CLINICAL STUDY PROTOCOL

IND NUMBER: 079212

A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg Compared to Placebo for Relief of Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (NERD) After 4 Weeks and to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg for Relief of Heartburn in Subjects with NERD After 6 Months

PROTOCOL NO. NERD-301

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
Safety Contact:	[redacted]
Version of Protocol:	Version 3.0, Amendment 2
Date of Protocol:	25 April 2022
Previous Date and Version	09 February 2022, Version 2.0 (Amendment 1)

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg Compared to Placebo for Relief of Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (NERD) After 4 Weeks and to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg for Relief of Heartburn in Subjects with NERD After 6 Months
Protocol Number	NERD-301
Protocol Version and Date	Version 3.0 25 April 2022

[redacted]

Protocol Approval – Principal/Coordinating Investigator

Study Title	A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg Compared to Placebo for Relief of Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (NERD) After 4 Weeks and to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg for Relief of Heartburn in Subjects with NERD After 6 Months
Protocol Number	NERD-301
Protocol Version and Date	Version 3.0 25 April 2022

Protocol accepted and approved by:

Principal/Coordinating Investigator

[redacted]

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg Compared to Placebo for Relief of Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (NERD) After 4 Weeks and to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg for Relief of Heartburn in Subjects with NERD After 6 Months" 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 25 April 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 Boards/Independent Ethics Committees 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	28 September 2021	Original Protocol
Version 2.0 (Protocol Amendment 1)	09 February 2022	• To clarify the definition of symptomatic gastroesophageal reflux disease in inclusion criterion #4 • To add an exclusion criterion for active *Helicobacter pylori* infection during the Screening Period • To add collection of coronavirus-19 vaccination history • To clarify that an external biostatistician, not involved in study conduct, will generate the randomization schedule • To update the definition of the intent-to-treat analysis set
Version 3.0 (Protocol Amendment 2)	25 April 2022	• To move the endpoints of the percentage of days without nighttime heartburn and the percentage of days without daytime heartburn over the Placebo-controlled Treatment Period from secondary to exploratory endpoints • To delete the secondary endpoint of the percentage of subjects with onset of sustained resolution of heartburn by Day 3 • To modify the planned analysis of the primary and secondary endpoints to use a general linear model instead of a Wilcoxon rank-sum test • To modify the overall planned significance level for the study from 0.01 to the standard 0.05 • To clarify that the intent-to-treat and safety analysis sets for the Follow-up Period will be defined the same as these sets for the Extension Period • To correct the description of the calculation of the total N-GSSIQ score

Version	Date	Reasons for Amendment
Version 3.0 (Protocol Amendment 2; continued)	25 April 2022	• To clarify test methods for *Helicobacter pylori* infection • To add completion of the Study Subject Informational Questionnaire prior to randomization • To clarify in the Schedule of Events when the first dose of study drug in the Extension Period should be administered

Table of Contents

List of Tables

List of Figures

Protocol Synopsis

Protocol Number:	NERD-301
Title:	A Phase 3, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg Compared to Placebo for Relief of Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease (NERD) After 4 Weeks and to Evaluate the Efficacy and Safety of Vonoprazan 10 and 20 mg for Relief of Heartburn in Subjects with NERD After 6 Months
Sponsor:	Phathom Pharmaceuticals, Inc. 2150 East Lake Cook Road, Suite 800 Buffalo Grove, IL 60089 USA
Study Phase:	3
Study Sites:	Approximately 100 sites in the United States
Indication:	Relief of heartburn associated with NERD
Rationale:	Gastroesophageal reflux disease (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 NERD, 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 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. Vonoprazan belongs to a new class of acid-inhibitory agents called “potassium-competitive acid blockers” and is being developed for healing of all grades of EE and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, treatment of heartburn in NERD, and treatment of *Helicobacter pylori* infection. Vonoprazan at doses ≥10 mg has been shown in both single and multiple repeat-dosing studies to have a rapid onset of action and near maximal effect on pH holding time within 24 hours of dosing, which is maintained with chronic dosing. It is believed that this pharmacologic profile may make it an optimum agent for the treatment of NERD. This study will evaluate the safety and effectiveness of vonoprazan 10 mg and 20 mg to treat heartburn in patients with NERD.

Objectives:

Primary Efficacy:

- To assess the efficacy of vonoprazan (10 mg and 20 mg once daily [QD]) compared to placebo (QD) in relief of heartburn over 4 weeks in subjects with NERD.

Safety:

- To assess the safety of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in subjects with NERD over 4 weeks.
- To assess the long-term safety of vonoprazan (10 mg and 20 mg QD) over 6 months.

Secondary:

- To assess the use of rescue antacid with vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.

Study Population: Subjects ≥18 years of age with NERD confirmed by endoscopy during the Screening Period. Heartburn must be reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary.

Study Design: This is a Phase 3, multicenter, double-blind study of vonoprazan versus placebo assessing the relief of heartburn. Subjects with NERD (as confirmed by endoscopy) and heartburn symptoms will be randomized to receive vonoprazan 10 mg, vonoprazan 20 mg, or placebo QD for 4 weeks. Subjects will complete an electronic diary twice daily to record the presence and maximum severity of daytime and nighttime heartburn symptoms and use of rescue antacid throughout the study. Study-supplied rescue antacid will be allowed. After the Placebo-controlled Treatment Period, all subjects will receive blinded vonoprazan (10 mg or 20 mg QD) in the Extension Period.

Study Design (continued):

The study will include 4 periods:

Screening Period (Day -35 to Day -2): Subjects will provide informed consent and undergo screening assessments to determine study eligibility, and baseline assessment will be performed. Subjects will complete the electronic diary twice daily during the Screening Period. If all eligibility criteria are met, the subject will enter the study.

Placebo-controlled Treatment Period (Day -1 to Day 28): Subjects with NERD whose eligibility is confirmed will be randomized to receive vonoprazan 10 mg or 20 mg or placebo QD for 4 weeks. The date of the first dosing is defined as Day 1. An electronic diary will continue to be completed twice daily during the Placebo-controlled Treatment Period.

Extension Period (Day 29 to Day 169): Subjects randomized to vonoprazan 10 mg or 20 mg in the Placebo-controlled Treatment Period will continue to take the same dose in a blinded manner for an additional 20 weeks. Subjects randomized to placebo in the Placebo-controlled Treatment Period will be re-randomized to receive either vonoprazan 10 mg QD or vonoprazan 20 mg QD for 20 weeks. An electronic diary will continue to be completed twice daily during the Extension Period. The first dose of study drug for the Extension Period will be taken the day after the Week 4 visit.

Follow-up Period: A safety follow-up visit will occur 4 weeks after the last dose of study drug. An electronic diary will continue to be completed twice daily during the Follow-up Period.

A subject will be considered to have completed the study if the subject completes the safety follow-up visit.

Estimated Study Duration:

The total duration of the study is up to 33 weeks. The Screening Period is up to 5 weeks, Placebo-controlled Treatment Period is 4 weeks, Extension Period is 20 weeks, and safety follow-up is 4 weeks after last study drug administration.

Efficacy Assessments:	Primary: • The percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary. Secondary: • The percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary.
Safety Assessments:	Safety will be assessed by the following: • AEs • Laboratory test values (hematology, serum chemistry, urinalysis) • Serum gastrin and pepsinogen I/II levels • Electrocardiograms • Vital signs
Study Drug, Dosage, and Route of Administration:	Placebo-controlled Treatment Period: Blinded study drug (vonoprazan 10 mg, vonoprazan 20 mg, or placebo) to be taken orally QD for 4 weeks. Extension Period: Blinded study drug (vonoprazan 10 mg or vonoprazan 20 mg) to be taken orally QD for 20 weeks.
Sample Size:	A sample size of 250 subjects per treatment group provides greater than 90% power at the 0.05 2-sided level of significance using a two-sample t-test to detect a difference of 20% between a vonoprazan dose (50%) and placebo (30%) in the percentage of days without daytime or nighttime heartburn over the 4-week Placebo-controlled Treatment Period, assuming a common standard deviation of 35%.

Statistical Methods:

Primary Efficacy Endpoint:

For the primary endpoint of the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates.

Secondary Efficacy Endpoints:

For the percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates.

Safety:

Safety data will be summarized separately for the Placebo-controlled Treatment Period and the Extension Period.

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. Separate summaries will also be generated for treatment-related AEs overall and by severity.

Clinical laboratory tests, gastrin and pepsinogen I/II levels, electrocardiograms, and vital signs will be summarized with descriptive statistics at each visit by treatment group.

Version and Date of Protocol: Version 3.0
25 April 2022

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus-19
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
EPS	epigastric pain syndrome
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
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
HCV	hepatitis C virus
H pylori	*Helicobacter pylori*
IBS	irritable bowel syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
NERD	symptomatic non-erosive gastroesophageal reflux disease
N-GSSIQ	Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire
PAGI-QoL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index
PCAB	potassium-competitive acid blocker
PDS	postprandial distress syndrome
PPI	proton pump inhibitor
PSQI	Pittsburgh Sleep Quality Index
PT	preferred term
PTE	pretreatment event
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SOC	system organ class
SoE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
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 addition to the treatment of heartburn in patients with symptomatic non-erosive gastroesophageal reflux disease (NERD), vonoprazan is being developed for healing of all grades of erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *Helicobacter pylori* (*H 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 to develop, manufacture, and commercialize vonoprazan in the United States, Europe, and Canada.

1.1 Study Rationale

Vonoprazan at doses ≥10 mg has been shown in both single and multiple repeat-dosing studies to have a rapid onset of action and near maximal effect on pH holding time within 24 hours of dosing, which is maintained with chronic dosing. It is believed that this pharmacologic profile may make it an optimum agent for the treatment of NERD. This study will evaluate the safety and effectiveness of vonoprazan 10 mg and 20 mg to treat heartburn in patients with NERD.

1.2 Background

1.2.1 Epidemiology, Symptoms, and Current Treatments for NERD

Gastroesophageal reflux disease (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 [Vakil 2006]. The term GERD covers a spectrum of conditions, including NERD, EE, and Barrett's esophagus. The Genval workshop suggested that the definition of

NERD should be reserved for individuals who satisfy the definition of GERD but who do not have either Barrett's esophagus or definite endoscopic esophageal mucosal breaks (erosion or ulceration) [Dent 1999].

