**Protocol Number: NERD-201**

**Official Title: A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease**

**Document Date: 16 July 2021**

**NCT Number: NCT04799158**

# CLINICAL STUDY PROTOCOL

IND NUMBER: 079212

# A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease

## PROTOCOL NO. NERD-201

| | |
|---|---|
| **Sponsor:** | Phathom Pharmaceuticals, Inc.<br>2150 East Lake Cook Road, Suite 800<br>Buffalo Grove, IL 60089 USA |
| **Sponsor Contact:** | [redacted] |
| **Safety Contact:** | [redacted] |
| **Version of Protocol:** | Version 2.0, Amendment 1 |
| **Date of Protocol:** | 16 July 2021 |

## CONFIDENTIAL

# Protocol Approval – Sponsor Signatory

| | |
|---|---|
| **Study Title** | A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease |
| **Protocol Number** | NERD-201 |
| **Protocol Version and Date** | Version 2.0, Amendment 1<br>16 July 2021 |

Protocol accepted and approved by:

Vice President Clinical and Patient Safety

[redacted]

[redacted]

[redacted]

# Protocol Approval – Sponsor Signatory

| | |
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| **Study Title** | A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease |
| **Protocol Number** | NERD-201 |
| **Protocol Version and Date** | Version 2.0, Amendment 1<br>16 July 2021 |

Protocol accepted and approved by:

Chief Operating Officer

[redacted]

[redacted]

[redacted]

# Protocol Approval – Sponsor Signatory

| | |
|---|---|
| **Study Title** | A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease |
| **Protocol Number** | NERD-201 |
| **Protocol Version and Date** | Version 2.0, Amendment 1<br>16 July 2021 |

Protocol accepted and approved by:

Chief Medical Officer

[redacted]

[redacted]

[redacted]

# Protocol Approval – Lead Statistician

| | |
|---|---|
| **Study Title** | A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease |
| **Protocol Number** | NERD-201 |
| **Protocol Version and Date** | Version 2.0, Amendment 1<br><br>16 July2021 |

Protocol accepted and approved by:

**Lead Statistician**

[redacted]

[redacted]

[redacted]

# Protocol Approval – Principal/Coordinating Investigator

| | |
|---|---|
| **Study Title** | A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease |
| **Protocol Number** | NERD-201 |
| **Protocol Version and Date** | Version 2.0, Amendment 1<br>16 July2021 |

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 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 2.0, Amendment 1, dated 16 July 2021, 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

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# Protocol Synopsis

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|---|---|
| **Protocol Number:** | NERD-201 |
| **Title:** | A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 10 mg, 20 mg, and 40 mg Compared to Placebo for Relief of Episodic Heartburn in Subjects with Symptomatic Non-Erosive Gastroesophageal Reflux Disease |
| **Sponsor:** | Phathom Pharmaceuticals, Inc.<br>2150 East Lake Cook Road, Suite 800<br>Buffalo Grove, IL 60089 USA |
| **Study Phase:** | 2 |
| **Study Sites:** | Approximately 65 sites in the United States |
| **Indication:** | Patients with symptomatic NERD |
| **Rationale:** | Gastroesophageal reflux disease (GERD) is prevalent globally and represents one of the most common gastrointestinal diseases. The Montreal definition of 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 non-erosive gastroesophageal reflux disease (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.<br>Vonoprazan belongs to a new class of acid-inhibitory agents called "potassium-competitive acid blockers" and is being developed in the United States and Europe for healing of all grades of EE and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *Helicobacter pylori* infection.<br>Vonoprazan at doses from 10 mg to 40 mg has been shown in both single and multiple repeat-dosing studies to have a rapid onset of action after the first dose and near maximal effect on pH holding time within 24 hours of dosing, which is maintained with multiple dosing. It is believed that this pharmacologic profile may make it an optimum agent for the treatment of NERD utilizing an "On-Demand" dosing scheme. This study will evaluate the safety and effectiveness of vonoprazan 10 mg, 20 mg, and 40 mg to treat episodic heartburn in patients with symptomatic NERD after an initial 20 mg vonoprazan dose in an open-label Run-In Period. |

**Objectives:**

**Primary**

- To assess the efficacy of vonoprazan (10 mg, 20 mg, and 40 mg On-Demand) compared to placebo (On-Demand) in relief of episodic heartburn over 6 weeks in subjects with symptomatic NERD.
- To assess the safety of vonoprazan (10 mg, 20 mg, and 40 mg On-Demand) compared to placebo (On-Demand) in subjects with symptomatic NERD.

**Secondary**

- To assess the use of study medication and rescue antacid in subjects treated with vonoprazan (10 mg, 20 mg, and 40 mg On-Demand) compared to placebo (On-Demand) over the On-Demand Treatment Period.

