Protocol Number: VPED-102

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 Adolescents with Symptomatic Gastroesophageal Reflux Disease

NCT Number: NCT05343364

Document Date: 16 September 2022

CLINICAL STUDY PROTOCOL

IND NUMBER: 079212

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 Adolescents with Symptomatic Gastroesophageal Reflux Disease

PROTOCOL NO. VPED-102

Sponsor:	Phathom Pharmaceuticals, Inc. 2150 East Lake Cook Road, Suite 800 Buffalo Grove, IL 60089 USA
Sponsor Contact:	[redacted] Vice President Clinical and Patient Safety Telephone: [redacted]
Safety Contact:	[redacted] 24-Hour Safety Hotline: [redacted] 24-Hour Safety Hotline Fax: [redacted] or
Version of Protocol:	Version 3.0, Amendment 2
Date of Protocol:	14 September 2022
Previous Date and Version	11 April 2021, Version 2.0 (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 Adolescents with Symptomatic Gastroesophageal Reflux Disease
Protocol Number	VPED-102
Protocol Version and Date	Version 3.0 14 September 2022

PROTOCOL ACCEPTED AND APPROVED BY:

[redacted]

14-Sep-2022 | 08:33 PDT

[redacted]
Vice President, Clinical and Patient Safety
Phathom Pharmaceuticals, Inc.

Date

[redacted]

14-Sep-2022 | 12:31 CDT

[redacted]
Chief Operating Officer
Phathom Pharmaceuticals, Inc.

Date

[redacted]

16-Sep-2022 | 11:26 CDT

[redacted]
Chief Medical Officer
Phathom Pharmaceuticals, Inc.

Date

[redacted]

14-Sep-2022 | 09:11 CDT

[redacted]
Vice President, Biostatistics & Programming
Phathom Pharmaceuticals, Inc.

Date

[redacted]

14-Sep-2022 | 09:58 CDT

[redacted]
Clinical Pharmacology Consultant
Phathom Pharmaceuticals, Inc.

Date

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 Adolescents with Symptomatic Gastroesophageal Reflux Disease
Protocol Number	VPED-102
Protocol Version and Date	Version 3.0 14 September 2022

Protocol accepted and approved by:

Principal/Coordinating Investigator

[redacted]

[redacted]

14-Sep-2022

Signature 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 Adolescents with 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 Version 3.0, dated 14 September 2022, 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 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

Summary of Changes

Protocol Amendment History and Reasons for Amendment

Version	Date	Reasons for Amendment
Version 1.0	01 November 2021	Original Protocol
Version 2.0 (Protocol Amendment 1)	11 April 2022	• To clarify that subjects must be aged 12 to 17 years, inclusive, at time of informed consent and throughout study participation. • To clarify that only select sites will perform gastric pH monitoring in subjects deemed clinically indicated by the principal investigator. • To add that all study drug doses be taken on an empty stomach. • To add that the time and content of any meals consumed prior to taking study drug on Day 6 or Day 7 be recorded. • To add details for Day 7 dosing with respect to allowed water and meals. • To clarify that Day -1 assessments are only required for subjects undergoing gastric pH monitoring. • To clarify that Day 6 is an optional visit for subjects that check in to the clinic in the evening before starting Day 7 assessments. • Remove the Day 14 pharmacokinetic blood collection. • Remove morphology from electrocardiogram assessments.

Version	Date	Reasons for Amendment
Version 3.0 (Protocol Amendment 2)	14 September 2022	• Increased number of sites from 5 to 12 • Updated information about vonoprazan • Removed duplicate entry for sucralfate under excluded medications and treatments • Removed gastrin and pepsinogen I and II assessments • Removed optional Day 6 visit • Modified strategy to estimate PK parameters to a population based approach; as a result adjusted PK sampling schedule on Day 7, added PK sampling on Day 14, provided information on when time of dosing and meals should be collected and remove $T_{max,ss}$ and $t_{1/2z}$ PK parameters. • Removed required overnight stay for PK sampling due to revised sampling schedule • Added details to the 24-hour gastric pH monitoring • Moved symptom assessments from Day 8 to Day 7 • Updated Schedule of Events and Study Design to reflect above changes

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:	VPED-102
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 Adolescents with Symptomatic Gastroesophageal Reflux Disease
Sponsor:	Phathom Pharmaceuticals, Inc. 2150 East Lake Cook Road, Suite 800 Buffalo Grove, IL 60089 USA
Study Phase:	1
Study Sites:	Approximately 12 sites in the United States
Indication:	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, erosive esophagitis (EE), and Barrett's esophagus. When defining GERD as the presence of at least weekly heartburn and/or regurgitation, epidemiological studies reported prevalence estimates in adults of 18.1% to 27.8%, 8.8% to 25.9%, and 2.5% to 7.8% in North America, Europe, and East Asia, respectively. Two large studies in pediatric patients have reported that 18% experience weekly heartburn and 20% experience GERD symptoms. In addition, an analysis of 1.2 million insurance claims found that the incidence rate of GERD in patients aged 12 to 17 years increased by 34% from 2000 to 2005. Vonoprazan belongs to a new class of acid-inhibitory agents called “potassium-competitive acid blockers”. In the United States, vonoprazan in combination with amoxicillin or 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 and are age-based for adolescents 12 to 17 years of age.

Objectives:

Primary:

- To evaluate the pharmacokinetic profile of vonoprazan (10 or 20 mg once daily [QD]) in adolescent subjects with symptomatic GERD.

Safety:

- To evaluate the safety of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.

Exploratory:

- To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.

Study Population: Subjects 12 to 17 years of age, inclusive, with a medical history of symptoms of GERD for at least 3 months prior to screening.

Study Design: This is a Phase 1, uncontrolled, randomized, open-label, parallel-group, multiple-dose study in adolescents aged 12 to 17 years with 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. A total of 18 subjects will be enrolled into 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 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.

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:	The primary vonoprazan pharmacokinetic endpoints will include the following steady state parameters: • 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	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 • The Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form (PGSQ-A-SF) symptom and impact subscale as assessed by the adolescent at screening and Days 7 and 14 • 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 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 on an empty stomach with approximately 240 mL (8 oz) water between 7 and 10 am each day.

Sample Size:	Approximately 18 subjects will be enrolled with 9 subjects in each dose group. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age. 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 a pediatric population aged 12 to 17 years. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the PK profile.
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. The change from baseline (ie, screening assessment) to Days 7 and 14 in the PGSQ-A-SF symptom and impact subscale, as assessed by the adolescent, will be summarized overall and by vonoprazan dose. 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:	Version 3.0 14 September 2022

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
CFR	Code of Federal Regulations
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
hCG	human chorionic gonadotropin
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
LAR	legally authorized representative
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
PCAB	potassium-competitive acid blocker
PGSQ-A-SF	Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form

Abbreviation	Definition
popPK	population pharmacokinetic
PPI	proton pump inhibitor
PTE	pretreatment event
QD	once daily
SAE	serious adverse event
SoE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
Takeda	Takeda Pharmaceutical Company Limited
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

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 or 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 erosive esophagitis (EE) and relief of heartburn and maintenance of healing of all grades of EE and relief of heartburn.

In other countries, vonoprazan has been studied in additional acid-related diseases including gastric ulcer/duodenal ulcer healing, and for the prevention of recurrence of gastric or duodenal ulcer during nonsteroidal anti-inflammatory drug or aspirin administration. Vonoprazan has received regulatory approval in Japan, Russia, and other countries in Asia and Latin America for a variety of indications.

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 adolescent subjects with symptomatic GERD that provides an exposure similar to the exposures in adults after administration of vonoprazan 10 mg or 20 mg once daily (QD).

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]. Symptoms include heartburn, cough, epigastric pain, vomiting, and regurgitation. The term GERD covers a spectrum of conditions, including symptomatic non-erosive GERD, EE, and Barrett's esophagus.

When defining GERD as the presence of at least weekly heartburn and/or regurgitation, epidemiological studies reported prevalence estimates in adults of 18.1% to 27.8%, 8.8% to 25.9%, and 2.5% to 7.8% in North America, Europe, and East Asia, respectively [El-Serag 2014]. The prevalence of GERD symptoms has risen from 11.6% in 1995 to 1997 to 17.1% in 2006 to 2009 [Ness-Jensen 2012], and awareness of GERD has concomitantly increased in pediatric and adolescent populations [Gold 2002, Nelson 2000]. Two large studies in pediatric patients have reported that 18% experience weekly heartburn and 20% experience GERD symptoms [Chen 2014, Guimaraes 2010, Locke 1997]. In addition, an analysis of 1.2 million insurance claims found that the incidence rate of GERD in patients aged 12 to 17 years increased by 34% from 2000 to 2005 [Nelson 2009].

