests to be performed and the SoE (Section 13.1) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the

eCRF. The laboratory reports must be filed with the source documents. Abnormal laboratory findings that are expected with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

- All laboratory tests with abnormal values considered clinically significant during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Table 6-~~3~~4 , must be conducted in accordance with the laboratory manual and the SoE.
        - If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the unscheduled laboratory eCRF.

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be provided in the laboratory manual.

All study-required laboratory assessments will be performed by a central laboratory.

Table 6-4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices: MCV, MCH • Percent reticulocytes • WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils	
Clinical chemistry [a]	• Blood urea nitrogen • Creatinine • Total and direct bilirubin • ALT/SGPT • AST/SGOT • Alkaline phosphatase	• Total protein • Potassium • Sodium • Calcium • Glucose [b] • GGT
Routine urinalysis [c]	• Specific gravity, appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)	
Other screening tests	• Serology (HIV antibody, HBsAg, ~~and~~ HCV antibody, ~~hepatitis C,~~ HCV viral load RNA [qualitative]), hCG pregnancy test [d]	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; RBC: red blood cell; RNA: ribonucleic acid; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; WBC: white blood cell

a See Section ~~13.2~~ 13.3 for the appropriate guidance on reporting of abnormal liver function tests. For liver function test monitoring, see Section ~~13.2.1~~13.3.1 For temporary and permanent discontinuation of study drugs due to abnormal liver function tests, see Section ~~13.2.2 and Section 12.2.3~~ 13.3.2 and Section 13.3.3, respectively.

b Glucose will be obtained after an 8-hour fast at Visit 1 and at any unscheduled visit.

c At the discretion of the investigator.

d Only female subjects who have experienced menarche will have urine hCG; if the urine hCG test is positive confirm with serum hCG.

Investigators must document their review of each laboratory safety report.

Physical Examinations (Section 6.3.4)

Refer to the SoE (Section 13.1) for the timing and frequency for full and brief physical examinations, as well as height and body weight.

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, ~~and~~ neurological systems and Tanner staging (Section 13.5). Height and body weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, and gastrointestinal systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Electrocardiograms (Section 6.3.6)

Refer to the SoE (Section 13.1) for the timing and frequency of ECG assessments.

A single, standard 12-lead ECG recording will be made after the subject has been in the supine position for at least 5 minutes. ECGs will be read and interpreted centrally by a pediatric cardiologist for eligibility during Screening and on Day 14. A single repeat measurement is permitted ~~at~~ during screening period for eligibility determination. ~~Measurements of the following intervals will be reported: PR interval, RR interval, QT interval, and QRS interval. The QT interval adjusted for heart rate will be derived in the electronic database from the RR and QT intervals, using the Fridericia method.~~ Assessments ~~should~~ will include ~~comments on~~ whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant)~~; rhythm; the presence of arrhythmia or conduction defects; any evidence of myocardial infarction; and ST-segment, T-wave, and U-wave abnormalities~~.

Statistical and Analytical Plan (Section 7)

This section describes the statistical and analytical methods to be used for the study. ~~A statistical analysis plan will provide further details of the statistical methods for the analysis.~~

Sample Size Calculations (Section 7.1)

Approximately 18 subjects are expected to be enrolled with 9 subjects in each dose group. Attempts will be made to enroll subjects across the ≥ 6 to < 12 years age range. Because this is a pharmacokinetic and safety trial with no comparator, there is no power determination affecting the sample size. The sample size of approximately 18 subjects is considered sufficient to assess the pharmacokinetics, safety, and tolerability of vonoprazan in this population. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the PK profile.

Analysis Sets (Section 7.2)

The pharmacokinetic population will include subjects who receive at least 1 dose of study drug and have sufficient concentration data to support accurate estimation of at least 1 pharmacokinetic parameter.

The pharmacodynamic population will include subjects who receive at least 1 dose of study drug and have sufficient pH data to support calculation of pharmacodynamic parameters.

The safety population will include all subjects who receive at least 1 dose of study drug.

Pharmacokinetic Analyses (Section 7.3.1)

The individual pharmacokinetic parameter estimates in Table 6-1 will be summarized descriptively by vonoprazan dose.