**Study Population:** Subjects aged 18 years of age or older with symptomatic NERD confirmed by endoscopy.

**Key Inclusion and Exclusion Criteria**

**Run-In Period**

**Main Inclusion Criteria:**

- The subject identified their main symptom as heartburn, a burning sensation in the retrosternal area (behind the breastbone).
- History of episodes of heartburn for 6 months or longer prior to screening.
- Heartburn reported on 4 or more days during any 7 consecutive days in the Screening Period as recorded in the electronic diary.

**Main Exclusion Criteria:**

- Endoscopically confirmed EE.
- The subject has active irritable bowel syndrome or had a flare of IBS requiring therapy within the prior 6 months.
- The subject has a history of, or is suspected of having, functional upper gastrointestinal disorders such as functional dyspepsia or functional heartburn diagnosed by the Rome IV criteria.

**On-Demand Treatment Period**

**Main Inclusion Criteria:**

- The subject has stable disease, ie, no heartburn in the last 7 days of the Run-In Period.
- The subject completes the Run-In Period and continues to fulfill all eligibility criteria for the Run-In Period (except heartburn inclusion criteria).

- Subject completes at least 80% of diary entries over the Run-In Period, including 80% of the entries for the last 7 days.

**Study Design:**

This is a Phase 2, multicenter, double-blind study of vonoprazan versus placebo assessing the relief of episodic heartburn. Subjects with symptomatic NERD (as confirmed by endoscopy) and heartburn symptoms will receive open-label vonoprazan 20 mg once daily (QD) for 4 weeks. Subjects with stable disease (ie, no heartburn on the last 7 days of the Run-In Period) will be randomized to receive vonoprazan 10 mg, 20 mg, 40 mg or placebo On-Demand for 6 weeks. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid (if needed) in all periods. During the On-Demand Treatment Period, a more detailed diary will also document time of study drug administration and when heartburn relief occurs.

The study will include 4 periods:

**Screening Period:** Subjects will provide informed consent and undergo screening assessments to determine study eligibility (including endoscopy to confirm absence of EE). Subject will have to discontinue proton pump inhibitors and histamine-$_2$ receptor antagonists during this period. Study-supplied rescue antacid will be allowed if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid. If all eligibility criteria are met, the subject will enter the Run-In Period.

**Run-In Period:** Subjects with symptomatic NERD whose eligibility is confirmed will receive open-label vonoprazan 20 mg QD for 4 weeks to treat heartburn. Study-supplied rescue antacid will be allowed if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid.

**On-Demand Treatment Period:** Subjects who have stable disease (ie, no heartburn on the last 7 days of the Run-In Period) and are compliant with the diary and study medication will be randomized to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo On-Demand (but no more than 1 dose within 24 hours) for 6 weeks to treat episodic heartburn. Study-supplied rescue antacid will be allowed 3 hours after taking study medication if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid. In addition, a more detailed diary will also document time of study drug administration and when heartburn relief occurs. Subjects will be contacted by phone weekly during the first 3 weeks to assess their understanding of diary instructions and On-Demand dosing and to emphasize the importance of completing the diary assessments.

**Follow-up Period:** A safety follow-up visit will occur 1 week after completing the On-Demand Treatment Period to assess adverse events

| | |
|---|---|
| | (AEs) and serum gastrin. Study-supplied rescue antacid will be allowed if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid. |
| **Estimated Study Duration:** | The total duration of the study is up to 16 weeks. Screening Period is up to 5 weeks, the Run-In Period is 4 weeks, and the On-Demand Treatment Period is 6 weeks. A follow-up visit will occur 1 week after completing the On-Demand Treatment Period. |
| **Efficacy Assessments:** | **Primary Endpoints**<br>• The percentage of evaluable[(a)] heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug [(b)]<br><br>[(a)] An evaluable heartburn episode is an episode for which study drug was taken and for which the subject completed at least one entry in the heartburn episode diary.<br>[(b)] For a heartburn episode to be considered completely relieved, a subject must not have taken rescue antacid within 3 hours of taking study drug.<br>**Secondary Endpoints**<br>• The percentage of evaluable heartburn episodes completely relieved within 3 hours after taking study drug<br>• The percentage of evaluable heartburn episodes for each subject that are completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug<br>• The mean number of tablets of rescue antacid taken per day over the On-Demand Treatment Period<br>• The percentage of subjects with complete relief of heartburn within 3 hours after the first episode and with no further heartburn reported for 24 hours after taking study drug<br>• The percentage of days study drug was taken over the On-Demand Treatment Period<br>• The percentage of 24-hour heartburn-free days over the On-Demand Treatment Period |
| **Safety Assessments:** | Safety will be assessed by the following:<br>• AEs<br>• Laboratory test values (hematology, serum chemistry, urinalysis); serum gastrin and pepsinogen I/II levels<br>• Electrocardiograms (ECGs)<br>• Vital signs |

**Study Drug, Dosage, and Route of Administration:** Open-label vonoprazan 20 mg QD will be taken during the 4-week Run-In Period. Blinded study drug (vonoprazan 10 mg, 20 mg, or 40 mg or placebo) will be taken for the treatment of an On-Demand heartburn episode (only once in a 24-hour period) during the 6-week On-Demand Treatment Period. Study drug will be taken orally with approximately 240 mL (8 oz) water. Rescue antacid will be provided.