Typically, management of GERD has included lifestyle changes (eg, diet, weight loss, or sleeping position), over-the-counter antacids, histamine-2 receptor antagonists (H_2RAs), and more recently, proton pump inhibitors (PPIs). Proton pump inhibitors are considered superior to H_2RAs for healing of EE and relief of GERD symptoms and have become the pharmacological mainstay for treatment of adult and adolescent 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 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. It also binds to 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 [Jenkins 2015]. 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 to 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, which showed a rapid rise in pH 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 was 43%, 63%, and 86%, respectively, and by Day 7 was 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 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 there was no evidence of a dose-related increase in adverse effects with vonoprazan from 5 mg to 40 mg QD, and the safety profile of vonoprazan was similar to that of lansoprazole. As of 25 December 2021, the global cumulative postmarketing patient exposure to vonoprazan is estimated to be approximately 70 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 adolescents with 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 and are age-based for adolescents 12 to 17 years of age.

The proposed doses are based on simulations using a population pharmacokinetic (popPK) model. The 2-compartment linear popPK model for vonoprazan was developed with adult

data from 13 studies in healthy volunteers, 1 study in EE patients and 1 study in GERD patients. The final dataset consisted of 1,179 subjects (769 Asian and 410 Western).

For the pediatric dose simulations, the popPK model for vonoprazan was updated to incorporate body size and maturation correction factors, appropriate to predict vonoprazan exposure in infants, children, and adolescents. Different model assumptions in terms of (i) the allometric weight scaling exponent (as estimated in the adult data or fixed at 0.75) and (ii) if or if not to correct for enzyme maturation in infants were compared.

The resulting models were used to simulate posterior distributions of area under the drug concentration-time curve at steady state (AUC_{ss}) in both adults and pediatrics for a series of pediatric candidate doses. Matching pediatric doses were selected to limit the predicted percentage of pediatrics with an exposure exceeding the adult reference exposure (median AUC_{ss}) at 50 to 60%.

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 adolescent subjects with symptomatic GERD.	• $C_{max,ss}$, AUC_{τ}, CL/F, V_z/F
Safety	
• To evaluate the safety of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.	• Adverse events • Laboratory test values (hematology, serum chemistry, urinalysis) • Electrocardiograms • Vital signs
Exploratory	
• To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.	• The severity of GERD symptoms at screening and Days 7 and 14 as assessed by the investigator • The PGSQ-A-SF symptom and impact subscale as assessed by the adolescent at screening and Days 7 and 14 • 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

AUC_{τ}: area under the plasma concentration-time curve during the dosing interval τ; CL/F: apparent oral clearance; $C_{max,ss}$: maximum observed drug concentration at steady state; GERD: gastroesophageal reflux disease; PGSQ A-SF: Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form; QD: once daily; V_z/F: apparent volume of distribution

3 Investigational Plan

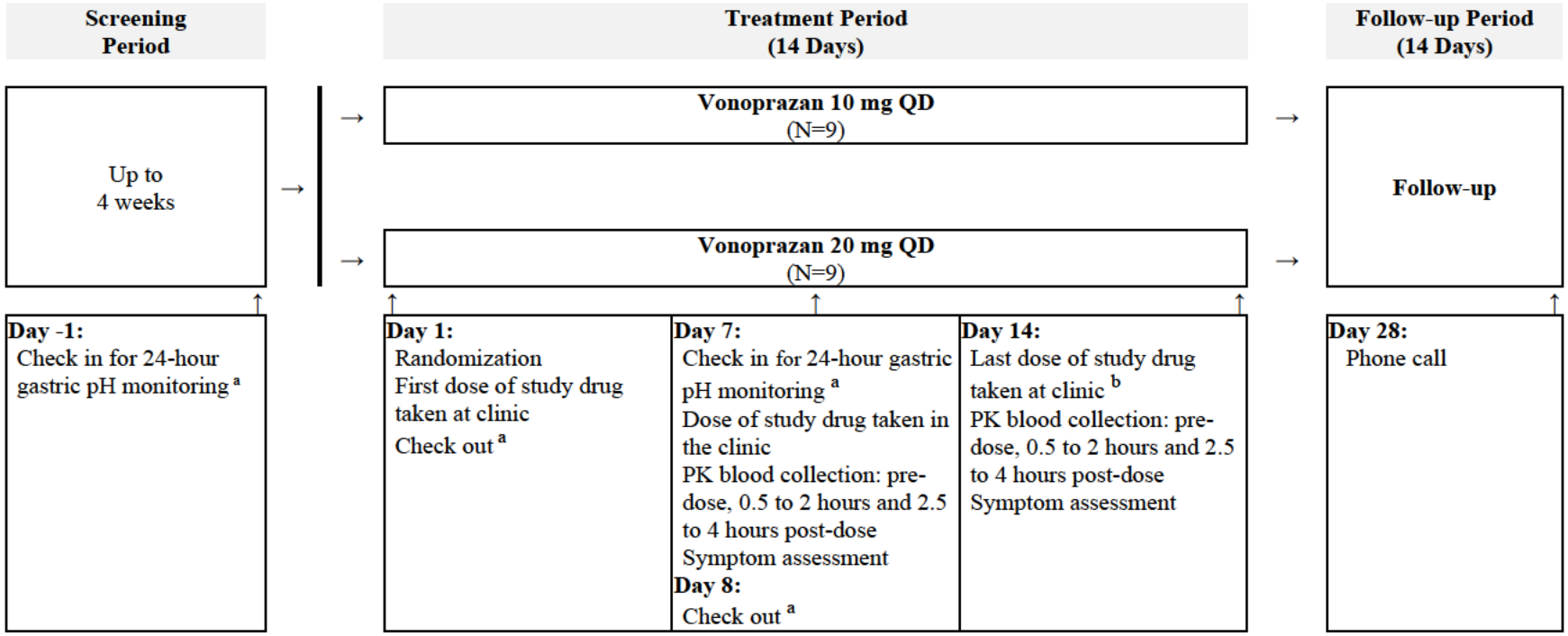
3.1 Study Design

This is a Phase 1, uncontrolled, randomized, open-label, parallel-group, multiple-dose study in adolescents aged 12 to 17 years with 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. A total of 18 subjects will be enrolled into 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.

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

Figure 3-1 Study Scheme



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.

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

Note: Sample sizes are approximate. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age.

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 vonoprazan 10 mg or vonoprazan 20 mg QD.

Follow-up Period (2 weeks): 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 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.

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, 2-dose design was selected to provide unbiased estimates of the vonoprazan pharmacokinetic and safety profile across doses likely to be efficacious. Dose justification is provided in Section 1.3. A placebo control group was not considered practical or ethical in the symptomatic, pediatric population.

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 would suggest that, if effective, the onset of resolution of heartburn in symptomatic GERD pediatric patients would be similar or potentially earlier than PPIs.

This study may include patients with symptomatic GERD, with or without EE. The EE healing rate after 2 weeks of treatment with vonoprazan 20 mg QD was estimated from the results of Study TAK-438/CCT-002, which enrolled adult subjects with endoscopically confirmed EE of Los Angeles Classification Grades A to D. Of the 204 vonoprazan-treated subjects evaluated at Week 2, the majority (90.7%) were healed. Based on these data, the proposed 14-day treatment duration will provide clinical benefit to EE subjects, 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 12 sites in the United States and will randomize 18 subjects (9 subjects per vonoprazan dose group) in the Treatment Period.

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 12 to 17 years of age, inclusive, at the time of informed consent signing and throughout study participation.

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.

3. The subject has a medical history of 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.

4. The subject has symptoms of at least moderate heartburn severity based on the GERD Symptom Assessment-Investigator scale performed at screening.

5. The subject must be able to swallow study drug.

6. Parent or legal guardian (ie, legally authorized representative [LAR]) is willing and able to complete the informed consent process and comply with study procedures and visit schedule. The participating subject will provide assent as applicable.

7. A female subject of childbearing potential who is or may be sexually active with a nonsterilized male partner agrees to routinely use adequate contraception from the signing of informed consent until 2 weeks after the last dose of study drug as detailed in 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 their 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 who 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 such as fundoplication.

9. The subject has any abnormal laboratory test values at the start of 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, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 8000, and titanium oxide, or red or yellow ferric oxide).

11. The subject used any prescription (excluding hormonal birth control) or over-the-counter medications (including CYP3A4 inducers), including herbal or nutritional supplements, 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.

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. Female subject has a positive pregnancy test at screening or check in or is lactating.

14. The subject has a positive urine drug or alcohol result at screening.

15. The subject has positive results at screening for human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus.

16. 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 signs 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 event (PTE), AEs, and any serious adverse events (SAEs).

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

4.1.4 Lifestyle Considerations

Subjects will be instructed to maintain usual food intake, sleep habits, consistent activity, and caffeine intake throughout the study.

Consumption of 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 and throughout the study will be prohibited.

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 the last dose of study drug in the Treatment Period.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects 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 electronic case report form (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 13.3 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 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 Boards (IRBs), 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 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 signs 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 medical record.