The following pharmacokinetic parameters will be considered the primary endpoints for the study: $C_{max,ss}$, AUC_{τ}, CL/F, V_z/F.

Pharmacodynamic Analyses (Section 7.3.2)

Mean pH and the percentage of time above pH 4, 5, and 6 at baseline (Day -1) and Day 7 will be summarized for the subset of subjects for whom intragastric pH monitoring is available.

Efficacy Analyses (Section 7.3.3)

The severity of GERD symptoms at baseline and Days 7 and 14, as assessed by the investigator, will be summarized overall and by vonoprazan dose.

Interim Analyses (Section 7.3.5)

No formal interim analyses will be performed in this study.

However, a popPK analysis of interim data from a subset of subjects may be conducted prior to completion of enrollment to assess whether plasma exposure in pediatric subjects aged ≥ 6 to < 12 years is within the range observed in adults receiving the same dose.

Data Quality Assurance (Section 8)

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R2) risk and quality processes described in the applicable procedural documents and Regulation 536/2014 of the European Parliament and of the council of 16 April 2014 on clinical trials on medicinal products for human use and repealing Directive 2001/20/EC. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management [DHHS 2018]. The

sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Ethical Conduct of the Study (Section 9.2)

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

All potential serious breaches must be reported to the sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol which is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Investigator's Obligations (Section 10)

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

The Investigator will also be responsible for providing oversight of the conduct of the study or site, including oversight of all personnel involved in the study, and adherence to all applicable laws and regulations as set forth in the Clinical Trial Agreement.

Personnel involved in conducting this study will be qualified by education, training and experience prior to performing their respective tasks.

External Data Monitoring Committee (Section 11.1.1)

An external data monitoring committee will not be used for this study. This is a Phase 1 study with 14 days dosing and adverse events will be evaluated on an ongoing basis. Additionally, vonoprazan has a well characterized safety profile in adults.

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

~~The study results will be posted on publicly available clinical trial registers.~~The sponsor will submit to clinical trial registries a summary of the results of the clinical trial and where applicable a summary that is understandable to a layperson, and the clinical study report health authorities, within 6 months after the end of the study. The investigator is encouraged to share the summary results with the LARs and study subjects, as appropriate.

Appendix 1: Schedule of Events (Section 13.1)

	Screening Period		Treatment Period					Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day -1 [a]**	**Day 1**	**Phone Call Day 6**	**Day 7**	**Day 8 [a]**	**Phone Call Day 13**	**ET/ Day 14**	**Phone Call Day 28**	**Unscheduled Visit [b]**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Informed consent [c]	X									
Inclusion/exclusion criteria	X	X	X							
Demographic and medical history	X									
~~Medication History~~	~~X~~									
Physical examination [d]	X				X			X		X
Vital signs [e]	X		X		X			X		X
Weight and height [f]	X				X			X		
Prior/Concomitant medications	X	X	X		X	X		X	X	X
Concurrent medical conditions	X									
Hepatitis B and C; HIV [g]	X									
Clinical laboratory tests [h]	X				X			X		X
Pregnancy test [i]	X		X		X			X		
Guidance on avoidance of pregnancy [i]	X		X		X			X		
12-lead electrocardiogram [j]	X							X		
GERD Symptom Assessment-Investigator	X				X			X		
Randomization [k]			X							
Dispense study drug [l]			X		X					
Study drug administration (at clinic) [l]			X		X			X		
Gastric pH monitoring [a]		X			X	X				
PK blood sample collection **Day 7**: pre-dose, 0.5 to 1.5 hour and 2.5 to 3.5 hours post dose. **Day 14:** pre-dose, 1 to 2 hours and 3 to 4 hours post dose. [m]					X			X		
Drug return/accountability					X			X		
Telephone call to subject				X			X	X	X	
AE/pretreatment event assessment [n]	X	X	X		X			X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; HIV: human immunodeficiency virus, PK: pharmacokinetic; PTE: pretreatment event

a For subjects participating in the pharmacodynamic substudy, Visit 2 (Day -1) and Visit ~~5~~6 (Day 8) are only required for subjects undergoing gastric pH monitoring if clinically indicated at select sites. pH monitoring will be conducted on Day -1 for 24 hours and on Day 7 for 24 hours. pH probes would be placed on Days -1 and 7 and removed on Days 1 and 8.