**Sample Size:** The sample size for the On-Demand Treatment Period is calculated based on the following assumptions:

- Subjects will be randomized to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo with a randomization ratio of 1:1:1:1.
- Each subject experiences at least 4 evaluable heartburn episodes.
- Comparison between each dose of vonoprazan to placebo will be performed using the Fisher's Exact test.
- A clinically relevant difference of 15% between each dose of vonoprazan and placebo in the proportion of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug.

Based on these assumptions, a sample size of 200 heartburn episodes per treatment group (or 50 subjects with at least 4 heartburn episodes per treatment group) provides at least 80% statistical power at the 0.05 significance level. During the study if less than 200 subjects are projected to enroll into the On-Demand Treatment Period, additional subjects may be enrolled into the Run-In Period to ensure that a sufficient number of subjects enroll into the On-Demand Treatment Period.

Assuming 60% of subjects at the end of the Run-In Period do not meet the eligibility criteria for the On-Demand Treatment Period, approximately 500 subjects will be enrolled into the Run-In Period to achieve 200 subjects for the On-Demand Treatment Period.

**Statistical Methods:**

**Efficacy Analyses**

**Primary Efficacy Endpoint**

The percentage of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug will be compared between each dose of vonoprazan and placebo using Fisher's Exact test for the Intent-to-Treat (ITT) On-Demand set.

**Secondary Efficacy Endpoint**

All secondary endpoints will be analyzed for the ITT On-Demand set.

The following secondary endpoints will be compared for each dose of vonoprazan to placebo using Fisher's Exact test:

- The percentage of evaluable heartburn episodes completely relieved within 3 hours after taking study drug.
- The percentage of subjects with complete relief of heartburn within 3 hours after the first episode and with no further heartburn reported for 24 hours after taking study drug.

The following secondary endpoints will be compared for each dose of vonoprazan to placebo using a Wilcoxon rank-sum test:

- The percentage of evaluable heartburn episodes for each subject that are completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug.
- The percentage of days study drug was taken over the On-Demand Treatment Period.
- The mean number of tablets of rescue antacid taken per day over the On-Demand Treatment Period.
- The percentage of 24-hour heartburn-free days during the On-Demand Treatment Period.

**Safety Analyses**

Safety will be summarized separately for the Run-In Period and the On-Demand Treatment Period. For each period, safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I/II levels, ECGs, and vital signs.

| | |
|---|---|
| **Version and Date of Protocol:** | Version 2.0, Amendment 1; 16 July 2021 |

# List of Abbreviations

| Abbreviation | Definition |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| CFR | Code of Federal Regulations |
| CONSORT | Consolidated Standards of Reporting Trials |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EE | erosive esophagitis |
| EMA | European Medicines Agency |
| EPS | epigastric pain syndrome |
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GERD | gastroesophageal reflux disease |
| GGT | gamma-glutamyl transferase |
| $H_2RA$ | histamine-$_2$ receptor antagonist |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| 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 |
| NERD | non-erosive gastroesophageal reflux disease |

| Abbreviation | Definition |
|---|---|
| PAGI-QoL | Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life |
| PAGI-SYM | Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index |
| PD | pharmacodynamic(s) |
| PDS | postprandial distress syndrome |
| PPI | proton pump inhibitor |
| PT | preferred term |
| PTE | pretreatment adverse event |
| QD | once daily |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | system organ class |
| SoE | schedule of events |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| ULN | upper limit of normal |

# Summary of Changes

Protocol Amendment History and Reasons for Amendment

| Version | Date | Reasons for Amendment |
|---|---|---|
| Version 1.0 | 25 Jan 2021 | Original Protocol |
| Version 2.0 (Protocol Amendment 1) | 16 July 2021 | • To update the IBS exclusion criterion to exclude active IBS or a flare requiring therapy within prior 6 months<br>• To add 2 telephone contacts at Week 1 and Week 2 of the On-Demand Treatment Period.<br>• To clarify that compliance with diary and study medication is required for entry into the On-Demand Treatment Period.<br>• To change baseline serum gastrin level to be unblinded during the study.<br>• To increase the number of subjects expected to be enrolled into the Run-In Period to 500 subjects to ensure that a sufficient number of subjects enroll into the On-Demand Treatment Period.<br>• To clarify that use of prescription cannabinoids/tetrahydrocannabinol is exclusionary.<br>• To clarify that Run-In failures should undergo assessments from the Week 4 Run-In Period. |

# 1 Introduction

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 erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, treatment of *Helicobacter pylori* infection, and treatment of heartburn in patients with symptomatic non-erosive gastroesophageal reflux disease (NERD).