- 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

Discontinued or withdrawn subjects will not be replaced.

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 instructed to take randomized study drug orally 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. Any missed doses should be noted by the subject and communicated to clinic staff to record in the eCRF.

For the Days 6 and 13 dose, subjects will note the time it was taken and if they took the dose on an empty stomach. If the dose on Days 6 or 13 was not taken on an empty stomach, the subject is to note the time and content of any meal consumed prior to taking their study drug dose. Clinic staff will record this information in the eCRF.

Subjects will be instructed not to eat any food or take study drug on the mornings of Days 7 14 prior to their arrival at the clinic. If a subject consumes any food prior to arrival, the time and content of the meal is to be noted by the subject and recorded in the eCRF by clinic staff.

On Days 7 and 14, subjects will take their study drug dose in the clinic. 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 meal 30-60 minutes after study drug dosing per the clinic’s standard procedures.

5.3 Identity of Investigational Product

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

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

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Vonoprazan tablets will be distributed 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 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 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 will be assessed by direct questioning and counting returned 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. Treatment start and stop dates will also be recorded in the eCRF.

If subjects exhibit poor compliance as assessed by tablet counts, the LARs and subjects should be counseled on the importance of good compliance to the study dosing regimen.

5.8 Prior and Concomitant Therapy

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.

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	End of treatment
CYP3A4 substrates with a narrow therapeutic index	14 days prior to Day 1	End of treatment
Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy)	30 days prior to Day 1	Follow-up phone call
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

Note: 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.

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 immediately with the principal investigator and the medical monitor 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

Subjects (or parents/caregivers) will be asked to note the exact time they took their study drug dose on Days 6 and 13 and if they took the dose on an empty stomach. If the dose was not taken on an empty stomach, the subject is to note the time and content of any meal consumed prior to taking their study drug dose on Days 6 and 13. Clinic staff will record this information in the eCRF.

Subjects will arrive in the morning on Days 7 and 14 for pharmacokinetic sampling. They should not eat or take the vonoprazan study medication before arriving to the clinic; the time and content of any meal consumed prior to arrival at the clinic is to be recorded in the eCRF by clinic staff. Subjects will be released from 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 those days, one pre-dose sample will be collected prior to the morning administration of vonoprazan. Two additional samples will be collected after drug

administration: one between 0.5 and 2 hours post-dose and one between 2.5 and 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded.

Samples will be collected into appropriate blood collection tubes as specified by the bioanalytical laboratory. Details of blood 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 0.1 to 100 µg/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. 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

If deemed clinically indicated by the principal investigator, gastric pH will be measured and recorded continuously for a 24-hour period on scheduled days 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 will commence 30 to 60 minutes prior to treatment administration. 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). To minimize the discomfort of probe insertion, administration of a topical anesthetic (lidocaine) will be permitted. After each 24-hour recording period, the flashcard will be removed from the recorder and the pH data will be transferred to the computer.

6.2 Efficacy Assessments

6.2.1 Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form Questionnaire

The Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form (PGSQ-A-SF) questionnaire will be administered at the times specified in

Table 13-1. Responses will be recorded directly on each questionnaire. The data from the questionnaires will be entered into the eCRF, and the originals will remain at the site as source documentation.

The symptom subscale measures the number of days over the past 7 days on which subjects experience each individual symptom, where 1=0 days; 2=1 or 2 days; 3=3 or 4 days; 4=5 or 6 days; and 5=every day (7 days). Mean symptom subscale score is the mean of the 7 individual symptom item scores. The impact subscale measures the impact of symptoms on school, family, and social activities in the past 7 days, where 1=never; 2=almost never; 3=sometimes; 4=almost always; and 5=always. Mean impact subscale score is the mean of the 4 individual impact item scores. A copy of the questionnaire is presented in Section 13.4.1.

6.2.2 GERD Symptom Assessment-Investigator

The GERD Symptom Assessment-Investigator scale evaluates 5 symptoms of GERD: heartburn, acid regurgitation, dysphagia, belching and epigastric pain. The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit will be assessed. The severity for each symptom will be recorded on the eCRF as either none, mild, moderate, severe or very severe. For consistency, the assessment should be performed by the same person throughout the study, if possible. Symptom and severity definitions are presented in Section 13.4.2.

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 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 can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or relationship to the 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 in that period.

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:
    a. May require intervention to prevent items 1 through 5 above
    b. May include any event or symptoms described in the medically significant AE list (Table 6-2)
    c. 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 have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >3 × the upper limit of normal (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 13.3).

6.3.1.1.4 Adverse Event 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
Bone fracture

For additional details on liver function monitoring, see Section 13.3.

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 electrocardiogram [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 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 cerebrovascular 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].

[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, IRBs 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 and the IRB, 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 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 the 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, 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, 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 4 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 female subject 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. Note that laboratory tests at screening may be used to assess for alternative etiologies of a subject's symptoms. 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. Total volume of blood to be collected during the study will be documented in the ICF.

All study-required laboratory assessments will be performed by a central laboratory. Investigators must document their review of each laboratory safety report.

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 (fasting) [b] • GGT
Routine urinalysis	• 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	• Urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine per site's standard procedures • Urine alcohol per site's standard procedures • hCG pregnancy test [c] • Serology (HIV antibody, HBsAg, and HCV antibody; hepatitis C, viral load RNA [d] [qualitative])	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; 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 13.3 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.

c Only female subjects with childbearing potential will have urine hCG; if positive, confirm with serum hCG.

d Reflex - if hepatitis C positive.

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 weight.

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and body weight will also be 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 recordings will be made after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at screening 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 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.

6.4 Safety Monitoring Committee

A Safety Monitoring Committee is not planned for this study.

7 Statistical and Analytical Plan

7.1 Sample Size Calculations

Approximately 18 subjects will be enrolled with 9 subjects in each dose group. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age. 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 a pediatric population aged 12 to 17 years. 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

Details of all statistical analyses will be described in a separate statistical analysis plan.

7.3.1 Pharmacokinetic Analyses

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

7.3.2 Efficacy/Pharmacodynamic 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.

The change from baseline to Days 7 and 14 in the PGSQ-A-SF symptom and impact subscale, as assessed by the adolescent, will be summarized overall and by vonoprazan dose.

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 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 vonoprazan dose and overall, as well as by severity and relationship to study drug.

Actual values and changes from baseline to each visit for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by vonoprazan dose at each time point using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results.

7.3.4 Other Analyses

Baseline demographic variables will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. The frequency and percentage of subjects who withdraw or discontinue from the study and the reason for withdrawal or discontinuation will also be summarized.

7.3.5 Interim Analyses

No formal interim analyses will be performed in this study.

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. 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 final 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

Federal regulations and the ICH guidelines require that approval be obtained from an IRB 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. Documentation of all IRB approvals and of the IRB compliance with ICH Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairperson or designee and must identify the IRB 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. The investigator must promptly supply the sponsor or its designee, the IRB, 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.

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 submission. Once reviewed, the consent and assent materials will be submitted by the investigator to his or her IRB 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 but will not result in protocol amendments.

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.

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(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to the following:

- IRB 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
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- 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-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(R2). 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(R2) 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 according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB 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 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.

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 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 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 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 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 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 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 study results will be posted on publicly available clinical trial registers. The investigator is encouraged to share the summary results with the LARs and study subjects, as appropriate.

12 Reference List

Chen JH, Wang HY, Lin HH, Wang CC, Wang LY. Prevalence and determinants of gastroesophageal reflux symptoms in adolescents. J Gastroenterol Hepatol 2014;29(2):269-75.

Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for industry: E6(R2) Good Clinical Practice: Integrated Addendum to E6(R1) March 2018. [cited 2021 Jan 12] Available from: https://www.fda.gov/media/93884/download

El-Serag HB, Sweet S, Winchester CC, Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014;63(6):871-80.

Engevik AC, Kaji I, Goldenring JR. The physiology of the gastric parietal cell. Physiol Rev 2020;100(2):573-602.

Gold BD, Freston JW. Gastroesophageal reflux in children: pathogenesis, prevalence, diagnosis, and role of proton pump inhibitors in treatment. Paediatr Drugs 2002;4(10):673-85.

Gold BD, Gunasekaran T, Tolia V, et al. Safety and symptom improvement with esomeprazole in adolescents with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2007;45(5):520-9.

Gremse D, Winter H, Tolia V, et al. Pharmacokinetics and pharmacodynamics of lansoprazole in children with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2002;35:S319-26.

Guimaraes EV, Guerra PV, Penna FJ. Management of gastroesophageal reflux disease and erosive esophagitis in pediatric patients: focus on delayed-release esomeprazole. Ther Clin Risk Manag 2010;6:531-7.

Gunasekaran T, Gupta S, Gremse D, et al. Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability. J Pediatr Gastroenterol Nutr 2002;35:S327-35.