When defining GERD as the presence of at least weekly heartburn and/or regurgitation, epidemiological studies reported prevalence estimates 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]. Clinical studies have demonstrated that heartburn severity and intensity are similar in patients with EE and those with NERD [Smout 1997]. The impact of heartburn severity on patients' quality of life was also similar in both EE and NERD [Carlsson 1998, Venables 1997], and sleep dysfunction was also similar [Yi 2007]. In contrast to EE, NERD is mostly viewed as a non-progressive disease and the treatment approach is symptom-driven [Savarino 2017].

To date, proton pump inhibitors (PPIs) have been shown to be the most effective available antisecretory agents for relieving GERD symptoms, healing the injured mucosa, and maintaining a healed mucosa [Freston 2004]. A meta-analysis demonstrated that the relative risk for heartburn remission in placebo-controlled trials of patients with NERD was 0.68 (95% confidence interval [CI]: 0.59-0.78) for PPIs versus placebo [Savarino 2017].

Proton pump inhibitors are recommended for treatment of NERD for 4 to 8 weeks. The 2013 American College of Gastroenterology "Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease" recommends that for patients who require long-term PPI therapy, PPIs should be administered in the lowest effective dose [Katz 2013]. A study of pantoprazole and esomeprazole has shown that in NERD patients the median time to onset of symptom relief is 2 days and median time to sustained symptom relief is 10 to 13 days [Monnikes 2005]. This finding is consistent with the known mechanism of action of PPIs, in which there is a build-up effect on acid suppression after repeated daily dosing.

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 active and inactive proton pumps: Vonoprazan inhibits acid secretion by competitively inhibiting the binding of potassium ions to the H+, K+-ATPase. Vonoprazan selectively concentrates in the parietal cells in both the resting and stimulated states, binds to the active pumps, 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 once daily (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. This is significantly longer than the half-life of conventional PPIs (<2 hours) [Shin 2013].

- Metabolism: Vonoprazan is predominantly metabolized by cytochrome P450 (CYP)3A4/5, which lacks a high degree of genetic polymorphism as compared with CYP2C19, which is the primary enzyme responsible for the metabolism of PPIs [Shin 2013].

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

The pharmacokinetic and pharmacodynamic profiles of vonoprazan were assessed in multiple studies, including Study TAK-438_107, which showed 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 2 studies in Japan to evaluate the treatment of heartburn in subjects with NERD (TAK-438/CCT-201 [Kinoshita 2016] and Vonoprazan-3001 [Kinoshita 2019]). Although there was a trend in favor of vonoprazan for the proportion of heartburn-free days (primary endpoint) between treatment groups, the difference did not reach statistical significance.

Phathom is currently conducting a Phase 2, dose-ranging study in subjects with NERD (NERD-201) to evaluate the potential for vonoprazan as an on-demand therapeutic option for treating heartburn episodes. Subjects receive open-label vonoprazan 20 mg QD during a 4-week Run-In Period. Subjects with stable disease (ie, no heartburn on the last 7 days of the Run-In Period) are randomized to receive either vonoprazan 10 mg, 20 mg, 40 mg, or placebo taken as needed during a 6-week On-Demand Treatment Period.

The safety profile of vonoprazan in Phase 3 studies across indications showed there was no evidence of a dose-related increase in adverse effects with vonoprazan, and the safety profile of vonoprazan was similar to that of lansoprazole. As of 16 June 2021, the global cumulative post-marketing patient exposure to vonoprazan is estimated to be over 68 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 the treatment of heartburn in patients with NERD.

1.3 Justification for Dose

Selection of the vonoprazan 10 mg and 20 mg doses for the Placebo-controlled Treatment Period and Extension Period is based on a 7-day multiple repeat-dose study conducted by Takeda in healthy subjects administered vonoprazan 10 mg, 20 mg, 30 mg, and 40 mg. In this study, intragastric pH was measured for 24 hours before and after receiving the first dose, for 24 hours after the Day 4 dose and for 48 hours after receiving the Day 7 dose of vonoprazan. Following a single 20-mg dose of vonoprazan, the onset of the antisecretory effect as measured by intragastric pH is rapid and occurs within 2 to 3 hours. The elevated intragastric pH compared to placebo is maintained for over 24 hours. The inhibitory effect of vonoprazan on acid secretion increases somewhat with repeated daily dosing and steady state is achieved by Day 4. The pharmacodynamic effect is dose dependent, with the percentage of time pH>4 at steady state averaging 60% following a 10-mg dose and 85% following a 20-mg dose for 7 days.

In Japan, vonoprazan 20 mg QD is the approved daily dose in the healing of EE and has also been shown to relieve heartburn in these patients [Ashida 2018]. Both vonoprazan 20 mg QD and 10 mg QD are approved for the maintenance of healing of EE and demonstrated sustained relief of heartburn. These doses are also being evaluated in the United States and Europe for the healing of EE (20 mg) and maintenance of healed EE (10 mg and 20 mg). Based on the pharmacodynamic profile, vonoprazan 20 mg QD has the potential to be more effective than vonoprazan 10 mg QD in NERD patients and therefore both 10 mg and 20 mg doses will be evaluated in this Phase 3 study.

2 Study Objectives and Endpoints

The purpose of this study is to demonstrate the efficacy and safety of vonoprazan relative to placebo in the Placebo-controlled Treatment Period and to describe the long-term efficacy and safety of vonoprazan in the Extension Period.

2.1 Primary Efficacy Objective and Endpoint

The primary efficacy objective and corresponding endpoint are presented in Table 2-1.

Table 2-1 Primary Efficacy Objective and Endpoint

Objective	Endpoint
Primary Efficacy: Placebo-controlled Treatment Period	
• To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in relief of heartburn over 4 weeks in subjects with NERD.	• The percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary.

NERD: symptomatic non-erosive gastroesophageal reflux disease; QD: once daily

2.2 Safety Objectives and Endpoints

Safety objectives with corresponding endpoints are presented in Table 2-2.

Table 2-2 Safety Objectives and Endpoints

Objectives	Endpoints
Safety: Placebo-controlled Treatment Period and Extension Period	
• To assess the safety of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in subjects with NERD over 4 weeks. • To assess the long-term safety of vonoprazan (10 mg and 20 mg QD) over 6 months.	• Safety will be assessed by the following: o AEs o Laboratory test values (hematology, serum chemistry, urinalysis); serum gastrin and pepsinogen I/II levels o ECGs o Vital signs

AE: adverse event; ECG: electrocardiogram; NERD: symptomatic non-erosive gastroesophageal reflux disease; QD: once daily

2.3 Secondary Efficacy Objective and Endpoint

The secondary efficacy objective and corresponding endpoint are presented in Table 2-3.

Table 2-3 Secondary Efficacy Objective and Endpoint for the Placebo-controlled Treatment Period

Objectives	Endpoint
• To assess the use of rescue antacid with vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.	• The percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary.

NERD: symptomatic non-erosive gastroesophageal reflux disease; QD: once daily

2.4 Exploratory Endpoints

Exploratory endpoints for the Placebo-controlled Treatment Period include:

- The percentage of days without daytime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The percentage of days without nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The percentage of days without daytime or nighttime heartburn over the last 7 days of the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of daytime and nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of daytime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The time to sustained resolution of heartburn during the Placebo-controlled Treatment Period (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary)

- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) questionnaire

- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL) questionnaire

- The change from baseline to the end of the Placebo-controlled Treatment Period for the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L)

- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire (N-GSSIQ)

- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Pittsburgh Sleep Quality Index (PSQI) questionnaire

Exploratory endpoints for the Extension Period include:

- The percentage of days without daytime or nighttime heartburn over the Extension Period as assessed by the daily diary

- The percentage of days without nighttime heartburn over the Extension Period as assessed by the daily diary

- The percentage of days without daytime heartburn over the Extension Period as assessed by the daily diary

- The percentage of days without daytime or nighttime heartburn from Week 4 to Week 8 in subjects re-randomized at Week 4 from placebo to either vonoprazan 10 mg or 20 mg

- The mean severity of daytime and nighttime heartburn over the Extension Period as assessed by the daily diary

- The mean severity of daytime heartburn over the Extension Period as assessed by the daily diary
- The mean severity of nighttime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without rescue antacid use over the Extension Period as assessed by the daily diary
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the PAGI-SYM questionnaire
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the PAGI-QoL questionnaire
- The change from baseline to Week 12 and Week 24 of the Extension Period for the EQ-5D-5L
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the N-GSSIQ
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the PSQI

Exploratory endpoints for the Follow-up Period include:

- The percentage of days without daytime or nighttime heartburn during the Follow-up Period as assessed by the daily diary
- The percentage of days without rescue antacid use over the Follow-up Period as assessed by the daily diary