Vonoprazan has been studied in a number of acid-related diseases, including EE healing and maintenance, gastric ulcer/duodenal ulcer healing, and for the prevention of recurrence of a gastric or duodenal ulcer during nonsteroidal anti-inflammatory drugs or aspirin administration and has received regulatory approval in Japan and other countries in Asia and Latin America for these indications.

## 1.1 Study Rationale

Vonoprazan at doses from 10 mg to 40 mg has been shown in both single and multiple repeat-dosing studies to have a rapid onset of action after the first dose and near maximal effect on pH holding time within 24 hours of dosing, which is maintained with multiple doses. It is believed that this pharmacologic profile may make it an optimum agent for the treatment of NERD utilizing an “on-demand” dosing scheme. This study will evaluate the safety and effectiveness of vonoprazan 10 mg, 20 mg, and 40 mg to treat episodic heartburn in patients with symptomatic NERD who have stable disease after treatment with vonoprazan 20 mg in an open-label Run-In Period.

## 1.2 Background

Gastroesophageal reflux disease (GERD) is prevalent globally and represents one of the most common gastrointestinal diseases. The Montreal definition of GERD is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications (Vakil et al 2006). The term GERD covers a spectrum of conditions, including NERD, 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 (El-Serag et al 2014). Proton pump inhibitors (PPIs) are currently the most effective available anti-secretory agents for relieving GERD symptoms, healing the injured mucosa, and maintaining a healed mucosa (Freston 2004).

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, including on-demand or intermittent therapy (Katz et al 2013). On-demand therapy is a self-managed therapeutic strategy in which patients take acid-suppressing medications as needed based on symptoms of heartburn. Proton pump inhibitors are recommended for treatment of symptomatic NERD for 4 to 8 weeks. None of the PPIs are approved for on-demand therapy in the United States. While esomeprazole and rabeprazole are approved for on-demand treatment of symptomatic GERD in Europe, the primary endpoints of these studies that support this were based on subject satisfaction with treatment and study discontinuation rates, rather than directly measuring relief of active heartburn episodes (Talley et al 2001; Talley et al 2002; Bytzer et al 2004). Studies with PPIs have shown that in NERD patients the median time to first report of symptom relief takes 2 days and for sustained symptom relief 10 to 13 days. This finding is consistent with the known mechanism of action of PPIs, in which there is a build-up effect on the inhibition of acid output after repeated daily dosing. Nevertheless, PPIs are still recommended as needed or On-Demand for the treatment of GERD (Katz et al 2013). Published systematic reviews and meta-analysis show that the on-demand management of NERD with PPIs has been reported to be a favorable approach for patients as maintenance treatment for NERD (Pace et al 2007; Khan et al 2018). Moreover, patient adherence and satisfaction with on-demand treatment is greater than with continuous PPI treatment with the potential to limit the concerns of adverse events (AEs) and reduce the pill burden for patients.

To date, only over-the-counter histamine-$_2$ receptor antagonists ($H_2$RAs) are approved in the US for on-demand treatment of heartburn; however, these agents have their own limitations related to having to dose more than once a day, dosing with food, and the development of tachyphylaxis upon continued use (Colin-Jones 1995).

In contrast to EE, NERD is mostly viewed as a non-progressive disease and the treatment approach is symptom-driven (Savarino et al 2017). Reflux symptoms do not occur on a daily basis in NERD patients, so continuous dosing may not be warranted in these patients. There are limited data evaluating vonoprazan on-demand in NERD. The available data suggest on-demand therapy is potentially an effective alternative to continuous treatment. In a study published by Hoshikawa et al evaluating vonoprazan 20 mg on-demand for NERD, the authors concluded that on-demand therapy is as effective as continuous PPI maintenance

therapy in terms of patient satisfaction and the majority of the patients preferred the on-demand approach over continuous maintenance treatment (Hoshikawa et al 2019). Similar results are reported with PPI treatment, where on-demand therapy was non-inferior to continuous, but on-demand also reduced medication usage (Bayerdörffer et al 2016).

The pharmacokinetic and pharmacodynamic (PD) 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.

[redacted] conducted 2 studies in Japan to evaluate the treatment of heartburn in subjects with NERD (TAK-438/CCT-201 [Kinoshita et al 2016] and Vonoprazan-3001 [Kinoshita et al 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. The learnings from these studies are being applied in the current NERD study. Phathom plans to add measures to select an appropriate NERD population and reduce inclusion of functional heartburn patients. Phathom plans to use an electronic diary data collection tool to allow timely and accurate capture of patient symptoms. In addition, a wider dose range of vonoprazan is being explored than what has been studied in the [redacted] Japan program.

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 both continuous dosing and on-demand use for the treatment of heartburn in patients with symptomatic NERD.