James L, Walson P, Lomax K, et al. Pharmacokinetics and tolerability of rabeprazole sodium in subjects aged 12 to 16 years with gastroesophageal reflux disease: an open-label, single- and multiple-dose study. Clin Ther 2007;29(9):2082-92.

Jenkins H, Sakurai Y, Nishimura A, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 2015;41(7):636-48.

Kukulka M, Wu J, Perez MC. Pharmacokinetics and safety of dexlansoprazole MR in adolescents with symptomatic GERD. J Pediatr Gastroenterol Nutr 2012;54(1):41–7.

Kukulka M, Nudurupati S, Perez MC. Pharmacokinetics and safety of dexlansoprazole MR in pediatric patients with symptomatic gastroesophageal reflux disease. Clin Exp Gastroenterol 2014;7:461–71.

Li J, Zhao J, Hammer-Maansson JE, et al. Pharmacokinetic properties of esomeprazole in adolescent patients aged 12 to 17 years with symptoms of gastroesophageal reflux disease: a randomized, open label study. Clin Ther 2006;28(3):419-27.

Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112(5):1448-56.

Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during childhood: a pediatric practice-based survey. Pediatric Practice Research Group. Arch Pediatr Adolesc Med 2000;154(2):150–4.

Nelson SP, Kothari S, Wu EQ, Beaulieu N, McHale JM, Dabbous OH. Pediatric gastroesophageal reflux disease and acid-related conditions: trends in incidence of diagnosis and acid suppression therapy. J Med Econ 2009;12(4):348–55.

Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Changes in prevalence, incidence and spontaneous loss of gastro-oesophageal reflux symptoms: a prospective population-based cohort study, the HUNT study. Gut 2012;61(10):1390-7.

Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2018;66(3):516-54.

Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects-a randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42(6):719-30.

Scarpignato C, Hunt RH. The potential role of potassium-competitive acid blockers in the treatment of gastroesophageal reflux disease. Curr Opin Gastroenterol 2019;35(4):344–55.

Scott DR, Munson KB, Marcus EA, Lambrecht NW, Sachs G. The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+ -ATPase. Aliment Pharmacol Ther 2015;42(11-12):1315-26.

Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil 2013;19(1):25-35.

Tolia V, Bishop PR. Tsou VM, et al. Multicenter, randomized, double-blind study comparing 10, 20 and 40 mg pantoprazole in children (5- 11 years) with symptomatic gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2006;42(4):384-91.

Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global, evidence-based consensus. Am J Gastroenterol 2006;101(8):1900-20.

Zannikos PN, Doose DR, Leitz GJ, et al. Pharmacokinetics and tolerability of rabeprazole in children 1 to 11 years old with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2011;52(6):691-701.

Zhao J, Li J, Hammer-Maansson JE, et al. Pharmacokinetic properties of esomeprazole in children aged 1 to 11 years with symptoms of gastroesophageal reflux disease: a randomized, open-label study. Clin Ther 2006;28(11):1868-76.

13 Appendices

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events

	Screening Period		Treatment Period			Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day -1 [a]**	**Day 1**	**Day 7**	**Day 8 [a]**	**ET Day 14**	**Phone Call Day 28**	**Unscheduled Visit [b]**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Informed consent [c]	X							
Inclusion/exclusion criteria	X	X	X					
Demographic and medical history	X							
Smoking status and alcohol use	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		
Concomitant medications	X	X	X	X	X	X	X	X
Concurrent medical conditions	X							
Hepatitis B and C; HIV [g]	X							
Urine drug screen [h]	X							
Clinical laboratory tests [i]	X			X		X		X
Pregnancy test [j]	X			X		X		
Guidance on avoidance of pregnancy	X			X		X		
12-lead electrocardiogram [k]	X			X		X		
GERD Symptom Assessment-Investigator	X			X		X		
PGSQ-A-SF	X			X		X		
Randomization [l]			X					
Dispense study drug [m]			X	X				
Study drug administration [m]			X	X		X		
In-patient check in/out [n]		X	X	X	X			
24 hour Gastric pH monitoring [o]		X		X				
PK blood sample collection [p]				X		X		
Drug return/accountability				X		X		
AE/pretreatment event assessment [q]	X	X	X	X	X	X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus, PGSQ-A-SF: Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form; PK: pharmacokinetic

a Visit 2 and Visit 5 only required for subjects undergoing gastric pH monitoring at select sites.

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). 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 Urine drug/alcohol screen will occur at screening per the site standard procedures.

i Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Glucose will be obtained after an 8-hour fast at all visits. Blood draws should follow vital signs or electrocardiograms.

j Only female subjects with childbearing potential will have urine hCG; if positive, confirm with serum hCG.

k 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 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. 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.

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

m Subjects will self-administer study drug, possibly with assistance from the parent/caregiver. Study drug will be dispensed and administered in the clinic on Days 1, 7, and 14. Study drug for at-home administration will be dispensed on Day 1 (to be taken on Days 2-6) and Day 7 (to be taken on Days 8-13). Study drug should be taken every day between 7 and 10 am on an empty stomach. The exact time of dosing on Day 6 and Day 13, if the dose was taken on an empty stomach should be noted by the subject or parent/caregiver and recorded by clinic staff upon arrival at the clinic. Subjects will be instructed not to eat any food or take study drug on the morning of Days 7 and 14 prior to their arrival at the clinic. If a subject consumes any food prior to the dose on Days 6 and 13 or prior to arrival at the clinic on Days 7 or 14, the time and content of the meal is to be noted and recorded in the eCRF by clinic staff. On Days 7 and 14, water is permitted as desired except for the period 1 hour before and 1 hour after administration of study drug (other than as permitted for study drug dosing). Subjects will be provided a meal 30-60 minutes after study drug dosing on Days 7 and 14 per the clinic's standard procedures.

n Check in on Day -1 and Check out on Day 1 and Check in on Day 7 and Check out on Day 8 (as determined by PI) is only for subjects who will undergo 24-hour gastric pH monitoring.

o Gastric pH monitoring on Day -1 for 24 hours and on Day 7 for 24 hours; only if clinically indicated.

p Blood samples for PK analysis of vonoprazan in plasma will be collected on Days 7 and 14. On both days, one pre-dose sample will be collected prior to the morning administration of vonoprazan and two additional samples will be collected after drug administration: one between 0.5 and 2 hours post-dose and one between 2.5 and 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded in the source and eCRF.

q 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 IU/L 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 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 13-2 at any time during treatment, the study drug should be permanently discontinued:

Table 13-2 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 Pediatric Gastro esophageal Symptom and Quality of Life Questionnaire Adolescent-Short Form Questionnaire

Completed by Children and Adolescents 9-17 Years of Age

Hello!

We would like to know how you have been feeling over the past 7 days. Please answer the following questions. There are no "right" or "wrong" answers. Everyone has different feelings and will answer these questions differently. If you're not sure how to answer a question, just give the best answer you can.

Instructions:

For each question, you will write an "X" in the box, like this: ☒

So every question will have only one box filled in with an "X".

There is no hurry - you can take as long as you need to answer the questions.

** If you have any questions before you begin or while you're answering the questions, please ask! **

Let's Begin.

Turn the page. ☞

1. Read each statement below and tell us on how many days in the past 7 days you had each of these.

In the past 7 days, on how many days did you…	None (0 days)	1 or 2 days	3 or 4 days	5 or 6 days	Everyday (7 days)
a) have hurting or burning in your stomach above your belly button	❒	❒	❒	❒	❒
b) have hurting or burning in your chest	❒	❒	❒	❒	❒
c) have a sore throat or burning in your throat	❒	❒	❒	❒	❒
d) feel sick to your stomach or nauseated like you might throw up	❒	❒	❒	❒	❒
e) taste throw up in your mouth	❒	❒	❒	❒	❒
f) burp a lot	❒	❒	❒	❒	❒
g) have trouble falling asleep because of any of these problems	❒	❒	❒	❒	❒

Go to the next page.☞

Please Read:

We have a few questions for you about how your stomach/chest/throat problems may have affected your

EVERYDAY LIFE. There are no "right" or "wrong" answers.

By "stomach/chest/throat" problems, we mean things like stomach pain, chest pain, throat pain, throwing up, and all of the things listed on the previous pages.

---

2. Please read each statement below and tell us how often you felt that way in the past 7 days.

In the past 7 days…	Never	Almost never	Sometimes	Almost always	Always
a) because of my stomach/chest/throat problems, I **didn't feel like doing anything**	❒	❒	❒	❒	❒
b) because of my stomach/chest/throat problems, I **couldn't eat what I wanted**	❒	❒	❒	❒	❒
c) because of my stomach/chest/throat problems, I **couldn't drink what I wanted**	❒	❒	❒	❒	❒
d) because of my stomach/chest/throat problems, I was in a **bad mood**	❒	❒	❒	❒	❒

You're finished!