b At an unscheduled visit, the following procedures are to be completed with additional procedures at the investigator's discretion: a brief physical examination, vital sign measurements, concomitant medication assessment, AE assessment, and clinical laboratory tests. If the visit results in premature termination, then all procedures outlined for the final visit should be performed.

c Informed consent will be signed by the subject's legally authorized representative prior to any activity in the study. Subject assent (if applicable) may be obtained as required per site guidelines.

d A complete physical examination will be performed at screening (at minimum, assessment of skin, cardiovascular, respiratory, gastrointestinal, ~~and~~ neurological systems and Tanner staging). A brief physical examination will be performed at other visits (at minimum, assessment of skin, cardiovascular, respiratory, and gastrointestinal systems). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

e Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.

f Height collected only at screening.

g Hepatitis B surface antigen, hepatitis C virus antibody, and HIV type 1 and 2 antibodies.

h Clinical laboratory testing will include hematology, serum chemistry, and urinalysis (if deemed necessary by the PI). Blood draws should follow vital signs or electrocardiograms.

i Only female-born subjects~~, Tanner stage 2 development~~ who have reached menarche, will require guidance on avoidance of pregnancy and urine or serum hCG; if urine hCG is positive, confirm with serum hCG.

j Single 12-lead electrocardiogram recordings will be made after the subject has been in the supine position for at least 5 minutes at screening. A pediatric cardiologist will interpret the ECG for eligibility and any abnormality. A single repeat measurement is permitted at screening for eligibility determination ~~Measurements of the following intervals will be reported: PR interval, RR interval, QRS interval, and QT interval. The QT interval adjusted for heart rate will be derived in the electronic database from the RR and QT intervals, using the Fridericia method.~~after the read by a pediatric cardiologist. Assessments should include comments on whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant)~~; rhythm; the presence of arrhythmia or conduction defects; any evidence of myocardial infarction; and ST segment, T wave, and U wave abnormalities.~~ An ECG will be collected at the final visit and interpreted by a pediatric cardiologist.

k Subject will be randomized to study treatment after all eligibility criteria have been met.

l Study drug will be administered in the clinic on Days 1, 7, and 14. ~~On Days 7 and 14, subjects will be provided a meal 30-60 minutes after study drug dosing per the clinic's standard procedures.~~Study drug should be taken every day between 7 and 10 am preferably prior to eating any breakfast or food. Study drug for at home administration will be dispensed on Day 1 (to be taken on Days 2 to 6) and Day 7 (to be taken on Days 8 to 13). At home, parents/caregivers will administer study drug to subjects. ~~Study drug should be taken every day between 7 and 10 am.~~ Clinic staff will review instructions with parents/LARs for administering study drug at home and completing the Study Drug Reminder Card. Phone call reminders may be conducted as required.

m ~~Gastric pH monitoring on Day -1 for 24 hours and on Day 7 for 24 hours; only if clinically indicated. pH probes would be placed on Days -1 and 7 and removed on Days 1 and 8.~~ Blood samples for PK analysis of vonoprazan in plasma will be collected on Days 7 and 14. ~~On both~~On Day 7 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 0.5 to 1.5 hours post-dose and one between 2.5 to 3.5 hours post-dose. On Day 14 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan ~~and~~ along with two additional samples ~~will be~~ collected after drug administration: one between ~~0.5~~1 to 2 hours post-dose and one between ~~2.5 and~~ 3 to 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded in the source and eCRF.
If a subject terminates early, an attempt should be made to collect one blood sample if it can be collected within 24 hours following the last dose of study drug. The exact date and time of the early termination sample must be recorded.

n Collection of pretreatment events will start after the informed consent form has been signed. Adverse events will be assessed from time of informed consent signing until the follow-up visit and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

Appendix 2: Contraceptive Guidance (Section 13.2)

Contraception Guidance:

From signing of informed consent, throughout the duration of the study, and for 2 weeks after the last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

> *Females NOT of childbearing potential are defined as those who are premenarchal, have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with a follicle-stimulating hormone level >40 International units per liter or at least 5 years since last regular menses, confirmed before any study drug is implemented).
>
> **Sterilized males should be at least 1-year post vasectomy and should have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

Note: If the childbearing potential of a subject changes after start of the study (eg, a premenarchal female subject experiences menarche) or the risk of pregnancy changes (eg, a female subject who is not heterosexually active becomes active), the participant must discuss this with the investigator, who should determine if the female subject must begin a highly effective method of contraception or a male participant must use a condom.