## 1.3 Justification for Dose

Selection of the vonoprazan 20 mg dose for the Run-In Period and the vonoprazan 10 mg, 20 mg, and 40 mg doses for the On-Demand Treatment Period of Study NERD-201 is based on the following studies:

- [redacted] conducted a 7-day multiple repeat-dose study in healthy subjects administered with 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 of vonoprazan. On

Day 1, vonoprazan quickly raised intragastric pH in a dose-dependent manner with 10 mg, 20 mg, and 40 mg doses achieving a mean pH of 4 between 2 to 4 hours after dosing. The vonoprazan 40 mg dose maintains pH above 4 for 24 hours after a single dose.

- A recent study compared vonoprazan 20 mg to lansoprazole 30 mg and famotidine 20 mg (Ohkuma et al 2018). Gastric pH was measured for 6 hours after dosing. Over this period, the mean pH was similar between vonoprazan (4.30) and famotidine (4.45) and both were higher than lansoprazole (2.65).

Based on the PD profile, vonoprazan 20 mg and 40 mg are more likely to be suitable for on-demand dosing; however, Phathom proposes to also assess vonoprazan 10 mg to confirm the lowest effective dose.

To date, the vonoprazan 40 mg once-daily (QD) dose has been evaluated in 248 subjects with a maximum duration of 8 weeks. In Phase 2, 3, and 4 studies, the safety of vonoprazan 20 mg and 40 mg are comparable.

The 20 mg dose for the vonoprazan Run-In Period was selected based on the historical data from Japan where vonoprazan 20 mg is the recommended daily dose in the healing of EE and has also shown to relieve heartburn in these patients (Ashida et al 2018). While this dose has not yet been shown to be effective in NERD as a daily dose, it is considered a safe and logical dose to be selected for the Run-In Period of this study.

Overall, the proposed doses of vonoprazan 10 mg, 20 mg, and 40 mg are appropriate for this Phase 2 study to explore the on-demand use.

# 2 Study Objectives and Endpoints

## 2.1 Primary Objectives and Endpoints

**Table 2-1 Primary Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| • To assess the efficacy of vonoprazan (10 mg, 20 mg, and 40 mg On-Demand) compared to placebo (On-Demand) in relief of episodic heartburn over 6 weeks in subjects with symptomatic NERD. | • The percentage of evaluable[(a)] heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug[(b)] |
| • To assess the safety of vonoprazan (10 mg, 20 mg, and 40 mg On-Demand) compared to placebo (On-Demand) in subjects with symptomatic NERD. | • Safety will be assessed by the following:<br>o AEs<br>o Laboratory test values (hematology, serum chemistry, urinalysis); serum gastrin and pepsinogen I/II levels<br>o ECGs<br>o Vital signs |

Abbreviations: AEs, adverse events; ECGs, electrocardiograms; NERD, non-erosive gastroesophageal reflux disease.

(a) An evaluable heartburn episode is an episode for which study drug was taken and for which the subject completed at least one entry in the heartburn episode diary.

(b) For a heartburn episode to be considered completely relieved, a subject must not have taken rescue antacid within 3 hours of taking study drug.

## 2.2 Secondary Objectives and Endpoints

**Table 2-2 Secondary Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| • To assess the use of study medication and rescue antacid in subjects treated with vonoprazan (10 mg, 20 mg, and 40 mg On-Demand) compared to placebo (On-Demand) over the On-Demand Treatment Period. | **Secondary:**<br>• The percentage of evaluable[(a)] heartburn episodes completely relieved within 3 hours after taking study drug[(b)]<br>• The percentage of evaluable[(a)] heartburn episodes for each subject that are completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug<br>• The mean number of tablets of rescue antacid taken per day over the On-Demand Treatment Period<br>• The percentage of subjects with complete relief of heartburn within 3 hours after the first episode and with no further heartburn reported for 24 hours after taking study drug<br>• The percentage of days study drug was taken over the On-Demand Treatment Period<br>• The percentage of 24-hour heartburn-free days over the On-Demand Treatment Period |