Thank you for filling out this questionnaire!

13.4.2 GERD Symptom Assessment-Investigator

The following 5 symptoms of GERD will be evaluated.

Symptom	Definition
Heartburn	A burning feeling in the mid-epigastric area and/or chest
Acid regurgitation	Flow of sour or bitter fluid into the mouth
Dysphagia	Difficulty in swallowing
Belching	The voiding of gas from the stomach through the mouth, which may have been associated with acid regurgitation
Epigastric pain	Central upper abdominal pain

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: 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.

13.5.1 Protocol Amendment 1

Synopsis (Study Population)

Subjects 12 to 17 years of age, inclusive, with a medical history of symptoms of GERD for at least 3 months prior to screening.

Synopsis (Study Design)

Subjects will be confined to the clinic for pharmacokinetic testing. Blood samples for pharmacokinetic testing will be collected on Day 7 for 24 hours. Select sites will perform gastric pH monitoring in subjects ~~if~~ deemed clinically indicated by the principal investigator~~,~~. ~~g~~Gastric pH ~~may~~ will be monitored for 24 hours beginning on Day -1 and on Day 7.

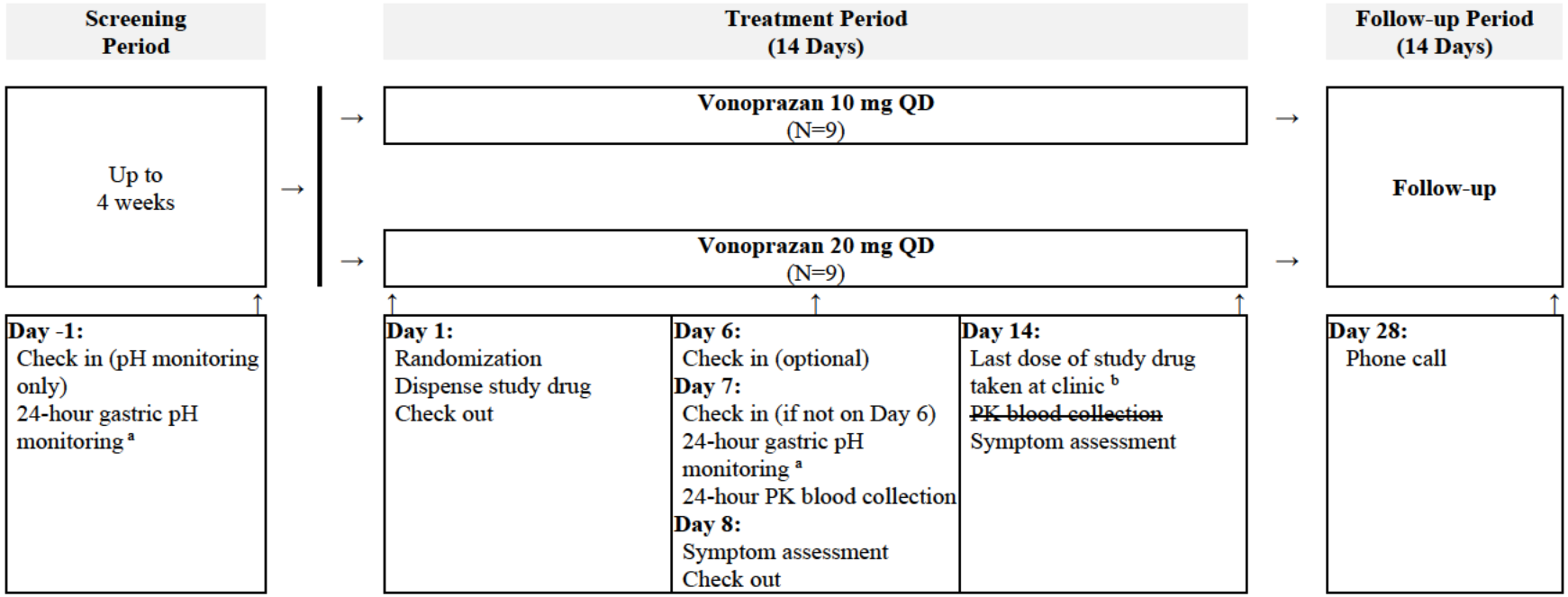
Synopsis (Study Drug, Dosage, and Route of Administration)

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 with approximately 240 mL (8 oz) water between 7 and 10 am each day.

Study Design (Section 3.1)

Subjects will be confined to the clinic for pharmacokinetic testing. Blood samples for pharmacokinetic testing will be collected on Day 7 for 24 hours. Select sites will perform gastric pH monitoring in subjects ~~if~~ deemed clinically indicated by the principal investigator~~,~~. ~~g~~Gastric pH ~~may~~ will be monitored for 24 hours beginning on Day -1 and on Day 7.

Figure 3-1 Study Scheme



PK: pharmacokinetic; QD: once daily

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

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

Note: Sample sizes are approximate. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age.

Inclusion Criteria (Section 4.1.1)

1. The subject is 12 to 17 years of age, inclusive, at the time of informed consent signing and throughout study participation.

Lifestyle Considerations (Section 4.1.4)

Consumption of 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 and throughout the study will be prohibited.

Treatments Administered (Section 5.2)

Subjects will be instructed to take randomized study drug orally each morning between 7 and 10 am on an empty stomach with approximately 240 mL (8 oz) water ~~between 7 and 10 am daily~~. Subjects will take study drug at the clinic on Days 1, 7, 8, and 14; otherwise, study drug will be taken on an outpatient basis. Any missed doses should be noted by the subject and communicated to clinic staff to record in the eCRF.

For the Day 6 dose, subjects will note the time it was taken and if they took the dose on an empty stomach. If the dose was not taken on an empty stomach, the subject is to note the time and content of any meal consumed prior to taking their study drug dose on Day 6. Clinic staff will record this information in the eCRF.

Subjects who do not check in to the clinic on the optional Day 6 visit will be instructed not to eat any food or take study drug on the morning of Day 7 prior to their arrival at the clinic. If a subject consumes any food prior to arrival, the time and content of the meal is to be noted by the subject and recorded in the eCRF by clinic staff.

On Day 7, subjects will take their study drug dose in the clinic. Water is permitted as desired, except for 1 hour before and 1 hour after administration (other than is permitted for study drug dosing). Subjects will be provided a meal 30-60 minutes after study drug dosing per the clinic's standard procedures.

Pharmacokinetic Assessments (Section 6.1.1)

Subjects (or parents/caregivers) will be asked to ~~record~~ note the exact time they took their study drug dose on Day 6 and if they took the dose on an empty stomach. If the dose was not taken on an empty stomach, the subject is to note the time and content of any meal consumed prior to taking their study drug dose on Day 6. Clinic staff will record this information in the eCRF.

Subjects may either return to the clinic in the evening of Day 6 or in the morning on Day 7 (before 7 am) for pharmacokinetic sampling on Day 7. If subjects return to the clinic in the morning on Day 7, they should not eat or take the vonoprazan study medication before returning to the clinic; the time and content of any meal consumed prior to arrival at the clinic is to be recorded in the eCRF by clinic staff. Subjects will be released from the clinic on Day 8 after pharmacokinetic sampling and study procedures are completed. ~~On Day 14, subjects will return to the clinic between 7 and 10 am for a predose pharmacokinetic sample.~~

Blood samples for pharmacokinetic analysis of vonoprazan in plasma will be collected on Day 7 within 30 minutes prior to the morning administration of vonoprazan and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after drug administration. ~~for the assessment of steady state. On Day 14, a single pharmacokinetic sample will be collected within 30 minutes prior to the morning administration of vonoprazan.~~ Pharmacokinetic sampling should be timed to occur last and as close to the scheduled time window as possible.

Electrocardiograms (Section 6.3.6)

A single, standard 12-lead ECG recordings will be made after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at screening 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 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; ~~morphology;~~ any evidence of myocardial infarction; and ST-segment, T-wave, and U-wave abnormalities.