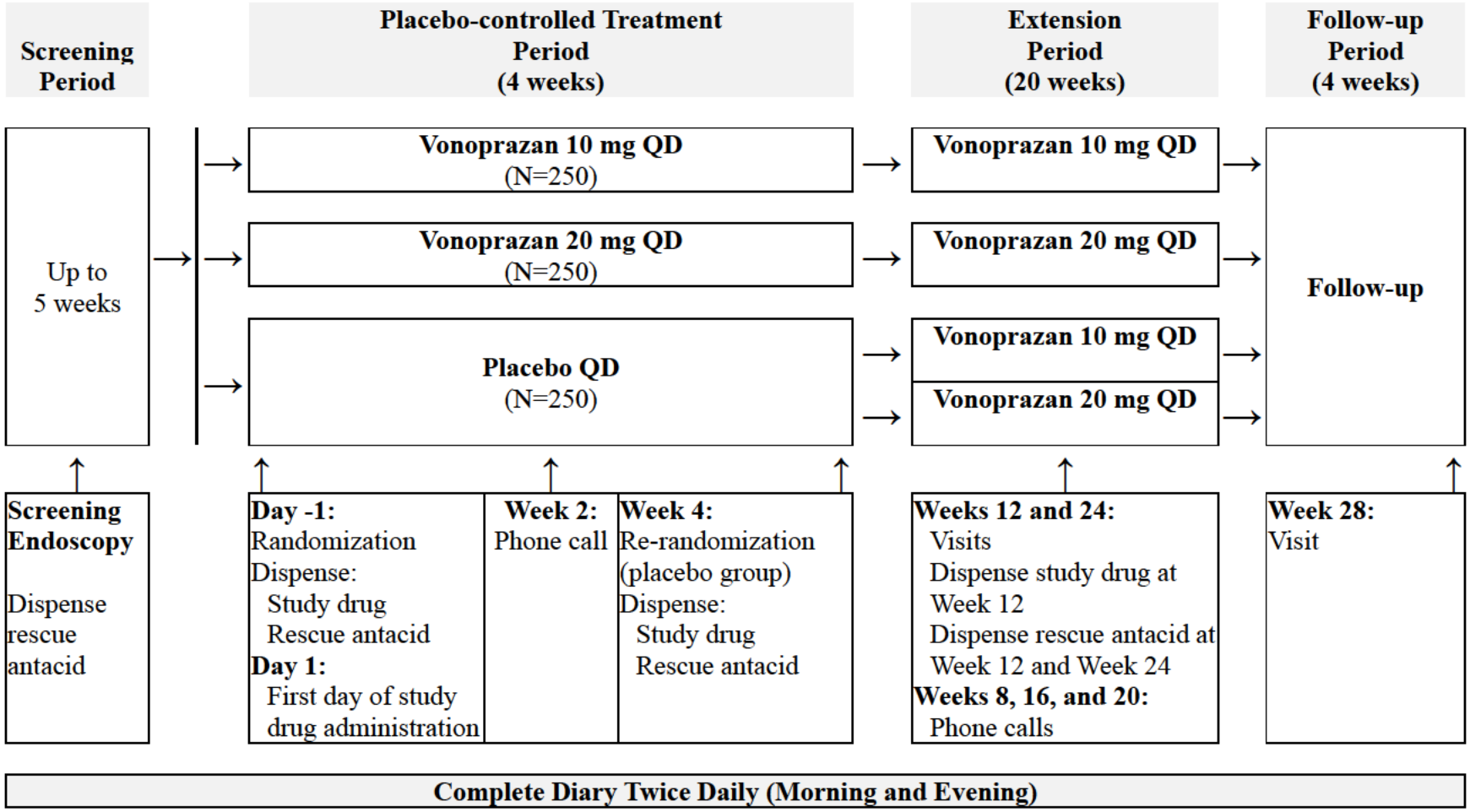
3 Investigational Plan

3.1 Study Design

This is a Phase 3, multicenter, double-blind study of vonoprazan versus placebo assessing the relief of heartburn. Subjects with NERD (as confirmed by endoscopy) and heartburn symptoms will be randomized to receive vonoprazan 10 mg, vonoprazan 20 mg, or placebo QD for 4 weeks. Subjects will complete an electronic diary twice daily to record the presence and maximum severity of daytime and nighttime heartburn symptoms and use of rescue antacid throughout the study. Study-supplied rescue antacid will be allowed. After the Placebo-controlled Treatment Period, all subjects will receive blinded vonoprazan (10 mg or 20 mg QD) in the Extension Period.

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

Figure 3-1 Study Scheme



QD: once daily

Note: Rescue antacid will be dispensed as needed.

The study will include 4 periods (see the schedule of events [SoE] in Section 13.1 for details):

Screening Period (Day -35 to Day -2): Subjects will provide informed consent and undergo screening assessments to determine study eligibility, and baseline assessment will be performed. Subjects will complete the electronic diary twice daily during the Screening Period. If all eligibility criteria are met, the subject will enter the study.

Placebo-controlled Treatment Period (Day -1 to Day 28): Subjects with NERD whose eligibility is confirmed will be randomized to receive vonoprazan 10 mg or 20 mg or placebo QD for 4 weeks. The date of the first dosing is defined as Day 1. An electronic diary will continue to be completed twice daily during the Placebo-controlled Treatment Period.

Extension Period (Day 29 to Day 169): Subjects randomized to vonoprazan 10 mg or 20 mg in the Placebo-controlled Treatment Period will continue to take the same dose in a blinded manner for an additional 20 weeks. Subjects randomized to placebo in the Placebo-controlled Treatment Period will be re-randomized to receive either vonoprazan 10 mg QD or vonoprazan 20 mg QD for 20 weeks. An electronic diary will continue to be completed twice daily during the Extension Period. The first dose of study drug for the Extension Period will be taken the day after the Week 4 visit.

Follow-up Period: A safety follow-up visit will occur 4 weeks after the last dose of study drug. An electronic diary will continue to be completed twice daily during the Follow-up Period.

A subject will be considered to have completed the study if the subject completes the safety follow-up visit.

3.1.1 Rationale of Study Design

3.1.1.1 Rationale for the Placebo-controlled Treatment Period

The Placebo-controlled Treatment Period is designed to demonstrate the superiority of vonoprazan 10 mg and 20 mg QD to placebo in relief of heartburn over 4 weeks in subjects with NERD. Double-blind, parallel-group, placebo-controlled designs are considered optimal for providing unbiased estimates of efficacy. Four weeks of treatment is consistent with the duration of studies to evaluate efficacy for the treatment of heartburn and is also an acceptable duration to allow a placebo-controlled arm.

3.1.1.2 Rationale for the Extension Period and Follow-up Period

An Extension Period is included to assess the long-term safety and efficacy of vonoprazan (10 mg and 20 mg QD) in relief of heartburn in subjects with NERD. The 6-month duration was deemed sufficient to evaluate long-term safety in the NERD population and will also allow the evaluation of the persistence of vonoprazan efficacy. It is not considered ethical to expose subjects to 24 weeks of placebo. Therefore, subjects who receive placebo in the Placebo-controlled Treatment Period will be re-randomized to receive either vonoprazan 10 mg QD or vonoprazan 20 mg QD in the Extension Period.

A safety follow-up visit is planned at 4 weeks after the last dose of study drug. Subjects who discontinue the study will also have a safety follow-up visit.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

This study will be conducted at approximately 100 sites in the United States and will randomize approximately 750 subjects (250 subjects per treatment group) in the Placebo-controlled Treatment Period.

A Study Subject Informational Questionnaire should be completed for each randomized subject (prior to randomization) as a tool to assess eligibility for the study. The completed questionnaire should be filed with the subject's study records at the site.

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 ≥18 years of age at the time of informed consent signing.

2. In the opinion of the investigator or subinvestigators, the subject is capable of understanding and complying with protocol requirements, including compliance with the electronic diary.

3. The subject signs and dates a written informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures. The subject is informed of the full nature and purpose of the study, including possible risks and side effects. The subject has the ability to cooperate with the investigator. Ample time and opportunity should be given to read and understand verbal and/or written instructions.

4. The subject has a diagnosis of symptomatic GERD with heartburn as the subject's predominant symptom prior to the Screening Period, as documented in the subject's medical record.

5. History of onset of heartburn at least 6 months prior to the Screening Period.

6. Heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary.

7. A female subject of childbearing potential who is or may be sexually active with a non-sterilized male partner agrees to routinely use adequate contraception from the signing of informed consent until 4 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 endoscopically confirmed EE during the Screening Period. Endoscopy conducted during the Screening Period should be performed after subjects meet Inclusion Criterion 6 (ie, heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary).

2. The subject has active irritable bowel syndrome (IBS) or has had a flare of IBS requiring therapy within the prior 6 months.

3. The subject has a history of or is suspected of having functional upper gastrointestinal disorders, such as:

    a. Functional heartburn, as described in the Rome IV Criteria (Section 13.4.1)

    b. Functional dyspepsia as described in the Rome IV Criteria (Section 13.4.2)

4. The subject has endoscopic Barrett's esophagus (>1 cm of columnar-lined esophagus) and/or definite dysplastic changes in the esophagus.

5. The subject has any other clinically significant condition affecting the esophagus, including eosinophilic esophagitis; esophageal varices; viral or fungal infection; esophageal stricture; a history of radiation therapy, radiofrequency ablation, endoscopic mucosal resection, or cryotherapy to the esophagus; or any history of caustic or physiochemical trauma (including sclerotherapy or esophageal variceal band ligation). However, subjects diagnosed with Schatzki's ring (mucosal tissue ring around lower esophageal sphincter) or hiatal hernia are eligible to participate.

6. The subject has scleroderma (systemic sclerosis) or systemic lupus erythematosus.

7. The subject has a history of surgery or endoscopic treatment affecting gastroesophageal reflux, including fundoplication and dilation for esophageal stricture (except dilation for a Schatzki's ring) or a history of gastric or duodenal surgery (except endoscopic removal of benign polyps).

8. The subject has an active gastric or duodenal ulcer within 4 weeks before the first dose of study drug.

9. The subject requires or is expected to require use of prescription or non-prescription PPIs or H_2RAs throughout the study.

10. The subject has received any investigational compound (including those in post-marketing studies) within 30 days prior to the start of the Screening Period or vonoprazan in a clinical trial at any time (including participation in Study NERD-201). A subject who has been screen failed from another clinical study and who has not been dosed may be considered for enrollment in this study.

11. The subject is a study site employee, 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, spouse, parent, child, sibling) or who may have consented under duress.

12. The subject has had clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to the Screening Period.

13. The subject has Zollinger-Ellison syndrome or other gastric acid hypersecretory conditions.

14. 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). Skin testing may be performed according to local standard practice to confirm hypersensitivity.

15. The subject has a history of alcohol abuse, illegal drug use, or drug addiction within the 12 months prior to screening, or regularly consumes >21 units of alcohol (1 unit = 12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine)

per week based on self-report. Subjects must have a negative urine drug screen for cannabinoids/tetrahydrocannabinol (including prescription cannabinoids) and non-prescribed medications during the Screening Period.

16. The subject is taking any excluded medications or treatments listed in the protocol, including prescription cannabinoids/tetrahydrocannabinol (Section 5.9.1).

17. If female, the subject is pregnant, lactating, or intending to become pregnant before, during, or within 4 weeks after participating in this study, or intending to donate ova during such time period.

18. The subject has a history or clinical manifestations of significant central nervous system, cardiovascular, pulmonary, hepatic, renal, metabolic, other gastrointestinal, urological, endocrine, or hematological disease that, in the opinion of the investigator, would confound the study results or compromise subject safety.

19. The subject requires hospitalization or has surgery scheduled during the course of the study (from Visit 1 to end of Follow-up Period at Visit 10) or has undergone major surgical procedures within 30 days prior to the Screening Period.

20. The subject has a history of malignancy (including mucosa-associated lymphoid tissue lymphoma) or has been treated for malignancy within 5 years prior to the start of the Screening Period (Visit 1). (The subject may be included in the study if he/she has cured cutaneous basal cell carcinoma or cervical carcinoma in situ).

21. The subject has acquired immunodeficiency syndrome or human immunodeficiency virus infection, or tests positive for the hepatitis B surface antigen, hepatitis C virus (HCV) antibody, or HCV-ribonucleic acid (RNA). However, subjects who test positive for HCV antibody but negative for HCV-RNA are permitted to participate.

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

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

b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × the upper limit of normal (ULN) or total bilirubin >2 × ULN (except for subjects with a diagnosis of Gilbert's syndrome).