| Objectives | Endpoints |
|---|---|
| | **Exploratory:**<br>**On-Demand Treatment Period**<br>• The percentage of evaluable[(a)] heartburn episodes completely relieved within 30 minutes or 1, 1.5, or 2 hours and with no further heartburn reported for 24 hours after taking study drug[(b)]<br>• The percentage of evaluable[(a)] heartburn episodes that are completely relieved within 30 minutes or 1, 1.5, or 2 hours after taking study drug[(b)]<br>• The percentage of evaluable[(a)] heartburn episodes that improved at 30 minutes or 1, 1.5, 2, or 3 hours after taking study drug[(b)]<br>• The percentage of episodes for which subjects continue to be heartburn-free after 24 or 48 hours of taking study drug<br>• The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours with no further heartburn reported for 24 hours after taking study drug[(b)]<br>• The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours after taking study drug[(b)]<br>• The percentage of subjects with complete relief of the first episode of heartburn within 3 hours after taking study drug<br>• The mean number of days between heartburn episodes[(b)]<br>• The percentage of days without daytime heartburn over the On-Demand Treatment Period<br>• The percentage of days without nighttime heartburn over the On-Demand Treatment Period<br>• The mean severity of daytime and nighttime heartburn over the On-Demand Treatment Period<br>• The mean severity of nighttime heartburn over On-Demand Treatment Period<br>• The mean severity of daytime heartburn over the On-Demand Treatment Period<br>• The percentage of days without rescue antacid use over the On-Demand Treatment Period<br>• The change from baseline to the end of the On-Demand Treatment Period for each subscale and the total score of the PAGI-SYM questionnaire<br>• The change from baseline to the end of the On-Demand Treatment Period for each subscale and the total score of the PAGI-QoL questionnaire<br>• The patient global impression of change in GERD symptoms at the end of the On-Demand Treatment Period<br>• The patient global impression of severity in GERD symptoms over the last 7 days of the On-Demand Treatment Period<br>• The percentage of subjects with each dosing preference |

| Objectives | Endpoints |
|---|---|
| | **Run-In Period**<br>• The percentage of 24-hour heartburn-free days over the Run-In Period<br>• The percentage of days without daytime heartburn over the Run-In Period<br>• The percentage of days without nighttime heartburn over the Run-In Period<br>• The mean severity of daytime and nighttime heartburn over the Run-In Period<br>• The mean severity of nighttime heartburn over the Run-In Period<br>• The mean severity of daytime heartburn over the Run-In Period<br>• The percentage of days without rescue antacid use over the Run-In Period<br>• The change from baseline to the end of the Run-In Period for each subscale and the total score of the PAGI-SYM questionnaire<br>• The change from baseline to the end of the Run-In Period for each subscale and the total score of the PAGI-QoL questionnaire<br>• The patient global impression of change in GERD symptoms at the end of the Run-In Period<br>• The patient global impression of severity in GERD symptoms over the last 7 days of the Run-In Period |

Abbreviations: GERD, gastroesophageal reflux disease; PAGI-QoL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; PAGI-SYM, Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index.

(a) An evaluable heartburn episode is an episode for which study drug was taken and for which the subject completed at least one entry in the heartburn episode diary.

(b) For a heartburn episode to be considered completely relieved, a subject must not have taken rescue antacid within 3 hours of taking study drug.