Table 13-1 Schedule of Events

	Screening Period		Treatment Period				Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day -1 [a]**	**Day 1**	**Day 6 [b]**	**Day 7**	**Day 8**	**ET Day 14**	**Phone Call Day 28**	**Unscheduled Visit [ac]**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	
Informed consent [bd]	X								
Inclusion/exclusion criteria	X	X	X						
Demographic and medical history	X								
Smoking status and alcohol use	X								
Medication history	X								
Physical examination [ce]	X					X	X		X
Vital signs [df]	X		X			X	X		X
Weight and height [eg]	X					X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X								
Hepatitis B and C; HIV [fh]	X								
Urine drug screen [gi]	X								
Clinical laboratory tests [hj]	X					X	X		X
Serum gastrin/pepsinogen I and II levels [ik]			X			X	X		
Pregnancy test [jl]	X					X	X		
Guidance on avoidance of pregnancy	X					X	X		
12-lead electrocardiogram [km]	X					X	X		
GERD Symptom Assessment-Investigator	X					X	X		
PGSQ-A-SF	X					X	X		
Randomization [ln]			X						
Dispense study drug [mo]			X			X			
Study drug administration (at home) [mo]				X					
Study drug administration (at clinic) [mo]			X		X	X	X		
In-patient check in [np]		X ~~(pH only)~~		X ~~(optional)~~	X (by 7 am)				
In-patient check out [np]			X (pH only)			X			
Gastric pH monitoring [eq]		X			X				
PK blood sample collection [pr]					X		~~X~~		
Drug return/accountability					X		X		
AE/pretreatment event assessment [qs]	X	X	X	X	X	X	X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus, PGSQ-A-SF: Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form; PK: pharmacokinetic

a Visit 2 (Day -1) is only required for subjects undergoing gastric pH monitoring at select sites.

b Visit 4 (Day 6) is an optional visit for subjects that check in to the clinic in the evening before starting Day 7 assessments.

~~a~~c 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.

~~b~~d 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.

~~c~~e A complete physical examination will be performed at screening (at minimum, assessment of skin, cardiovascular, respiratory, gastrointestinal, and neurological systems). 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.

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

~~e~~g Height collected only at screening.

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

~~g~~i Urine drug/alcohol screen will occur at screening per the site standard procedures.

~~h~~j Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Glucose will be obtained after an 8-hour fast at all visits. Blood draws should follow vital signs or electrocardiograms.

~~i~~k Subject should be fasting for 12 hours. Blood sample for gastrin will be collected prior to study drug dosing.

~~j~~l Only female subjects with childbearing potential will have urine hCG; if positive, confirm with serum hCG.

~~k~~m 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 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. 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; ~~morphology;~~ any evidence of myocardial infarction; and ST-segment, T-wave, and U-wave abnormalities.

~~l~~n Subject will be randomized to study treatment after all eligibility criteria have been met.

~~m~~o Subjects will self-administer study drug, possibly with assistance from the parent/caregiver. Study drug will be dispensed and administered in the clinic on Days 1, 7, 8 and 14. Study drug for at-home administration will be dispensed on Day 1 (to be taken on Days 2-6) and Day 8 (to be taken on Days 9-13). Study drug should be taken every day between 7 and 10 am on an empty stomach. The exact time of dosing on Day 6 and if the dose was taken on an empty stomach should be noted by the subject or parent/caregiver and recorded by clinic staff upon arrival at the clinic. Subjects who do not check in to the clinic on the optional Day 6 visit will be instructed not to eat any food or take study drug on the morning of Day 7 prior to their arrival at the clinic. If a subject consumes any food prior to the dose on Day 6 or prior to arrival at the clinic on Day 7, the time and content of the meal is to be noted and recorded in the eCRF by clinic staff. On Day 7, water is permitted as desired except for the period 1 hour before and 1 hour after administration of study drug (other than as permitted for study drug dosing). Subjects will be provided a meal 30-60 minutes after study drug dosing on Day 7 per the clinic's standard procedures.

~~n~~p Check in on Day -1 is only for subjects who will undergo 24-hour gastric pH monitoring. Subjects may check in on Day 6 or Day 7 (as determined by site). Day 7 check in must occur no later than 7 am.

~~o~~q Gastric pH monitoring on Day -1 for 24 hours and on Day 7 for 24 hours; only if clinically indicated.

~~p~~r Blood samples for PK analysis of vonoprazan in plasma will be collected on Day 7 within 30 minutes prior to the morning administration of vonoprazan and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after drug administration ~~for the assessment of steady state. On Day 14, a single PK sample within 30 minutes prior to the morning administration of vonoprazan.~~ PK sampling should be timed to occur last and as close to the scheduled time window as possible.

~~e~~s 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.

13.5.2 Protocol Amendment 2

Synopsis (Study Sites)

Approximately ~~5~~ 12 sites in the United States

Synopsis (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, erosive esophagitis (EE), and Barrett's esophagus. When defining GERD as the presence of at least weekly heartburn and/or regurgitation, epidemiological studies reported prevalence estimates in adults of 18.1% to 27.8%, 8.8% to 25.9%, and 2.5% to 7.8% in North America, Europe, and East Asia, respectively. Two large studies in pediatric patients have reported that 18% experience weekly heartburn and 20% experience GERD symptoms. In addition, an analysis of 1.2 million insurance claims found that the incidence rate of GERD in patients aged 12 to 17 years increased by 34% from 2000 to 2005.

Vonoprazan belongs to a new class of acid-inhibitory agents called “potassium-competitive acid blockers”. In the United States, vonoprazan in combination with amoxicillin or 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~~, and treatment of *Helicobacter pylori* infection~~.

The pediatric doses for this study were selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD and are age-based for adolescents 12 to 17 years of age.

Synopsis (Study Design)

This is a Phase 1, uncontrolled, randomized, open-label, parallel-group, multiple-dose study in adolescents aged 12 to 17 years with 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. A total of 18 subjects will be enrolled into the study.

~~Subjects will be confined to the clinic for pharmacokinetic testing.~~ Blood samples for pharmacokinetic testing will be collected on Days 7 and 14 ~~for 24 hours~~. 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 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.

Synopsis (Study Pharmacokinetic Assessments)

The primary vonoprazan pharmacokinetic endpoints will include the following steady state parameters ~~measured on Day 7~~:

- Maximum observed drug concentration at steady state ($C_{max,ss}$)
- Area under the plasma concentration-time curve during the dosing interval τ (AUC_{τ})
- ~~Time at steady state to reach $C_{max,ss}$ ($T_{max,ss}$)~~
- ~~Terminal elimination half-life ($t_{1/2z}$)~~
- Apparent oral clearance (CL/F)
- Apparent volume of distribution (V_z/F)

Synopsis (Efficacy and Pharmacodynamic Assessments)

Efficacy and pharmacodynamic characteristics will be assessed by the following:

- The severity of GERD symptoms at screening and Days ~~8~~7 and 14 as assessed by the investigator
- The Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form (PGSQ-A-SF) symptom and impact subscale as assessed by the adolescent at screening and Days ~~8~~7 and 14
- 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

Synopsis (Safety Assessments)

Safety will be assessed by the following:

- AEs
- Laboratory test values (hematology, serum chemistry, urinalysis)
- ~~Serum gastrin and pepsinogen I and II levels~~
- Electrocardiograms
- Vital sign

Synopsis (Sample Size)

Approximately 18 subjects will be enrolled with 9 subjects in each dose group. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age. 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 a pediatric population aged 12 to 17 years. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the PK profile.

Synopsis (Statistical Methods)

Pharmacokinetic Endpoints:
Individual pharmacokinetic ~~parameters on Day 7~~ parameter estimates will be summarized descriptively by vonoprazan dose. ~~Descriptive statistics will include number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, geometric coefficient of variation, median, minimum, and maximum, as appropriate.~~
Efficacy and Pharmacodynamic Endpoints:
The severity of GERD symptoms at screening and Days ~~8~~7 and 14, as assessed by the investigator, will be summarized overall and by vonoprazan dose.
The change from baseline (ie, screening assessment) to Days ~~8~~7 and 14 in the PGSQ-A-SF symptom and impact subscale, as assessed by the adolescent, will be summarized overall and by vonoprazan dose.
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, ~~gastrin and pepsinogen I and II levels,~~ electrocardiograms, and vital signs will be summarized with descriptive statistics at each time point by treatment group.

Introduction (Section 1)

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 or 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 erosive esophagitis (EE) and relief of heartburn~~,~~ and maintenance of healing of all grades of EE ~~and relief of heartburn, and treatment of *Helicobacter pylori* infection~~.

In other countries, vonoprazan has been studied in additional acid-related diseases including gastric ulcer/duodenal ulcer healing, and for the prevention of recurrence of gastric or duodenal ulcer during nonsteroidal anti-inflammatory drug or aspirin administration. Vonoprazan has received regulatory approval in Japan, Russia, and other countries in Asia and Latin America for a variety of indications.

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.

Vonoprazan (Section 1.1.1)

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 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 a~~ctive and inactive~~ proton pumps: Vonoprazan inhibits acid secretion by competitively inhibiting the binding of potassium ions to the H+, K+-ATPase. Vonoprazan may selectively concentrate~~s~~ in the parietal cells in both the resting and stimulated state~~s~~, . It also binds to ~~the~~ active pumps in a noncovalent and reversible manner~~, and remains associated with the active and inactive pumps~~. 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 [Jenkins 2015]. This is significantly longer than the half-life of conventional PPIs (<2 hours) [Shin 2013].