23. The subject tests positive for active *H pylori* infection during the Screening Period, after ≥4 weeks free from antibiotics and bismuth and ≥2 weeks free from PPIs and histamine-2 receptor antagonists (H_2RAs).

4.1.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the Placebo-controlled 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), adverse events (AEs), and any serious adverse events (SAEs).

Screen failures are expected to promptly return the electronic diary to the investigational site.

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

4.1.4 Lifestyle Considerations

Subjects should be instructed as follows:

1. To refrain from excessive drinking and eating, an extreme diet change (eg, change to an extremely high-fat diet), or excessive exercise throughout the study.

2. Not to donate blood during the study, and to report on any such donation immediately.

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 performed 4 weeks after completing the last dose of study drug in the Extension Period.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time (eg, Placebo-controlled Treatment Period, Extension 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 of the study drug or withdrawal of the subject from 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) /Independent Ethics Committees (IECs), or regulatory agency terminates the study.

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

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

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

4.2.2 Handling of Withdrawals

Subjects 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.

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 (as described for the

Early Termination Visit). Subjects who fail to return for final assessments will be contacted by the site to make every attempt to comply with the protocol.

Subjects who discontinue study drug or active participation in the study (including screen failures) are expected to promptly return the electronic diary to the investigational site.

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 he or she signs the ICF, repeatedly fails to return for scheduled visits during the Placebo-controlled Treatment Period or Extension Period, and 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:

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

2. Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (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.

3. Should the subject continue to be unreachable, he/she 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

An interactive response technology (IRT) system will be used to administer the randomization schedule.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1:1 ratio by the IRT system to 1 of the following 3 groups during the Placebo-controlled Treatment Period:

- Vonoprazan 10 mg QD for 4 weeks
- Vonoprazan 20 mg QD for 4 weeks
- Placebo QD for 4 weeks

Following completion of the Placebo-controlled Treatment Period at Week 4, all subjects will be assigned study drug for the Extension Period by the IRT system. Subjects randomized to placebo during the Placebo-controlled Treatment Period will be re-randomized to receive vonoprazan 10 mg or vonoprazan 20 mg QD for the 20-week Extension Period. Subjects randomized to 1 of the 2 vonoprazan treatment groups during the Placebo-controlled Treatment Period will continue to receive the same vonoprazan dose during the Extension Period.

An external biostatistician 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. The external biostatistician will not be involved in study conduct or have access to efficacy and/or safety data while the study is ongoing.

5.2 Treatments Administered

Blinded study drug will be dispensed during both the Placebo-controlled Treatment Period and Extension Period. Subjects will be instructed to take the assigned study drug orally with approximately 240 mL (8 oz) water at about the same time each day.

5.3 Rescue Antacid

Up to 12 tablets of Gelusil® per day (not more than 4 tablets at one time) may be used as rescue antacid during the Screening, Placebo-controlled Treatment, Extension, and Follow-up Periods. Use of Gelusil should be documented in the electronic diary.

5.4 Identity of Investigational Product and Rescue Antacid

5.4.1 Vonoprazan and Placebo

Vonoprazan study medication will be supplied as 10-mg and 20-mg capsules. The tablet drug product will be over-encapsulated into Swedish Orange DB-A capsules containing microcrystalline cellulose at the contract manufacturing organization, [redacted] manufactures the vonoprazan drug substance. [redacted] manufactures the vonoprazan tablet drug product.

The placebo for vonoprazan product will be a Swedish Orange DB-A capsule containing microcrystalline cellulose manufactured at the contract manufacturing organization, [redacted]

The over-encapsulated vonoprazan 10-mg and 20-mg dose strengths and placebo will be identical in appearance.

5.4.2 Rescue Antacid

Sites will be provided with Gelusil as rescue antacid. The sites will dispense rescue antacid on the first day of the Screening Period, and as needed during the Placebo-controlled Treatment, Extension, and Follow-up Periods.

5.5 Management of Clinical Supplies

5.5.1 Study Drug Packaging and Storage

Over-encapsulated vonoprazan and placebo will be distributed in blister cards 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.

Gelusil rescue antacid will be supplied in the original commercial package with a protocol-specific ancillary label and will be shipped by [redacted] Gelusil must be stored in a secure area (eg, a locked cabinet) under the conditions specified on the commercial label (below 30°C [86°F]) and remain in the original container until dispensed.

Sites should refer to the pharmacy manual for reporting temperature excursions.

5.5.2 Study Drug and Rescue Antacid 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.

The investigator will maintain accurate records of receipt of all rescue antacid, including dates of receipt. In addition, accurate records will be kept regarding when rescue antacid is dispensed in the study. Subjects should return all unused rescue antacid.

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

5.6 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 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.

5.6.1 Treatment of Overdose

In the event of drug overdose, the subject should be treated symptomatically.

5.7 Blinding

The study treatment blind during the Placebo-controlled Treatment Period and the Extension Period will be maintained using the IRT.

A double-blind design is employed for the Placebo-controlled Treatment Period so that both the investigators and the subjects will be unaware of the treatment assignment. Moreover, study center staff involved in study drug administration and study endpoint assessments, [redacted] personnel, and the Phathom team, including the study statistician, will be blinded to the treatment received during the Placebo-controlled Treatment Period. The final study report will include all data, including all endpoints after all subjects have completed the study, the database is locked, and the study is unblinded.

During the Extension Period, both investigators and subjects will remain blinded to the subject's individual treatment assignment through the Extension Period.

Following the interim analysis (if performed; see Section 7.3.4), Phathom and [redacted] would be unblinded to the treatment assignment of individual subjects during the Placebo-controlled Treatment Period.

5.7.1 Breaking the Blind

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, the investigator will be able to access the IRT to determine the subject’s treatment group assignment. The investigator will, whenever possible, discuss options with the medical monitor before unblinding. The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information (except the time) must be recorded on the eCRF. If any site personnel are unblinded, administration of the investigational drug must be stopped immediately, and the subject must be withdrawn from the study.

5.8 Study Compliance

5.8.1 Treatment Compliance

As subjects will self-administer study drug (vonoprazan or placebo) at home, compliance with study drug is to be assessed as specified in SoE (Section 13.1). Compliance will be assessed by direct questioning and counting returned capsules at scheduled site visits, which will be documented in the source documents and eCRF.

A record of the number of study drug capsules 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.

Noncompliance is defined as taking less than 80% or more than 120% of study drug during any evaluation period (visit to visit). Subjects exhibiting poor compliance as assessed by capsule counts should be counseled on the importance of good compliance to the study dosing regimen.

5.8.2 Diary Compliance

Diary noncompliance within the Placebo-controlled Treatment Period and the Extension Period is defined as completing less than 80% of study diary entries in the respective study period.

Subjects exhibiting poor compliance as assessed by diary entries must be contacted as soon as it is discovered, and retrained by site staff.

5.9 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

Complete coronavirus-19 (COVID-19) vaccination history (including more than 30 days prior to the Screening Period) must be recorded.

Subjects are to be instructed not to 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 should be collected.

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

5.9.1 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 Visit
Antacids (except study-supplied Gelusil)	Screening Period	Follow-up Visit
H_2RAs	Screening Period [a]	Follow-up Visit
PPIs	Screening Period [a]	Follow-up Visit
Antibiotics	Screening Period [a]	Screening Period [a]
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	14 days prior to Day 1	End of Extension Period
CYP3A4 substrates with a narrow therapeutic index (eg, cyclosporine and tacrolimus)	14 days prior to Day 1	End of Extension Period
Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy)	30 days prior to Day 1	Follow-up Visit
Other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth, sucralfate	30 days prior to Day 1 [a]	Follow-up Visit
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	Follow-up Visit
Prescription cannabinoids/tetrahydrocannabinol	14 days prior to start of Screening Period	Follow-up Visit

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

a Subjects should be free of antibiotics and bismuth for ≥4 weeks and free of H_2RAs and PPIs for ≥2 weeks before the Screening Period test for active *Helicobacter pylori* infection.

6 Study Assessments and Procedures

Prior to undergoing any protocol-specific procedures or assessments, all potential subjects must sign and date the ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. 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. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue 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 Endoscopy and *H pylori* Testing During the Screening Period

During the Screening Period (Day -35 to Day -2), an endoscopy will be performed on all subjects to confirm the absence of EE. The screening endoscopy should be performed after the subject meets Inclusion Criterion 6 (heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary) and will be assessed by the investigator.

During the Screening Period (Day -35 to Day -2), subjects will be tested for active *H pylori* infection (ie, serology testing is not acceptable) after being free from antibiotics and bismuth for ≥4 weeks and free from PPIs and H_2RAs for ≥2 weeks. The test will be performed locally, using a FDA approved testing method. Approved testing methods include, but are not limited to, rapid urease, stool antigen tests, and urea breath tests. Any other type of test should be discussed with the [redacted] Medical Monitor and Sponsor for approval.

6.2 Efficacy Assessments

6.2.1 Electronic Symptom Diary

Subjects will be given an electronic diary on the first day of the Screening Period. During the Screening, Placebo-controlled Treatment, Extension, and Follow-up Periods, subjects will complete the diary in the morning and evening.

Subjects should bring the electronic diary device to each site visit. Subjects, including screen failures, must return the devices that have been assigned to them upon completion/termination from the study.

6.2.1.1 Morning and Evening Diary

During the Screening, Placebo-controlled Treatment, Extension, and Follow-up Periods, subjects will document the presence and maximum severity of daytime and nighttime heartburn symptoms and use of rescue antacid twice daily in their diary. If the subject experiences no heartburn on any given day, they should still complete the diary to provide this information. The electronic diary should be completed every morning upon waking (to record the previous evening's maximum heartburn severity rating) and every evening before bedtime (to record that day's maximum heartburn severity rating). The last entry that the subject will make to their electronic diary should be on the morning of the Safety Follow-up Visit, prior to their site visit.

6.2.1.2 Severity Definitions

The severity of heartburn will be graded by the subject according to the definitions outlined in Table 6-1.