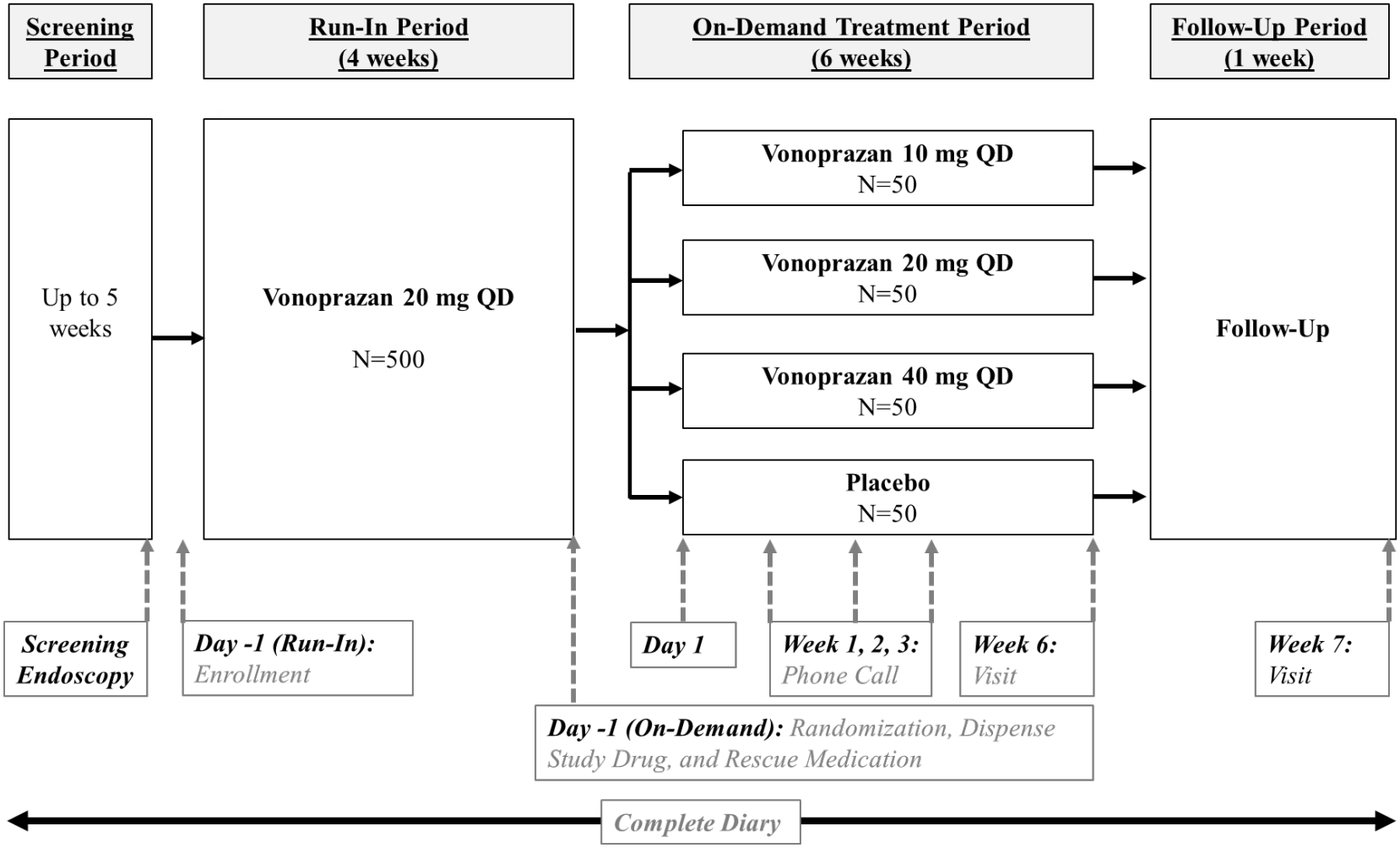
# 3 Investigational Plan

## 3.1 Study Design

This is a Phase 2, multicenter, double-blind study of vonoprazan versus placebo assessing the relief of episodic heartburn. Subjects with symptomatic NERD (as confirmed by endoscopy) and heartburn symptoms will receive open-label vonoprazan 20 mg QD for 4 weeks. Subjects with stable disease (ie, no heartburn on the last 7 days of the Run-In Period) will be randomized to receive either vonoprazan 10 mg, 20 mg, 40 mg or placebo On-Demand for 6 weeks. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid (if needed) in all periods. During the On-Demand Treatment Period, a more detailed diary will also document time of study drug administration and when heartburn relief occurs.

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

**Figure 3-1 Study Scheme**




Abbreviations: QD, once daily

The study will include 4 periods (see the schedule of events [SoE] in Appendix 1 [Section 13.1] for details):

1. **Screening Period:** Subjects will provide informed consent and undergo screening assessments to determine study eligibility (including endoscopy to confirm absence of EE). Study-supplied rescue antacid will be allowed if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid. If all eligibility criteria are met, the subject will be eligible to enter the Run-In Period.
2. **Run-In Period:** Subjects with symptomatic NERD whose eligibility is confirmed will receive open-label vonoprazan 20 mg QD for 4 weeks. Study-supplied rescue antacid will be allowed if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid.
3. **On-Demand Treatment Period:** Subjects who have stable disease (ie, no heartburn on the last 7 days of the Run-In Period) and are compliant with the Diary and study medication will be randomized to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo On-Demand for 6 weeks to treat episodic heartburn. Study drug should only be taken once in a 24-hour period. Study-supplied rescue antacid will be allowed 3 hours after taking study medication if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid. In addition, a more detailed diary will also document time of study drug administration and when heartburn relief occurs. Subjects will be contacted by phone weekly during the first 3 weeks to assess their understanding of diary instructions and On-Demand dosing and to emphasize the importance of completing the diary assessments.
4. **Follow-up Period:** A safety follow-up visit will occur 1 week after completing the On-Demand Treatment Period to assess AEs and serum gastrin. Study-supplied rescue antacid will be allowed if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid.

End-of-study: 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 Run-In Period

The Run-In Period is designed:

- To mimic clinical practice of first gaining control of the disease and heartburn episodes before transitioning to an "On-Demand" dosing scheme.
- To minimize inclusion of potential functional heartburn patients who do not truly have acid-related NERD prior to randomization.
- To emulate the future Phase 3 design that plans to have a Run-In Period for the reasons stated above.

Four weeks of treatment is consistent with the duration of studies for the treatment of heartburn and an appropriate duration to identify patients with stable disease.

#### 3.1.1.2 Rationale for the On-Demand Treatment Period

On-demand studies with $H_2$RAs ranged from 2 to 4 weeks in duration. It is anticipated that after 4 weeks of continuous treatment with vonoprazan, it may take several days for symptoms to return. Therefore, an On-Demand Treatment Period of 6 weeks is deemed an appropriate duration for Study NERD-201 to observe a sufficient number of episodes of heartburn for this study.

# 4 Subject Selection and Withdrawal Criteria

## 4.1 Selection of Study Population

This study will be conducted at approximately 65 sites in the United States and will enroll approximately 500 subjects in the Run-In Period to allow randomization of approximately 200 subjects (approximately 50 subjects per arm) in the On-Demand Treatment Period.