- Metabolism: Vonoprazan is ~~predominantly~~ metabolized by a combination of cytochrome P450 (CYP) isoforms including CYP3A4/5, which does not have ~~lacks~~ a high degree of genetic polymorphism as compared ~~with~~to 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, which showed a rapid rise in pH 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 was 43%, 63%, and 86%, respectively, and by Day 7 was 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 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 there was no evidence of a dose-related increase in adverse effects with vonoprazan from 5 mg to 40 mg QD, and the safety profile of vonoprazan was similar to that of lansoprazole. As of ~~16 June~~25 December 2021, the global cumulative postmarketing patient exposure to vonoprazan is estimated to be over ~~68~~70 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 adolescents with GERD.

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 adolescent subjects with symptomatic GERD.	• $C_{max,ss}$, AUC_{τ}, ~~$T_{max,ss}$, $t_{1/2z}$,~~ CL/F, V_z/F ~~on Day 7~~
Safety	
• To evaluate the safety of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.	• Adverse events • Laboratory test values (hematology, serum chemistry, urinalysis) • ~~Serum gastrin and pepsinogen I and II levels~~ • Electrocardiograms • Vital signs
Exploratory	
• To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg QD) in adolescent subjects with symptomatic GERD.	• The severity of GERD symptoms at screening and Days ~~8~~7 and 14 as assessed by the investigator • The PGSQ-A-SF symptom and impact subscale as assessed by the adolescent at screening and Days ~~8~~7 and 14 • 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

AUC_{τ}: area under the plasma concentration-time curve during the dosing interval τ; CL/F: apparent oral clearance; $C_{max,ss}$: maximum observed drug concentration at steady state; GERD: gastroesophageal reflux disease; PGSQ A-SF: Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form; QD: once daily; ~~$t_{1/2z}$: terminal elimination half-life; $T_{max,ss}$: time at steady state to reach $C_{max,ss}$;~~ V_z/F: apparent volume of distribution

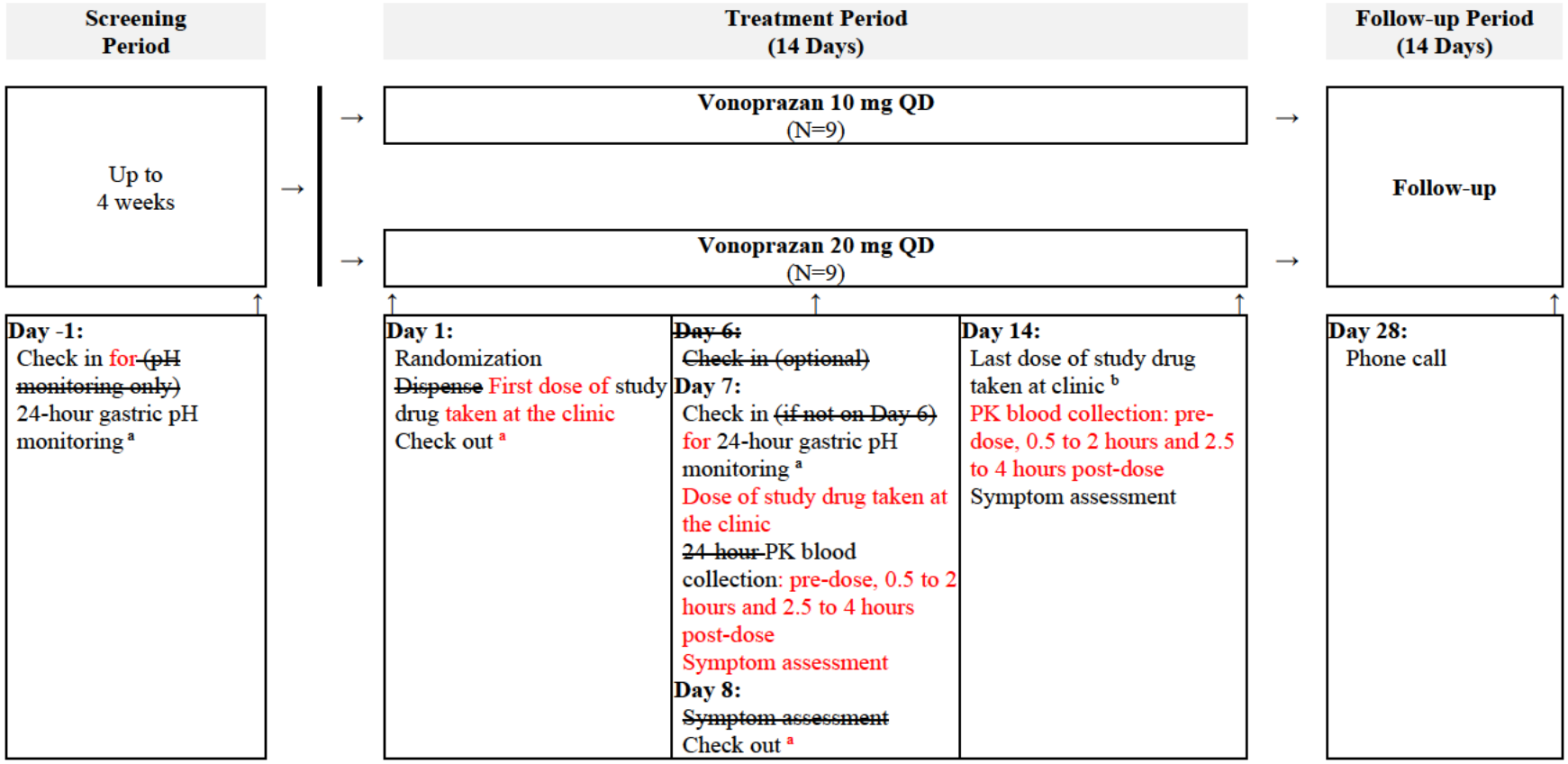
Study Design (Section 3.1)

This is a Phase 1, uncontrolled, randomized, open-label, parallel-group, multiple-dose study in adolescents aged 12 to 17 years with 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. A total of 18 subjects will be enrolled into the study.

~~Subjects will be confined to the clinic for pharmacokinetic testing.~~ Blood samples for pharmacokinetic testing will be collected on Days 7 and 14~~for 24 hours~~. 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.

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

Figure 3-1 Study Scheme



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.

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

Note: Sample sizes are approximate. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age.

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 vonoprazan 10 mg or vonoprazan 20 mg QD.

Follow-up Period (2 weeks): 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 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.

Selection of Study Population (Section 4.1)

This study will be conducted at approximately ~~5~~12 sites in the United States and will randomize 18 subjects (9 subjects per vonoprazan dose group) in the Treatment Period.

Exclusion Criteria (Section 4.1.2)

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

Treatments administered (Section 5.2)

Subjects will be instructed to take randomized study drug orally 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,~~ 8,~~ and 14; otherwise, study drug will be taken on an

outpatient basis. Any missed doses should be noted by the subject and communicated to clinic staff to record in the eCRF.

For the Days 6 and 13 dose, subjects will note the time it was taken and if they took the dose on an empty stomach. If the dose was not taken on an empty stomach, the subject is to note the time and content of any meal consumed prior to taking their study drug dose ~~on Day 6.~~ Clinic staff will record this information in the eCRF.

Subjects ~~who do not check in to the clinic on the optional Day 6 visit~~ will be instructed not to eat any food or take study drug on the mornings of Days 7 and 14 prior to their arrival at the clinic. If a subject consumes any food prior to arrival, the time and content of the meal is to be noted by the subject and recorded in the eCRF by clinic staff.

On Days 7 and 14, subjects will take their study drug dose in the clinic. 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 meal 30-60 minutes after study drug dosing per the clinic's standard procedures.

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
CYP3A4 substrates with a narrow therapeutic index	14 days prior to Day 1	End of treatment
Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy)	30 days prior to Day 1	Follow-up phone call
Other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth~~, sucralfate~~	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
Note: 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.

Pharmacokinetic Assessments (Section 6.1.1)

Subjects (or parents/caregivers) will be asked to note the exact time they took their study drug dose on Days 6 and 13 and if they took the dose on an empty stomach. If the dose was not taken on an empty stomach, the subject is to note the time and content of any meal consumed prior to taking their study drug dose on Days 6 and 13. Clinic staff will record this information in the eCRF.

Subjects ~~may either return to the clinic in the evening of Day 6 or~~ will arrive in the morning on Days 7 and 14 ~~(before 7 am)~~ for pharmacokinetic sampling. ~~on Day 7. If subjects return to~~

~~the clinic in the morning on Day 7, they~~ They should not eat or take the vonoprazan study medication before arriving ~~returning~~ to the clinic; the time and content of any meal consumed prior to arrival at the clinic is to be recorded in the eCRF by clinic staff. Subjects will be released from the clinic ~~on Day 8~~ 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. ~~within 30 minutes~~ On each of those days, one pre-dose sample will be collected prior to the morning administration of vonoprazan ~~and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after drug administration~~. ~~Pharmacokinetic sampling~~ Two additional samples will be collected after drug administration: one between 0.5 and 2 hours post-dose and one between 2.5 and 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded. ~~timed to occur last and as close to the scheduled time window as possible.~~

Samples will be collected into appropriate blood collection tubes as specified by the bioanalytical laboratory. Details of blood 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 0.1 to 100 µg/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 ~~derived~~ estimated using a non-linear mixed effects model ~~compartmental analysis methods~~ and will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than

scheduled or nominal sampling times, will be used in all computations using sampling time. Additional pharmacokinetic parameters may be ~~calculated~~ estimated as appropriate.