Table 6-1 Definitions of Heartburn Severity (Daytime/Nighttime) for the Screening, Placebo-controlled Treatment, Extension, and Follow-up Periods

Definitions of Daytime Heartburn Severity (Daytime=Awake Time)
Mild - Occasional heartburn, can be ignored, does not influence daily routine
Moderate - Heartburn cannot be ignored and/or occasionally influences daily routine
Severe - Heartburn present most of day and/or regularly influences daily routine
Very Severe - Constant heartburn and/or markedly influences daily routine

Definitions of Nighttime Heartburn Severity (Nighttime=Sleep Time)
Mild - Occasional heartburn, can be ignored, does not influence sleep
Moderate - Heartburn cannot be ignored and/or occasionally influences sleep
Severe - Heartburn present most of night and/or regularly influences sleep
Very Severe - Constant heartburn and/or markedly influences sleep

6.2.2 PAGI-SYM Questionnaire

Each subject will self-administer a paper version of the PAGI-SYM at the times specified in Table 13-1. Subjects will record their responses 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 PAGI-SYM questionnaire will include questions that ask about the severity of symptoms the subject may have related to his/her gastrointestinal problem. The questionnaire will consist of 20 items, each with response options based on a 6-point Likert scale and with a recall period of the previous 2 weeks. The items will be grouped into 6 subscales and a total score. Higher scores indicate worse symptoms.

6.2.3 PAGI-QoL Questionnaire

Each subject will self-administer a paper version of the PAGI-QoL at the times specified in Table 13-1. Subjects will record their responses 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 PAGI-QoL questionnaire will include questions that ask about how some of the gastrointestinal problems the subject may have experienced may have affected his/her quality of life. The questionnaire will consist of 30 items, each with response options based on a 6-point Likert scale and with a recall period of the previous 2 weeks. The items will be grouped into 5 subscales and a total score. Higher scores indicate worse quality of life.

6.2.4 EQ-5D-5L Questionnaire

Each subject will self-administer a paper version of the EQ-5D-5L at the times specified in Table 13-1. Subjects will record their responses 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 EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life. The EQ-5D-5L consists of a descriptive system and a visual analogue scale. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The visual analogue scale records the subject's self-rated health on a vertical scale.

The EQ-5D-5L will be converted into a single index value. The EQ-5D-5L index score will be on a scale from 0 (worst imaginable health state) to 1 (best imaginable health state).

6.2.5 PSQI Questionnaire

Each subject will self-administer a paper version of the PSQI at the times specified in Table 13-1. Subjects will record their responses 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 PSQI is a self-reported questionnaire which assesses sleep quality and disturbances over a 1-month recall period. The PSQI has 19 self-rated items organized into 7 subscales, each of which has a range of 0 to 3 points. The subscale measures consist of subjective sleep quality, sleep latency (ie, how long it takes to fall asleep), sleep duration, habitual sleep efficiency (ie, the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction. The 7 subscale scores are then added to produce a global score. Overall scores range from 0 to 21 with a lower score indicating better sleep quality.

6.2.6 N-GSSIQ

Each subject will self-administer a paper version of the N-GSSIQ at the times specified in Table 13-1. Subjects will record their responses 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 N-GSSIQ is a validated instrument to assess the severity and impact of nocturnal GERD symptoms over the past 2 weeks. The questionnaire is comprised of 20 items covering 3 subscales: Nocturnal GERD Symptom Severity (13 items; score range of 0 to 65), Morning Impact of Nocturnal GERD (2 items; score range of 0 to 10), and Concern about Nocturnal GERD (5 items; score range of 0 to 20). The subscale scores are calculated as the sum of the corresponding items for the subscale. The total N-GSSIQ score is calculated as the mean of the subscale scores for Nocturnal GERD Symptom Severity and Morning Impact of Nocturnal GERD only. Higher scores represent greater severity of symptoms, greater symptom impact, and greater concern.

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 who has signed informed consent to participate in a study 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:
    - May require intervention to prevent items 1 through 5 above
    - May include any event or symptoms described in the medically significant AE list (Table 6-2)
    - Exposes the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization

Table 6-2 Medically Significant Adverse Event List

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

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

If a subject is noted to have an ALT or AST value >3 × 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 described 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

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 subject signs the informed consent to participate in the study and 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:

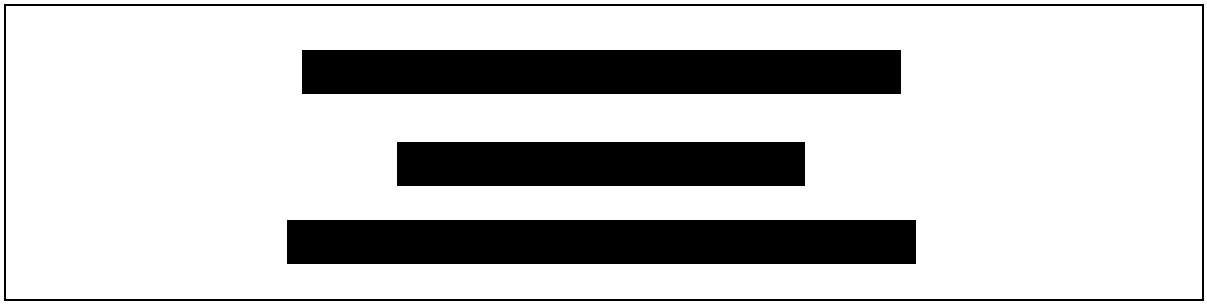
An SAE eCRF must be completed and submitted via Medidata Rave immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- 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 PPD Pharmacovigilance.



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 or IECs, and Regulatory Authorities

The sponsor designee [redacted] will be delegated the responsibility for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators, and the IRB/IEC, as applicable, in accordance with national regulations in the countries where the study is conducted. 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 by national regulations. The sponsor designee will also prepare an expedited report for other safety issues where these 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 product.

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 both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor/sponsor designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

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

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

If there is an increase in unexpected SAEs or if there is a change in the frequency and character of expected SAEs based on the known safety profile of vonoprazan, further

evaluation will be conducted to characterize these events and any impact on benefit/risk. Health authorities will be consulted to agree upon the appropriate action to be taken regarding the conduct of the study, including no change to the protocol, revision of the safety monitoring plan, suspension of enrollment, or discontinuation of the study.

6.3.2 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn, and any sponsor-supplied drug (vonoprazan active) should be immediately discontinued. If the pregnancy occurs during administration of active study drug, eg, after Visit 2 or within 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. Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. 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 (blinded or unblinded, as applicable). All pregnancies (whether subjects on active study drug or placebo) will be reported using the pregnancy form and will be followed up to final outcome. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

6.3.3 Laboratory Analyses

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

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

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

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

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

Table 6-4 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters	
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices: MCV, MCH • Percent reticulocytes • WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils	
Clinical chemistry [a]	• Blood urea nitrogen • Creatinine • Total and direct bilirubin • ALT/SGPT • AST/SGOT • Alkaline phosphatase	• Total protein • Potassium • Sodium • Calcium • Glucose (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 at Visits 2, 4, 6, 9, and 10 after fasting for 12 hours. Gastrin results from Visit 2 will not be blinded and will be reported to investigative sites. Gastrin at Visits 4, 6, 9, 10 and all pepsinogen I and II results will be blinded and will not be reported to investigative sites or other blinded personnel until after the study blind is broken.	
Other tests	• FSH if menopause is suspected [c] • Urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine • Serum hCG pregnancy test [d] at Visit 1 • Urine hCG pregnancy test [d] at Visits 2, 4, 6, 9, and 10 • Serology (HIV antibody, HBsAg, and HCV antibody; hepatitis C, viral load RNA [e] [qualitative])	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; 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 at Visit 1 and at any unscheduled visit.

c Required only for confirmation of postmenopausal females as defined in Section 13.2. Women whose duration of (consecutive) amenorrhea is borderline or open to doubt and where the investigator believes the subject to be menopausal by history should have confirmatory FSH drawn.

d As needed for women of childbearing potential. During the Treatment, Extension, and Follow-up Periods, serum pregnancy test will be performed if the urine pregnancy test is positive.

e Reflex - if hepatitis C positive.

Investigators must document their review of each laboratory safety report.

6.3.4 Physical Examinations

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

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal and neurological systems. Height and weight will also be measured and recorded.

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

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

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 body temperature (oral, temporal, or tympanic measurement), sitting blood pressure (resting more than 5 minutes), and heart rate (beats per minute).

6.3.6 Electrocardiograms

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

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, 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. A copy of the ECG trace should be kept with the subject's notes. For ECG results printed on thermal paper, nonthermal paper copies should be made to avoid degradation of trace over time.

6.4 Safety Monitoring Committee

A Safety Monitoring Committee is not planned for this study.

7 Statistical and Analytical Plan

This section describes the statistical and analytical methods to be used for the study. A statistical analysis plan will provide details of the statistical methods and definitions for the analysis of efficacy and safety endpoints. To preserve the integrity of the statistical analysis and study conclusions, the statistical analysis plan will be finalized before database lock.

7.1 Sample Size Calculations

A sample size of 250 subjects per treatment group provides greater than 90% power at the 0.05 2-sided level of significance using a two-sample t-test to detect a difference of 20% between a vonoprazan dose (50%) and placebo (30%) in the percentage of days without daytime or nighttime heartburn over the 4-week Placebo-controlled Treatment Period, assuming a common standard deviation of 35%.

7.2 Analysis Sets

Two analysis sets will be used in the statistical analysis: intent-to-treat (ITT) set and safety set as defined in the 2 following sections.

7.2.1 Intent-to-treat Set

For the Placebo-controlled Treatment Period, the ITT set will be defined as all subjects randomized into the Placebo-controlled Treatment Period who receive at least 1 dose of study drug during the Placebo-controlled Treatment Period.

For the Extension and Follow-up Periods, the ITT set will be defined as all subjects randomized into the Extension Period who receive at least 1 dose of study drug during the Extension Period.

The efficacy analyses will be conducted on the ITT set using the planned treatment.

7.2.2 Safety Set

For the Placebo-controlled Treatment Period, the safety set will be defined as all subjects randomized into the Placebo-controlled Treatment Period who receive at least 1 dose of study drug during the Placebo-controlled Treatment Period.

For the Extension and Follow-up Periods, the safety set will be defined as all subjects randomized into the Extension Period who receive at least 1 dose of study drug during the Extension Period.

Safety analyses will be conducted on the safety set using the actual treatment the subjects received.

7.3 Statistical Analysis Methodology

Summaries for data collected during the Placebo-controlled Treatment Period will be summarized by double-blind treatment group: vonoprazan 10 mg QD, vonoprazan 20 mg QD, or placebo QD.

Unless otherwise specified, summaries for data collected during the Extension and Follow-up Periods will be summarized for the following groups:

- Vonoprazan 10 mg QD during the Placebo-controlled Treatment and Extension Periods
- Vonoprazan 20 mg QD during the Placebo-controlled Treatment and Extension Periods
- Placebo QD during the Placebo-controlled Treatment Period and Vonoprazan 10 mg QD during the Extension Period
- Placebo QD during the Placebo-controlled Treatment Period and Vonoprazan 20 mg QD during the Extension Period

Unless otherwise specified, baseline will be the last assessment prior to the first dose of study drug in the Placebo-controlled Treatment Period.