Birth Control: Birth control methods considered acceptable for this study include:

Barrier methods (each time that you have intercourse):

- Male condom PLUS spermicide
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide

Intrauterine Devices

- Copper T PLUS condom or spermicide
- Progesterone T PLUS condom or spermicide

Hormonal Contraceptives

- Implants
- Hormone shot/injection
- Combined pill
- Minipill
- Patch
- Vaginal ring PLUS male condom and spermicide

During the course of the study, serum human chorionic gonadotropin (hCG) will be performed at screening and regular urine hCG pregnancy tests will be performed only for women of childbearing potential. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Section 13.1). Female subjects must have a negative urine hCG pregnancy test on Day -1 prior to study drug dispensation.

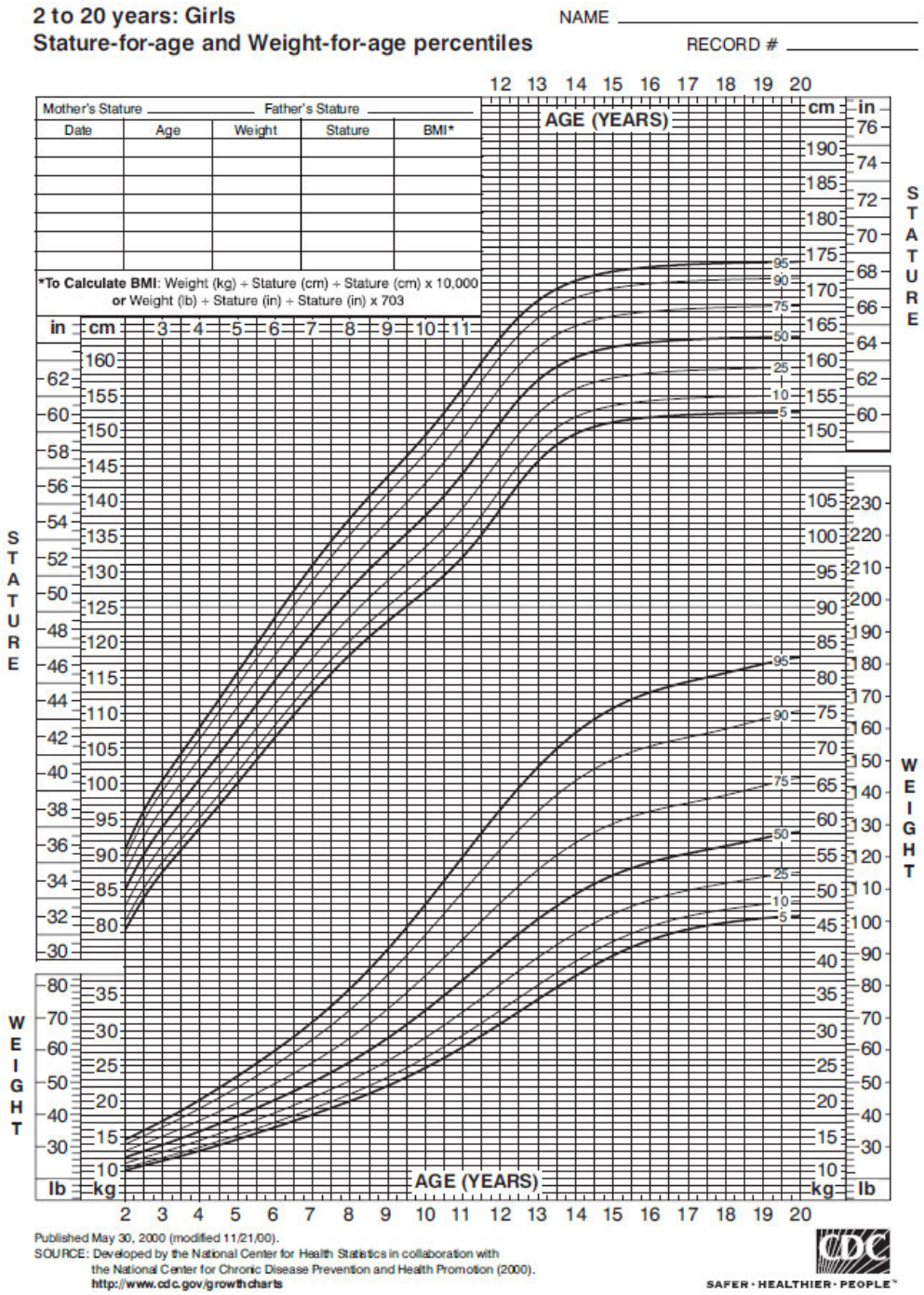
Appendix 5: Tanner Staging (Section 13.5)