Table 6-1 Pharmacokinetic Parameters to be ~~Calculated~~ Estimated using Vonoprazan Plasma Concentration ~~time~~ 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)
~~T_{max}~~	~~Time to reach C_{max}~~
~~$t_{1/2z}$~~	~~Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$~~
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 deemed clinically indicated by the principal investigator, gastric pH will be ~~determined~~ measured and recorded continuously for a 24-hour period on scheduled days 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 ~~monitored for 24 hours, as outlined in the SoE (Section 13.1)~~ sampled and recorded every 5 seconds. The 24-hour continuous pH recording session will commence 30 to 60 minutes prior to treatment administration. 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). To minimize the discomfort of probe insertion, administration of a topical anesthetic (lidocaine) will be permitted. After each 24-hour recording period, the flashcard will be removed from the recorder and the pH data will be transferred to the computer.

Adverse Event 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 6-3.

Table 6-3 Adverse Events of Special Interest List

Term
Hepatotoxicity
Severe cutaneous adverse reactions, including hypersensitivity
Clostridium difficile infections and pseudomembranous colitis
~~Hypergastrinemia~~
Bone fracture

Laboratory Analyses (Section 6.3.3)

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 (fasting) [b] • GGT
Routine urinalysis	• Specific gravity, appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)	
~~Serum gastrin and serum pepsinogen I and II levels~~	• ~~Measured as safety/pharmacodynamic biomarkers at Days 1 (prior to study drug dosing), 8, and 14 after fasting for 12 hours.~~	
Other screening tests	• Urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine per site's standard procedures • Urine alcohol per site's standard procedures • hCG pregnancy test [c] • Serology (HIV antibody, HBsAg, and HCV antibody; hepatitis C, viral load RNA [d] [qualitative])	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; 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 13.3 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.

c Only female subjects with childbearing potential will have urine hCG; if positive, confirm with serum hCG.

d Reflex - if hepatitis C positive.

Sample Size Calculation (Section 7.1)

Approximately 18 subjects will be enrolled with 9 subjects in each dose group. Attempts will be made to enroll an equal number of subjects between 12 to 15 and 16 to 17 years of age. 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 a pediatric population aged 12 to 17 years. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the PK profile.

Pharmacokinetic Analyses (Section 7.3.1)

~~Plasma concentration data will be summarized by time point for each vonoprazan dose using the following descriptive statistics: number of subjects, arithmetic mean, standard deviation, coefficient of variation, geometric mean, geometric coefficient of variation, median, minimum, and maximum, as appropriate.~~

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

Efficacy/Pharmacodynamic Analyses (Section 7.3.2)

The severity of GERD symptoms at baseline and Days ~~8~~7 and 14, as assessed by the investigator, will be summarized overall and by vonoprazan dose.

The change from baseline to Days ~~8~~7 and 14 in the PGSQ-A-SF symptom and impact subscale, as assessed by the adolescent, will be summarized overall and by vonoprazan dose.

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.

Schedule of Events (Section 13.1)

Table 13-1 Schedule of Events

	Screening Period		Treatment Period				Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day -1 [a]**	**Day 1**	**~~Day 6~~ [b]**	**Day 7**	**Day 8 [a]**	**ET Day 14**	**Phone Call Day 28**	**Unscheduled Visit [cb]**
Visit Number:	**1**	**2**	**3**	**~~4~~**	**~~5~~ 4**	**~~6~~5**	**~~7~~ 6**	**~~8~~7**	
Informed consent [dc]	X								
Inclusion/exclusion criteria	X	X	X						
Demographic and medical history	X								
Smoking status and alcohol use	X								
Medication history	X								
Physical examination [ed]	X				X	~~X~~	X		X
Vital signs [fe]	X		X		X	~~X~~	X		X
Weight and height [gf]	X				X	~~X~~	X		
Concomitant medications	X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X								
Hepatitis B and C; HIV [hg]	X								
Urine drug screen [ih]	X								
Clinical laboratory tests [j]	X				X	~~X~~	X		X
~~Serum gastrin/pepsinogen I and II levels [k]~~			~~X~~			~~X~~	~~X~~		
Pregnancy test [lj]	X				X	~~X~~	X		
Guidance on avoidance of pregnancy	X				X	~~X~~	X		
12-lead electrocardiogram [mk]	X				X	~~X~~	X		
GERD Symptom Assessment-Investigator	X				X	~~X~~	X		
PGSQ-A-SF	X				X	~~X~~	X		
Randomization [nl]			X						
Dispense study drug [om]			X		X	~~X~~			
~~Study drug administration (at home) [p]~~				~~X~~					
Study drug administration (at clinic) [om]			X		X	X	X		
~~In-patient check in [p]~~		~~X~~		~~X~~	~~X (by 7 am)~~				
In-patient check in/out [pn]		X	X ~~(pH only)~~		X	X			
Gastric pH monitoring [qo]		X			X				
PK blood sample collection [rp]					X		X		
Drug return/accountability					X		X		
AE/pretreatment event assessment [sq]	X	X	X	~~X~~	X	X	X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus, PGSQ-A-SF: Pediatric Gastro-esophageal Symptom and Quality of Life Questionnaire-Adolescent-Short Form; PK: pharmacokinetic

a Visit 2 ~~(Day -1)~~ and Visit 5 is only required for subjects undergoing gastric pH monitoring at select sites.

~~b Visit 4 (Day 6) is an optional visit for subjects that check in to the clinic in the evening before starting Day 7 assessments.~~

~~c~~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.

~~d~~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.

~~e~~d A complete physical examination will be performed at screening (at minimum, assessment of skin, cardiovascular, respiratory, gastrointestinal, and neurological systems). 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.

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

~~g~~f Height collected only at screening.

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

~~i~~h Urine drug/alcohol screen will occur at screening per the site standard procedures.

~~j~~i Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Glucose will be obtained after an 8-hour fast at all visits. Blood draws should follow vital signs or electrocardiograms.

~~k Subject should be fasting for 12 hours. Blood sample for gastrin will be collected prior to study drug dosing.~~

~~l~~j Only female subjects with childbearing potential will have urine hCG; if positive, confirm with serum hCG.

~~m~~k 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 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. 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.

~~n~~l Subject will be randomized to study treatment after all eligibility criteria have been met.

~~o~~m Subjects will self-administer study drug, possibly with assistance from the parent/caregiver. Study drug will be dispensed and administered in the clinic on Days 1, 7~~, 8~~ and 14. Study drug for at-home administration will be dispensed on Day 1 (to be taken on Days 2-6) and Day ~~8~~7 (to be taken on Days 8~~9~~-13). Study drug should be taken every day between 7 and 10 am on an empty stomach. The exact time of dosing on Day 6 and Day 13 and if the dose was taken on an empty stomach should be noted by the subject or parent/caregiver and recorded by clinic staff upon arrival at the clinic. Subjects ~~who do not check in to the clinic on the optional Day 6 visit~~ will be instructed not to eat any food or take study drug on the morning of Days 7 and 14 prior to their arrival at the clinic. If a subject consumes any food prior to the dose on Days 6 and 13 or prior to arrival at the clinic on Days 7 and 14, the time and content of the meal is to be noted and recorded in the eCRF by clinic staff. On Days 7 and 14, water is permitted as desired except for the period 1 hour before and 1 hour after administration of study drug (other than as permitted for study drug dosing). Subjects will be provided a meal 30-60 minutes after study drug dosing on Days 7 and 14 per the clinic's standard procedures.

~~p~~n Check in on Day -1 and Check out on Day 1 and Check in on Day 7 and Check out on Day 8 (as determined by PI) is only for subjects who will undergo 24-hour gastric pH monitoring. ~~Subjects may check in on Day 6 or Day 7 (as determined by site). Day 7 check in must occur no later than 7 am.~~

~~q~~o Gastric pH monitoring on Day -1 for 24 hours and on Day 7 for 24 hours; only if clinically indicated.

~~r~~p Blood samples for PK analysis of vonoprazan in plasma will be collected on Days 7 and 14. ~~within 30 minutes prior to the morning administration of vonoprazan and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after drug administration. PK sampling should be timed to occur last and as close to the scheduled time window as possible.~~ On both days, one pre-dose sample will be collected prior to the morning administration of vonoprazan and two additional samples will be collected after drug administration: one between 0.5 and 2 hours post-dose and one between 2.5 and 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded in the source and eCRF.

~~s~~q 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.