Continuous variables will be summarized using the mean, standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages. Statistical analysis will be performed using SAS software Version 9.4 or later.

7.3.1 Efficacy Analyses

7.3.1.1 Placebo-controlled Treatment Period

For the Placebo-controlled Treatment Period, each treatment comparison of vonoprazan 10 mg and of vonoprazan 20 mg to placebo will be tested at the 0.05 significance level.

Methodology for control of type I error for the comparisons of each dose group of vonoprazan to placebo for the primary and secondary efficacy endpoints will be addressed in the statistical analysis plan.

7.3.1.1.1 Primary Efficacy Endpoint for Placebo-controlled Treatment Period

For the primary endpoint of the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates.

7.3.1.1.2 Secondary Efficacy Endpoints for Placebo-controlled Treatment Period

For the percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates.

7.3.1.1.3 Exploratory Efficacy Endpoints for Placebo-controlled Treatment Period

Details for the analysis of the exploratory endpoints for the Placebo-controlled Treatment Period will be provided in the statistical analysis plan.

7.3.1.2 Extension Period

The percentage of days without daytime or nighttime heartburn, the percentage of days without nighttime heartburn, the percentage of days without daytime heartburn, and the

percentage of days without rescue antacid use over the Extension Period as assessed by the daily diary will be summarized.

Details for the analysis of the exploratory endpoints in the Extension Period will be provided in the statistical analysis plan.

7.3.1.3 Follow-up Period

The percentage of days without daytime or nighttime heartburn and the percentage of days without rescue antacid use over the Follow-up Period will be summarized.

7.3.2 Safety Analyses

Safety data will be summarized separately for the Placebo-controlled Treatment Period and the Extension Period.

Safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I and II levels, ECGs and vital signs.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT) overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related AEs overall and by severity. For tabulations of TEAE frequency, if a subject has more than 1 episode of the same event, the subject will be counted only once for that event. If a subject has more than 1 TEAE that is coded to the same PT, the subject will be counted only once for that PT. If a subject has more than 1 TEAE within a SOC, the subject will be counted only once for that SOC. In the tabulation of TEAE frequency by intensity, a subject will be counted only once using the highest severity for each PT and SOC.

Clinical laboratory tests, gastrin and pepsinogen I and II levels, ECGs, and vital signs will be summarized with descriptive statistics at each visit by treatment group. A summary of change from baseline at each visit will also be summarized by treatment group.

7.3.3 Other Analyses

For the Placebo-controlled Treatment and Extension Periods, demographics and other baseline characteristics will be summarized overall and by treatment group. Summary statistics (number of observations, mean, median, standard deviation, and range) will be generated for continuous variables (eg, age and weight). The number and percentage of subjects will be presented for categorical variables (eg, sex and race).

7.3.4 Interim Analyses

An analysis of the Placebo-controlled Treatment Period data may be performed after all subjects have completed the Placebo-controlled Treatment Period. The data for the Placebo-controlled Treatment Period would be locked and the blind broken to perform this analysis. This analysis would be conducted after all randomized subjects have completed the Placebo-controlled Treatment Period and no changes to the conduct of the Extension Period would be made based on the results from the Placebo-controlled Treatment Period.

Following the interim analysis, Phathom and [redacted] would be unblinded to the treatment assignment of individual subjects during the Placebo-controlled Treatment Period to perform this analysis. The treatment assignment would remain blinded to the investigative site.

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 Independent Ethics Committee or Institutional Review Board

Federal regulations, national regulations, and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC 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/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

A written informed consent in compliance with respective regulatory authority regulations shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. 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 should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before

the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF.

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

10 Investigator's Obligations

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

10.1 Confidentiality

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

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

10.2 Financial Disclosure and Obligations

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

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

10.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to the following:

1. IRB/IEC approval
2. Original investigator-signed investigator agreement page of the protocol
3. Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 for United States sites and equivalent form for non-United States sites
4. Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572 or equivalent form for non-United States sites
5. 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.
6. IRB/IEC-approved informed consent, 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
7. 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/IEC according to the timeline and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

10.7 Investigator's Final Report

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

10.8 Records Retention

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

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

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/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

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

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its

designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

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

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

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

11.3 Study Termination

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

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

11.4 Final Report

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

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

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

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13 Appendices

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Study Subject Informational Questionnaire	X	X										
Demographic and medical history	X											
Smoking status and alcohol use	X											
Medication history	X											
Physical examination [d]	X	X			X		X			X	X	X
Vital signs	X	X			X		X			X	X	X
Height	X											
Weight	X									X		
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X											
FSH [e]	X											
Hepatitis B and C; HIV	X											
Test for active *H pylori* infection [f]	X											
Urine drug screen	X											
Clinical laboratory test including hematology, serum chemistry, and urinalysis [g]	X				X		X			X	X	X
Fasting serum gastrin and pepsinogen I and II levels [h]		X			X		X			X	X	
Pregnancy test (serum hCG) [i]	X											
Pregnancy test (urine hCG) [i]		X			X		X			X	X	
Guidance on avoidance of pregnancy	X	X		X	X	X	X	X	X	X	X	

Table 13-1 Schedule of Events (continued)

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Electrocardiogram	X				X					X		
Distribute subject diary [j]	X											
Review subject diary		X		X	X	X	X	X	X	X	X	
PAGI-SYM		X			X		X			X		
PAGI-QoL		X			X		X			X		
EQ-5D-5L		X			X		X			X		
PSQI		X			X		X			X		
N-GSSIQ		X			X		X			X		
Endoscopy	X [k]											
Randomization		X			X [l]							
Dispense study drug		X [c]			X [l]		X					
Dispense rescue antacid (if needed)	X	X			X		X			X		
First day of study drug administration			X									
Drug return/accountability/ review treatment compliance				X	X	X	X	X	X	X	X	
AE/pretreatment event assessment	X	X		X	X	X	X	X	X	X	X	X

AE: adverse event; EQ-5D-5L: EuroQol 5-dimension 5-level questionnaire; ET: early termination; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; *H pylori*: *Helicobacter pylori*; N-GSSIQ: Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire; PAGI-SYM: Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index; PAGI-QoL: Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; PSQI: Pittsburgh Sleep Quality Index Questionnaire

a All screening assessments, except endoscopy, can be performed any time during the Screening Period (Day -35 to Day -2). The screening endoscopy should be performed after the subject has fulfilled Inclusion Criterion 6 (ie, heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary).

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 Date of randomization is defined as Day -1. The date of first dosing day is defined as Day 1.

d Full physical examination is performed at baseline (Visit 1); a brief physical examination is performed at all other visits.

e If menopause is suspected and is required only for confirmation of postmenopausal females as defined in Section 13.2. Women whose duration of (consecutive) amenorrhea is borderline or open to doubt and where the investigator believes the subject to be menopausal by history should have confirmatory FSH drawn.

f Performed after subjects have been free from antibiotics and bismuth for ≥4 weeks and free from proton pump inhibitors and histamine-2 receptor antagonists for ≥2 weeks. The test will be performed locally, using an approved testing method as per local standard of care.

g See Section 6.3.3 for all required laboratory assessments. Glucose should be obtained after an 8-hour fast at Visit 1 and at any unscheduled visit.

h Gastrin results at Visit 2 will not be blinded and will be reported to investigative sites. Gastrin at Visits 4, 6, 9, 10 and all pepsinogen I and II results will be blinded and will not be reported to investigative sites or other blinded personnel until after the study blind is broken.

i Only female subjects with childbearing potential.

j Subjects should be instructed to complete the electronic diary every morning upon waking (for nighttime symptoms) and every evening before bedtime (for daytime symptoms) on each day of the study during all periods. Subjects (including screen failures) are expected to promptly return the electronic diary to the investigational site upon completion/termination from the study.

k The Screening endoscopy can be performed any time during the Screening Period (Day -35 to Day -2); however, it should be performed after the subject has fulfilled Inclusion Criterion 6 (ie, heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary).

l Following completion of the Placebo-controlled Treatment Period at Week 4, all subjects will be assigned study drug for the Extension Period by the interactive response technology system. Subjects randomized to placebo during the Placebo-controlled Treatment Period will be re-randomized to receive vonoprazan 10 mg or vonoprazan 20 mg once daily for the 20-week Extension Period. Subjects randomized to 1 of the 2 vonoprazan treatment groups during the Placebo-controlled Treatment Period will continue to receive the same vonoprazan dose during the Extension Period. The first dose of study drug for the Extension Period will be taken the day after the Week 4 visit.

13.2 Appendix 2: Contraceptive Guidance

Contraception Guidance:

From signing of informed consent, throughout the duration of the study, and for 4 weeks after the last dose of study drug, female subjects of childbearing potential* who are sexually active with a non-sterilized 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 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 >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.

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 elevated baseline ALT or AST levels experience ALT or AST >5 × 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 7 days and preferably within 48 to 72 hours after the abnormality was found.

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

13.3.2 Considerations for Temporary Discontinuation of Study Drug

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

13.3.3 Permanent Discontinuation of Study Drug

If any of the circumstances occur as mentioned in Table 13-2 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 or elevated 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
PPD, Inc.
3900 Paramount Parkway
Morrisville, NC 27560

24-Hour Safety Contact Information
SAE Hotline: +1-888-483-7729
SAE Fax: +1-888-529-3580 or +1-919-654-3836

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: Rome IV Criteria

Rome IV Criteria (2016) is available at https://theromefoundation.org/rome-iv/rome-iv-criteria/.