Tanner Staging will be reported based on the following criteria:

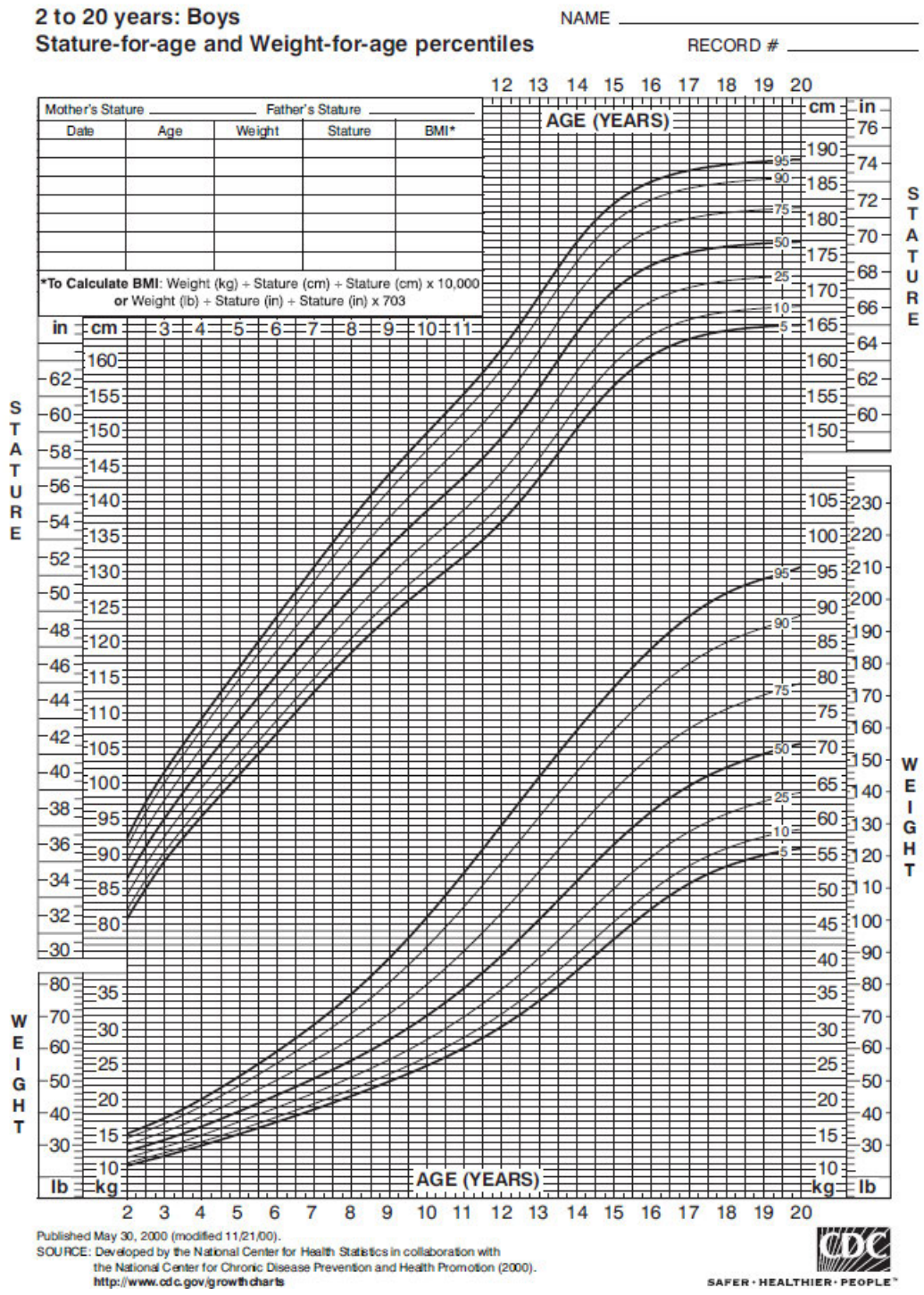
Boys – Development of external genitalia
Stage 1: Prepubertal
Stage 2: Enlargement of testes and scrotum; scrotal skin reddens and changes in texture
Stage 3: Enlargement of penis (length at first); further growth of testes
Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotal skin darker
Stage 5: Adult genitalia
Girls – Breast development
Stage 1: Prepubertal
Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola
Stage 3: Further enlargement of breast and areola; no separation of their contour
Stage 4: Areola and papilla form a secondary mound above level of breast
Stage 5: Mature stage: Projection of papilla only, related to recession of areola
Boys and girls – Pubic hair
Stage 1: Prepubertal (the pubic area may have vellus hair, similar to that of forearms)
Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia
Stage 3: Darker, coarser, and more curled hair, spreading sparsely over junction of pubes
Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs
Stage 5: Adult in type and quantity, with horizontal upper border

Appendix 6: National Center for Health Statistics Clinical Body Weight Charts with 5th and 95th Percentiles (Section 13.6)

13.6.1 Girls



13.6.2 Boys


2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles
NAME
RECORD #
Mother's Stature
Father's Stature
Date
Age
Weight
Stature
BMI*
*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
AGE (YEARS)
STATURE
WEIGHT
95
90
75
50
25
10
5
Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts
SAFER · HEALTHIER · PEOPLE™

13.7.2 Protocol Amendment 2

Exclusion Criteria (Section 4.1.2)

Subjects are not eligible for study participation if they meet any of the following exclusion criteria:

1. The subject has used prescription or non-prescription PPIs or H_2RAs within 7 days prior to randomization or requires use during the Treatment Period.

2. The subject has used sucralfate, or antacids within 1 day prior to randomization or requires their use during the Treatment Period.

3. The subject has received other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth from 30 days prior to Day 1 or requires their use during the course of the study.

4. The subject has received atazanavir sulfate or rilpivirine hydrochloride from 5 days prior to Day 1 or requires their use during the course of the study.

5. The subject has received any investigational compound (including vonoprazan) within 30 days prior to the start of the Screening Period.

6. The subject is an immediate family member or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, child, sibling) or subject may have consented under duress.

7. The subject requires hospitalization or has surgery scheduled during the course of the study or has undergone major surgical procedures within 30 days prior to the Screening Period.

8. The subject has undergone prior gastrointestinal surgeries.

9. The subject has any abnormal laboratory test values that are considered clinically significant in the opinion of the investigator during the Screening Period.

10. The subject has a history of hypersensitivity or allergies to vonoprazan (including the formulation excipients: D-mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, ascorbic acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 8000, and titanium dioxide, or red or yellow ferric oxide).

11. The subject has used any prescription or over-the-counter medications (including herbal or nutritional supplements), other than those already excluded in criteria 1 to 5 above, within 14 days before the first dose of study drug or throughout the study. That is, unless the medication(s) is permitted by the sponsor following a review of available data which confirms concomitant administration of the medication is unlikely to affect either the safety of the patient or the pharmacokinetics of vonoprazan.

12. The subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or other food products that may be CYP3A4 inhibitors (eg, vegetables from the mustard green family [kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard] and charbroiled meats) within 7 days (or 5 half-lives) before the first dose of study drug or throughout the study.

13. The subject has positive results at screening for human immunodeficiency virus, hepatitis B virus, or hepatitis C virus (HCV) infection at screening.

14. The subject has severe renal impairment (estimated glomerular filtration rate < 30 mL/min).

15. The subject has moderate to severe hepatic impairment (Child-Pugh Class B and Child-Pugh Class C).

16. The subject has any of the following abnormal laboratory test values at the start of the Screening Period:

    a. Creatinine levels: >~~2~~21 mg/dL (>~~177~~88 µmol/L).