13.4.1 Functional Heartburn

Functional Heartburn Diagnostic Criteria (Note: criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis with a frequency of at least twice a week)

- Burning retrosternal discomfort or pain
- No symptom relief despite optimal antisecretory therapy
- Absence of evidence that gastroesophageal reflux (elevated acid exposure time and/or symptom reflux association) or EE is the cause of the symptom
- Absence of major esophageal motor disorders (achalasia/esophagogastric junction outflow obstruction, diffuse esophageal spasm, jackhammer esophagus, absent peristalsis)

13.4.2 Functional Dyspepsia

Functional dyspepsia must fulfill criteria for postprandial distress syndrome (PDS; Section 13.4.2.1) and/or epigastric pain syndrome (EPS; Section 13.4.2.2)

Diagnostic criteria for Functional Dyspepsia (Note: criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis)

- *One or more* of the following:
- Bothersome postprandial fullness
- Bothersome early satiation
- Bothersome epigastric pain
- Bothersome epigastric burning

AND

- No evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms

13.4.2.1 Postprandial Distress Syndrome

Diagnostic criteria for PDS (Note: criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis) must include one or both of the following at least 3 days a week:

1. Bothersome postprandial fullness (ie, severe enough to impact on usual activities)
2. Bothersome early satiation (ie, severe enough to prevent finishing a regular size meal)

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy)

Supportive criteria

1. Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
2. Vomiting warrants consideration of another disorder
3. Heartburn is not a dyspeptic symptom but may often co-exist
4. Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
5. Other individual digestive symptoms or groups of symptoms (eg, from GERD and IBS) may co-exist with PDS

13.4.2.2 Epigastric Pain Syndrome

Diagnostic criteria for EPS (Note: Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis) must include one or both of the following symptoms at least 1 day a week:

- Bothersome epigastric pain (ie, severe enough to have an impact on usual activities)
- Bothersome epigastric burning (ie, severe enough to have an impact on usual activities)

No evidence of organic, systemic, or metabolic disease that is likely to explain the symptoms on routine investigations (including at upper endoscopy).

Supportive criteria

- Pain may be induced by ingestion of a meal, relieved by ingestion of a meal, or may occur while fasting
- Postprandial epigastric bloating, belching, and nausea can also be present
- Persistent vomiting likely suggests another disorder
- Heartburn is not a dyspeptic symptom but may often co-exist
- The pain does not fulfill biliary pain criteria
- Symptoms that are relieved by evacuation of feces or gas generally should not be considered as part of dyspepsia
- Other digestive symptoms (such as from GERD and IBS) may co-exist with EPS

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

Inclusion Criteria (Section 4.1.1.)

4. The subject ~~identified their main symptom as heartburn, a burning sensation in the retrosternal area (behind the breastbone)~~ has a diagnosis of symptomatic GERD with heartburn as the subject's predominant symptom prior to the Screening Period, as documented in the subject's medical record

5. History of ~~episodes~~ onset of heartburn ~~for~~ at least 6 months ~~or longer~~ prior to the Screening Period.

Exclusion Criteria (Section 4.1.2.)

23. The subject tests positive for active *H pylori* infection during the Screening Period, after ≥4 weeks free from antibiotics and bismuth and ≥2 weeks free from PPIs and histamine-2 receptor antagonists (H_2RAs).

Method of Assigning Subjects to Treatment Groups (Section 5.1)

~~Biostatistics~~ An external biostatistician 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. The external biostatistician will not be involved in study conduct or have access to efficacy and/or safety data while the study is ongoing.

Prior and Concomitant Therapy (Section 5.9)

Complete coronavirus-19 (COVID-19) vaccination history (including more than 30 days prior to the Screening Period) must be recorded.

Excluded Medications (Section 5.9.1)

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 Visit
Antacids (except study-supplied Gelusil)	Screening Period	Follow-up Visit
H_2RAs	Screening Period [a]	Follow-up Visit
PPIs	Screening Period [a]	Follow-up Visit
Antibiotics	Screening Period [a]	Screening Period [a]
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	14 days prior to Day 1	End of Extension Period
CYP3A4 substrates with a narrow therapeutic index (eg, cyclosporine and tacrolimus)	14 days prior to Day 1	End of Extension Period
Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy)	30 days prior to Day 1	Follow-up Visit
Other agents affecting digestive organs, including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth, sucralfate	30 days prior to Day 1 [a]	Follow-up Visit
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	Follow-up Visit
Prescription cannabinoids/tetrahydrocannabinol	14 days prior to start of Screening Period	Follow-up Visit

CYP: cytochrome P450 isoenzyme; H_2RA: histamine-2 receptor antagonist; PPI: proton pump inhibitor
a Subjects should be free of antibiotics and bismuth for ≥4 weeks and free of H2RAs and PPIs for ≥2 weeks before the Screening Period test for active Helicobacter pylori infection..

Endoscopy and H pylori Testing During the Screening Period (Section 6.1)

During the Screening Period (Day -35 to Day -2), subjects will be tested for active *H pylori* infection (ie, serology testing is not acceptable) after being free from antibiotics and bismuth for ≥4 weeks and free from PPIs and H2RAs for ≥2 weeks. The test will be performed locally, using an approved testing method as per local standard of care. Approved testing

methods include, but are not limited to, biopsy tests (rapid urease or histologic exam), stool tests, and urea breath tests.

Intent-to-treat Set (Section 7.2.1)

For the Placebo-controlled Treatment Period, the ITT set will be defined as all subjects randomized into the Placebo-controlled Treatment Period who receive at least 1 dose of study drug ~~and complete at least 1 diary entry~~ during the Placebo-controlled Treatment Period.

For the Extension Period, the ITT set will be defined as all subjects randomized into the Extension Period who receive at least 1 dose of study drug ~~and complete at least 1 diary entry~~ during the Extension Period.

Schedule of Events (Section 13.1, Appendix 1)

Table 13-1 Schedule of Events

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Demographic and medical history	X											
Smoking status and alcohol use	X											
Medication history	X											
Physical examination [d]	X	X			X		X			X	X	X
Vital signs	X	X			X		X			X	X	X
Height	X											
Weight	X									X		
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X											
FSH [e]	X											
Hepatitis B and C; HIV	X											
Test for active *H pylori* infection [f]	X											
Urine drug screen	X											
Clinical laboratory test including hematology, serum chemistry, and urinalysis [f,g]	X				X		X			X	X	X
Fasting serum gastrin and pepsinogen I and II levels [g,h]		X			X		X			X	X	
Pregnancy test (serum hCG) [h,i]	X											
Pregnancy test (urine hCG) [h,i]		X			X		X			X	X	
Guidance on avoidance of pregnancy	X	X		X	X	X	X	X	X	X	X	

Table 13-1 Schedule of Events (continued)

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Electrocardiogram	X				X					X		
Distribute subject diary [ij]	X											
Review subject diary		X		X	X	X	X	X	X	X	X	
PAGI-SYM		X			X		X			X		
PAGI-QoL		X			X		X			X		
EQ-5D-5L		X			X		X			X		
PSQI		X			X		X			X		
N-GSSIQ		X			X		X			X		
Endoscopy	X [jk]											
Randomization		X			X [kl]							
Dispense study drug		X [c]			X [kl]		X					
Dispense rescue antacid (if needed)	X	X			X		X			X		
First day of study drug administration			X									
Drug return/accountability/ review treatment compliance				X	X	X	X	X	X	X	X	
AE/pretreatment event assessment	X	X		X	X	X	X	X	X	X	X	X

AE: adverse event; EQ-5D-5L: EuroQol 5-dimension 5-level questionnaire; ET: early termination; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; *H pylori*: *Helicobacter pylori*; N-GSSIQ: Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire; PAGI-SYM: Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index; PAGI-QoL: Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; PSQI: Pittsburgh Sleep Quality Index Questionnaire

a All screening assessments, except endoscopy, can be performed any time during the Screening Period (Day -35 to Day -2). The screening endoscopy should be performed after the subject has fulfilled Inclusion Criterion 6 (ie, heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary).

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 Date of randomization is defined as Day -1. The date of first dosing day is defined as Day 1.

d Full physical examination is performed at baseline (Visit 1); a brief physical examination is performed at all other visits.

e If menopause is suspected and is required only for confirmation of postmenopausal females as defined in Section 13.2. Women whose duration of (consecutive) amenorrhea is borderline or open to doubt and where the investigator believes the subject to be menopausal by history should have confirmatory FSH drawn.

f Performed after subjects have been free from antibiotics and bismuth for ≥4 weeks and free from proton pump inhibitors and histamine-2 receptor antagonists for ≥2 weeks. The test will be performed locally, using an approved testing method as per local standard of care.

~~f~~g See Section 6.3.3 for all required laboratory assessments. Glucose should be obtained after an 8-hour fast at Visit 1 and at any unscheduled visit.

~~g~~h Gastrin results at Visit 2 will not be blinded and will be reported to investigative sites. Gastrin at Visits 4, 6, 9, 10 and all pepsinogen I and II results will be blinded and will not be reported to investigative sites or other blinded personnel until after the study blind is broken.

~~h~~i Only female subjects with childbearing potential.

~~i~~j Subjects should be instructed to complete the electronic diary every morning upon waking (for nighttime symptoms) and every evening before bedtime (for daytime symptoms) on each day of the study during all periods. Subjects (including screen failures) are expected to promptly return the electronic diary to the investigational site upon completion/termination from the study.

~~j~~k The Screening endoscopy can be performed any time during the Screening Period (Day -35 to Day -2); however, it should be performed after the subject has fulfilled Inclusion Criterion 6 (ie, heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary).

~~k~~l Following completion of the Placebo-controlled Treatment Period at Week 4, all subjects will be assigned study drug for the Extension Period by the interactive response technology system. Subjects randomized to placebo during the Placebo-controlled Treatment Period will be re-randomized to receive vonoprazan 10 mg or vonoprazan 20 mg once daily for the 20-week Extension Period. Subjects randomized to 1 of the 2 vonoprazan treatment groups during the Placebo-controlled Treatment Period will continue to receive the same vonoprazan dose during the Extension Period.

13.5.2 Protocol Amendment 2

Protocol Synopsis

Objectives:

Secondary:

- ~~To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in relief of nighttime heartburn over 4 weeks in subjects with NERD.~~
- ~~To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in relief of daytime heartburn over 4 weeks in subjects with NERD.~~
- To assess the use of rescue antacid with vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.
- ~~To assess the time to onset of sustained heartburn relief of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.~~

Efficacy Assessments:

Secondary:

- ~~The percentage of days without nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary.~~
- ~~The percentage of days without daytime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary.~~
- The percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary.
- ~~The percentage of subjects with onset of sustained resolution of heartburn by Day 3 (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary).~~

Sample Size:

A sample size of 250 subjects per treatment group provides greater than 90% power at the 0.05 2-sided~~1~~ level of significance using a two-sample t-test ~~Wilcoxon rank-sum test~~ to detect a difference of 20% ~~difference~~ between a vonoprazan dose (50%) and placebo (30%) in the percentage of days without daytime or nighttime heartburn over the 4-week Placebo-controlled Treatment Period, assuming a common standard deviation of 35%.