    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × the upper limit of normal (ULN) or total bilirubin >2 × ULN (except subjects with Gilbert Syndrome).

17. In the opinion of the investigator, the subject is not suitable for entry into the study.

Pregnancy (Section 3.3.2)

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug (vonoprazan active) should be immediately discontinued. If the pregnancy occurs during administration of active study drug, eg, after Visit 2 or within 42 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 6.3.1.3.2. If the subject (and LAR, if legally applicable) agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of the treatment the subject received. All pregnancies will be reported using the pregnancy form and will be followed up to final outcome. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

Prior and Concomitant Therapy (Section 5.8)

Any medication including H_2RAs and PPIs or vaccines (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of screening (or has received within 30 days before the time of screening) or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The LARs and subjects are to be instructed that the subject should not take any medications, including over-the-counter medications, without first consulting the investigator or subinvestigators. However, single-use medications for endoscopic examination and topical medications, including liniments, ophthalmic drops, nasal drops, ear drops, inhaled drugs, adhesive skin patches, and gargle (mouthwash) will be allowed, whether or not they are excluded or restricted.

The medical monitor should be contacted if there are any questions regarding prior or concomitant therapy.

Laboratory Analyses (Section 6.3.3)

Investigators must document their review of each laboratory safety report.

See Table 6-4 for the list of clinical laboratory tests to be performed and the SoE (Section 13.1) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Abnormal laboratory findings that are expected with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

- All laboratory tests with abnormal values considered clinically significant during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

    - All protocol-required laboratory assessments, as defined in Table 6-4 must be conducted in accordance with the laboratory manual and the SoE.

        - If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the unscheduled laboratory eCRF.

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be provided in the laboratory manual.

All study-required laboratory assessments will be performed by a central laboratory.

Table 6-4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices: MCV, MCH • Percent reticulocytes • WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils	
Clinical chemistry [a]	• Blood urea nitrogen • Creatinine • Total and direct bilirubin • ALT/SGPT • AST/SGOT • Alkaline phosphatase	• Total protein • Potassium • Sodium • Calcium • Glucose [b] • GGT
Routine urinalysis [c]	• Specific gravity, appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)	
Other screening tests	• Serology (HIV antibody, HBsAg, HCV antibody, HCV viral load RNA [qualitative]), hCG pregnancy test [d]	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; hCG: human chorionic gonadotropin; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; RBC: red blood cell; RNA: ribonucleic acid; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; WBC: white blood cell

a See Section 13.3 for the appropriate guidance on reporting of abnormal liver function tests. For liver function test monitoring, see Section 13.3.1. For temporary and permanent discontinuation of study drugs due to abnormal liver function tests, see Section 13.3.2 and Section 13.3.3, respectively.

b Glucose will be obtained ~~after an 8-hour fast~~ at Visit 1 and at any unscheduled visit.

c At the discretion of the investigator.

d Only female subjects who have experienced menarche will have urine hCG; if the urine hCG test is positive confirm with serum hCG.

Investigators must document their review of each laboratory safety report.

Physical Examinations (Section 6.3.4)

Refer to the SoE (Section 13.1) for the timing and frequency for full and brief physical examinations, as well as height and body weight.

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, neurological systems and Tanner staging (Section 13.5). Height and body weight will also be measured and recorded. The subject should be dressed in light clothing and without shoes when the body weight is being measured.

A brief physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, and gastrointestinal systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Appendix 1: Schedule of Events (Section 13.1)

	Screening Period		Treatment Period					Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day -1 [a]**	**Day 1**	**Phone Call Day 6**	**Day 7**	**Day 8 [a]**	**Phone Call Day 13**	**ET/ Day 14**	**Phone Call Day 28**	**Unscheduled Visit [b]**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	7	**8**	**9**	
Informed consent [c]	X									
Inclusion/exclusion criteria	X	X	X							
Demographic and medical history	X									
Physical examination [d]	X				X			X		X
Vital signs [e]	X		X		X			X		X
Weight and height [f]	X				X			X		
Prior/Concomitant medications	X	X	X		X	X		X	X	X
Concurrent medical conditions	X									
Hepatitis B and C; HIV [g]	X									
Clinical laboratory tests [h]	X				X			X		X
Pregnancy test [i]	X		X		X			X		
Guidance on avoidance of pregnancy [i]	X		X		X			X		
12-lead electrocardiogram [j]	X							X		
GERD Symptom Assessment-Investigator	X				X			X		
Randomization [k]			X							
Dispense study drug [l]			X		X					
Study drug administration (at clinic) [l]			X		X			X		
Gastric pH monitoring [a]		X	X		X	X				
PK blood sample collection **Day 7**: pre-dose, 0.5 to 1.5 hour and 2.5 to 3.5 hours post dose. **Day 14:** pre-dose, 1 to 2 hours and 3 to 4 hours post dose. [m]					X			X		
Drug return/accountability					X			X		
Telephone call to subject				X			X	~~X~~	X	
AE/pretreatment event assessment [n]	X	X	X		X			X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; HIV: human immunodeficiency virus, PK: pharmacokinetic; PTE: pretreatment event

a For subjects participating in the pharmacodynamic substudy, Visit 2 (Day -1) and Visit 6 (Day 8) are only required for subjects undergoing gastric pH monitoring if clinically indicated at select sites. pH monitoring will be conducted on Day -1 for 24 hours and on Day 7 for 24 hours. pH probes would be placed on Days -1 and 7 and removed on Days 1 and 8.

b At an unscheduled visit, the following procedures are to be completed with additional procedures at the investigator's discretion: a brief physical examination, vital sign measurements, concomitant medication assessment, AE assessment, and clinical laboratory tests. If the visit results in premature termination, then all procedures outlined for the final visit should be performed.

c Informed consent will be signed by the subject's legally authorized representative prior to any activity in the study. Subject assent (if applicable) may be obtained as required per site guidelines.

d A complete physical examination will be performed at screening (at minimum, assessment of skin, cardiovascular, respiratory, gastrointestinal, neurological systems and Tanner staging). A brief physical examination will be performed at other visits (at minimum, assessment of skin, cardiovascular, respiratory, and gastrointestinal systems). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

e Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.

f Height collected only at screening.

g Hepatitis B surface antigen, hepatitis C virus antibody, and HIV type 1 and 2 antibodies.

h Clinical laboratory testing will include hematology, serum chemistry, and urinalysis (if deemed necessary by the PI). Blood draws should follow vital signs or electrocardiograms.

i Only female-born subjects who have reached menarche, will require guidance on avoidance of pregnancy and urine or serum hCG; if urine hCG is positive, confirm with serum hCG.

j Single 12-lead electrocardiogram recordings will be made after the subject has been in the supine position for at least 5 minutes at screening. A pediatric cardiologist will interpret the ECG for eligibility and any abnormality. A single repeat measurement is permitted at screening for eligibility determination after the read by a pediatric cardiologist. Assessments should include comments on whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant). An ECG will be collected at the final visit and interpreted by a pediatric cardiologist.

k Subject will be randomized to study treatment after all eligibility criteria have been met.

l Study drug will be administered in the clinic on Days 1, 7, and 14. Study drug should be taken every day between 7 and 10 am preferably prior to eating any breakfast or food. Study drug for at home administration will be dispensed on Day 1 (to be taken on Days 2 to 6) and Day 7 (to be taken on Days 8 to 13). At home, parents/caregivers will administer study drug to subjects. Clinic staff will review instructions with parents/LARs for administering study drug at home and completing the Study Drug Reminder Card. Phone call reminders may be conducted as required.

m Blood samples for PK analysis of vonoprazan in plasma will be collected on Days 7 and 14. On Day 7 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 0.5 to 1.5 hours post-dose and one between 2.5 to 3.5 hours post-dose. On Day 14 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 1 to 2 hours post-dose and one between 3 to 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded in the source and eCRF.
If a subject terminates early, an attempt should be made to collect one blood sample if it can be collected within 24 hours following the last dose of study drug. The exact date and time of the early termination sample must be recorded.

n Collection of pretreatment events will start after the informed consent form has been signed. Adverse events will be assessed from time of informed consent signing until the follow-up visit and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.