Protocol Synopsis (continued)

Statistical Methods:

Primary Efficacy Endpoint:

For the primary endpoint of the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates. ~~Wilcoxon rank-sum test. A 2-sided 95% confidence interval computed from Welch's t-test will be calculated for the difference between each vonoprazan treatment group and the placebo treatment group for the primary endpoint (vonoprazan minus placebo).~~

Secondary Efficacy Endpoints:

For ~~the percentage of days without nighttime heartburn, the percentage of days without daytime heartburn, and~~ the percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates. ~~Wilcoxon rank-sum test~~

~~The percentage of subjects with onset of sustained resolution of heartburn by Day 3 will be compared between each vonoprazan treatment group and placebo using Fisher's exact test. Sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary.~~

Secondary Efficacy Objectives and Endpoints (Section 2.3)

The sSecondary efficacy objectives with and corresponding endpoints are presented in Table 2-3.

Table 2-3 Secondary Efficacy Objectives and Endpoints for the Placebo-controlled Treatment Period

Objectives	Endpoints
• To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in relief of nighttime heartburn over 4 weeks in subjects with NERD.	• The percentage of days without nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary.
• To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in relief of daytime heartburn over 4 weeks in subjects with NERD.	• The percentage of days without daytime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary.
• To assess the use of rescue antacid with vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.	• The percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary.
• To assess the time to onset of sustained heartburn relief of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.	• The percentage of subjects with onset of sustained resolution of heartburn by Day 3 (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary).

NERD: symptomatic non-erosive gastroesophageal reflux disease; QD: once daily

Exploratory Endpoints (Section 2.4)

Exploratory endpoints for the Placebo-controlled Treatment Period include:

- The percentage of days without daytime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The percentage of days without nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary

Selection of Study Population (Section 4.1)

This study will be conducted at approximately 100 sites in the United States and will randomize approximately 750 subjects (250 subjects per treatment group) in the Placebo-controlled Treatment Period.

A Study Subject Informational Questionnaire should be completed for each randomized subject (prior to randomization) as a tool to assess eligibility for the study. The completed questionnaire should be filed with the subject's study records at the site.

Endoscopy and H pylori Testing During the Screening Period (Section 6.1)

During the Screening Period (Day -35 to Day -2), subjects will be tested for active *H pylori* infection (ie, serology testing is not acceptable) after being free from antibiotics and bismuth for ≥4 weeks and free from PPIs and H_2RAs for ≥2 weeks. The test will be performed locally, using a~~n~~ FDA approved testing method ~~as per local standard of care~~. Approved testing methods include, but are not limited to, ~~biopsy tests~~ (rapid urease ~~or histological exam)~~, stool antigen tests, and urea breath tests. Any other type of test should be discussed with the PPD Medical Monitor and Sponsor for approval.

N-GSSIQ (Section 6.2.6)

Each subject will self-administer a paper version of the N-GSSIQ at the times specified in Table 13-1. Subjects will record their responses 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 N-GSSIQ is a validated instrument to assess the severity and impact of nocturnal GERD symptoms over the past 2 weeks. The questionnaire is comprised of 20 items covering 3 subscales: Nocturnal GERD Symptom Severity (13 items; score range of 0 to 65), Morning Impact of Nocturnal GERD (2 items; score range of 0 to 10), and Concern about Nocturnal GERD (5 items; score range of 0 to 20). ~~The total N-GSSIQ score is calculated as the sum of the scores of all items.~~ The subscale scores are calculated as the sum of the corresponding items for the subscale. The total N-GSSIQ score is calculated as the mean of the subscale scores for Nocturnal GERD Symptom Severity and Morning Impact of Nocturnal GERD

only. ~~with~~ Higher scores represent~~ing~~ greater severity of symptoms, greater symptom impact, and greater concern.

Sample Size Calculation (Section 7.1)

A sample size of 250 subjects per treatment group provides greater than 90% power at the 0.05 2-sided~~1~~ level of significance using a two-sample t-test ~~Wilcoxon rank-sum test~~ to detect a difference of 20% ~~difference~~ between a vonoprazan dose (50%) and placebo (30%) in the percentage of days without daytime or nighttime heartburn over the 4-week Placebo-controlled Treatment Period, assuming a common standard deviation of 35%.

Intent-to-Treat Set (Section 7.2.1)

For the Placebo-controlled Treatment Period, the ITT set will be defined as all subjects randomized into the Placebo-controlled Treatment Period who receive at least 1 dose of study drug during the Placebo-controlled Treatment Period.

For the Extension and Follow-up Periods, the ITT set will be defined as all subjects randomized into the Extension Period who receive at least 1 dose of study drug during the Extension Period.

The efficacy analyses will be conducted on the ITT set using the planned treatment.

Safety Set (Section 7.2.2)

For the Placebo-controlled Treatment Period, the safety set will be defined as all subjects randomized into the Placebo-controlled Treatment Period who receive at least 1 dose of study drug during the Placebo-controlled Treatment Period.

For the Extension and Follow-up Periods, the safety set will be defined as all subjects randomized into the Extension Period who receive at least 1 dose of study drug during the Extension Period.

Safety analyses will be conducted on the safety set using the actual treatment the subjects received.

Placebo-controlled Treatment Period (Section 7.3.1.1)

For the Placebo-controlled Treatment Period, each treatment comparison of vonoprazan 10 mg and of vonoprazan 20 mg to placebo will be tested at the 0.05~~1~~ significance level.

Methodology for control of type I error for the comparisons of each dose group of vonoprazan to placebo for the primary and secondary efficacy endpoints will be addressed in the statistical analysis plan.

Primary Efficacy Endpoint for Placebo-controlled Treatment Period (Section 7.3.1.1.1)

For the primary endpoint of the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates. ~~Wilcoxon rank-sum test. A 2-sided 95% confidence interval computed from Welch's t-test will be calculated for the difference between each vonoprazan treatment group and the placebo treatment group for the primary endpoint (vonoprazan minus placebo).~~

Secondary Efficacy Endpoints for Placebo-controlled Treatment Period (Section 7.3.1.1.2)

For ~~the percentage of days without nighttime heartburn, the percentage of days without daytime heartburn, and~~ the percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary, each of the vonoprazan treatment groups will be compared to the placebo treatment group using a general linear model with treatment group as factor and severity and frequency of heartburn at baseline as covariates. ~~Wilcoxon rank-sum test.~~

~~The percentage of subjects with onset of sustained resolution of heartburn by Day 3 will be compared between each vonoprazan treatment group and placebo using Fisher's exact test. Sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary.~~

Table 13-1 Schedule of Events

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Study Subject Informational Questionnaire	X	X										
Demographic and medical history	X											
Smoking status and alcohol use	X											
Medication history	X											
Physical examination [d]	X	X			X		X			X	X	X
Vital signs	X	X			X		X			X	X	X
Height	X											
Weight	X									X		
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X											
FSH [e]	X											
Hepatitis B and C; HIV	X											
Test for active *H pylori* infection [f]	X											
Urine drug screen	X											
Clinical laboratory test including hematology, serum chemistry, and urinalysis [g]	X				X		X			X	X	X
Fasting serum gastrin and pepsinogen I and II levels [h]		X			X		X			X	X	
Pregnancy test (serum hCG) [i]	X											
Pregnancy test (urine hCG) [i]		X			X		X			X	X	
Guidance on avoidance of pregnancy	X	X		X	X	X	X	X	X	X	X	

Table 13-1 Schedule of Events (continued)

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Electrocardiogram	X				X					X		
Distribute subject diary [j]	X											
Review subject diary		X		X	X	X	X	X	X	X	X	
PAGI-SYM		X			X		X			X		
PAGI-QoL		X			X		X			X		
EQ-5D-5L		X			X		X			X		
PSQI		X			X		X			X		
N-GSSIQ		X			X		X			X		
Endoscopy	X [k]											
Randomization		X			X [l]							
Dispense study drug		X [c]			X [l]		X					
Dispense rescue antacid (if needed)	X	X			X		X			X		
First day of study drug administration			X									
Drug return/accountability/ review treatment compliance				X	X	X	X	X	X	X	X	
AE/pretreatment event assessment	X	X		X	X	X	X	X	X	X	X	X

AE: adverse event; EQ-5D-5L: EuroQol 5-dimension 5-level questionnaire; ET: early termination; FSH: follicle-stimulating hormone; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; *H pylori*: *Helicobacter pylori*; N-GSSIQ: Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire; PAGI-SYM: Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index; PAGI-QoL: Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; PSQI: Pittsburgh Sleep Quality Index Questionnaire

a All screening assessments, except endoscopy, can be performed any time during the Screening Period (Day -35 to Day -2). The screening endoscopy should be performed after the subject has fulfilled Inclusion Criterion 6 (ie, heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary).

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 Date of randomization is defined as Day -1. The date of first dosing day is defined as Day 1.

d Full physical examination is performed at baseline (Visit 1); a brief physical examination is performed at all other visits.

e If menopause is suspected and is required only for confirmation of postmenopausal females as defined in Section 13.2. Women whose duration of (consecutive) amenorrhea is borderline or open to doubt and where the investigator believes the subject to be menopausal by history should have confirmatory FSH drawn.

f Performed after subjects have been free from antibiotics and bismuth for ≥4 weeks and free from proton pump inhibitors and histamine-2 receptor antagonists for ≥2 weeks. The test will be performed locally, using an approved testing method as per local standard of care.

g See Section 6.3.3 for all required laboratory assessments. Glucose should be obtained after an 8-hour fast at Visit 1 and at any unscheduled visit.

h Gastrin results at Visit 2 will not be blinded and will be reported to investigative sites. Gastrin at Visits 4, 6, 9, 10 and all pepsinogen I and II results will be blinded and will not be reported to investigative sites or other blinded personnel until after the study blind is broken.

i Only female subjects with childbearing potential.

j Subjects should be instructed to complete the electronic diary every morning upon waking (for nighttime symptoms) and every evening before bedtime (for daytime symptoms) on each day of the study during all periods. Subjects (including screen failures) are expected to promptly return the electronic diary to the investigational site upon completion/termination from the study.

k The Screening endoscopy can be performed any time during the Screening Period (Day -35 to Day -2); however, it should be performed after the subject has fulfilled Inclusion Criterion 6 (ie, heartburn reported on 4 or more days during any consecutive 7-day period of the Screening Period as recorded in the electronic diary).

l Following completion of the Placebo-controlled Treatment Period at Week 4, all subjects will be assigned study drug for the Extension Period by the interactive response technology system. Subjects randomized to placebo during the Placebo-controlled Treatment Period will be re-randomized to receive vonoprazan 10 mg or vonoprazan 20 mg once daily for the 20-week Extension Period. Subjects randomized to 1 of the 2 vonoprazan treatment groups during the Placebo-controlled Treatment Period will continue to receive the same vonoprazan dose during the Extension Period. The first dose of study drug for the Extension Period will be taken the day after the Week 4 visit.