Deviations from the inclusion and exclusion criteria will not be allowed since they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

### 4.1.1 Selection for Run-In Period

#### 4.1.1.1 Inclusion Criteria for Run-In Period

Subjects are eligible for enrollment in the Run-In Period of 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.
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 identified their main symptom as heartburn, a burning sensation in the retrosternal area (behind the breastbone).
5. History of episodes of heartburn for 6 months or longer prior to screening.
6. Heartburn reported on 4 or more days during any 7 consecutive days in 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 nonsterilized 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 Appendix 2 (Section 13.2) of this protocol.

#### 4.1.1.2 Exclusion Criteria for Run-In Period

Subjects are not eligible for study participation in the Run-In Period of the study if they meet any of the following exclusion criteria:

1. Endoscopically confirmed EE during the Screening Period assessed by the investigator. Endoscopy should be performed after subjects meet Inclusion Criteria 6. Any endoscopic confirmation performed in a routine clinical setting within 7 days before signing the informed consent is acceptable to use for the purpose of fulfilling the screening requirement.
2. The subject has active irritable bowel syndrome (IBS) or 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 heartburn diagnosed by the Rome IV criteria: (Appendix 4).
4. The subject has a history of or is suspected of having functional dyspepsia diagnosed by the Rome IV criteria (Appendix 4).
5. The subject has endoscopic Barrett's esophagus (>1 cm of columnar-lined esophagus) and/or definite dysplastic changes in the esophagus.
6. 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.
7. The subject has scleroderma (systemic sclerosis).

8. The subject has a history of surgery or endoscopic treatment affecting gastroesophageal reflux, including fundoplication and dilation for esophageal stricture (except Schatzki's ring) or a history of gastric or duodenal surgery (except endoscopic removal of benign polyps).
9. The subject has an active gastric or duodenal ulcer within 4 weeks before the first dose of study drug.
10. Use of prescription or non-prescription PPIs or $H_2$RAs throughout the study.
11. The subject has received vonoprazan in a clinical trial at any time or any other investigational compound (including those in post-marketing studies) within 30 days prior to the start of the Screening Period. 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.
12. 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.
13. The subject has cutaneous lupus erythematosus or systemic lupus erythematosus.
14. The subject has had clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to Screening.
15. The subject has Zollinger-Ellison syndrome or other gastric acid hypersecretory conditions.
16. 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, titanium oxide, or red or yellow ferric oxide). Skin testing may be performed according to local standard practice to confirm hypersensitivity.

17. The subject has a history of alcohol abuse, illegal drug use, drug addiction, 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 within the 12 months prior to screening. Subjects must have a negative urine drug screen for cannabinoids/tetrahydrocannabinol and non-prescribed medications at screening. Subjects taking prescription drugs (except prescription cannabinoids/tetrahydrocannabinol) will be allowed.
18. The subject is taking any excluded medications or treatments listed in the protocol (Section 5.9.2).
19. 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.
20. 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.
21. The subject requires hospitalization or has surgery scheduled during the course of the study or has undergone major surgical procedures within 30 days prior to the Screening Visit.
22. The subject has a history of malignancy (including MALToma) 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 recovered from cutaneous basal cell carcinoma or cervical carcinoma in situ).
23. The subject has AIDS or human immunodeficiency virus (HIV) infection, or tests positive for the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or HCV-RNA. However, subjects who test positive for HCV antibody but negative for HCV-RNA are permitted to participate.

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

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

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

#### 4.1.1.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the Run-In 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, pretreatment adverse event (PTE), AEs, and any serious adverse events (SAEs).

If a suspected erroneous laboratory result is obtained at screening, retesting of that laboratory parameter will be allowed at investigator discretion with medical monitor approval.

Subjects may be allowed to be rescreened upon discussion with medical monitor.

### 4.1.2 Selection for On-Demand Treatment Period

#### 4.1.2.1 Inclusion Criteria for On-Demand Treatment Period

Subjects are eligible for enrollment in the On-Demand Treatment Period of the study if they meet all of the following inclusion criteria:

1. The subject completes the Run-In Period, during which the subject was at least 80% compliant with open-label study drug.
2. The subject has stable disease, ie, no heartburn the last 7 days of the Run-In Period.
3. The subject continues to fulfill all eligibility criteria for the Run-In Period (except Inclusion Criteria 4).

4. Subject completes at least 80% of diary entries during Run-In Period, including 80% of diary entries over the last 7 days.

#### 4.1.2.2 Run-In Failures

Run-In failures refer to instances when subjects consent to participate in the clinical study, are subsequently entered in the Run-In Period of the study, and do not meet the eligibility criteria for the On-Demand Treatment Period. Run-In failures may also include those subjects who withdraw from the study drug or the study (Section 4.2) during the Run-In Period. Run-In failures who do not meet On-Demand entrance eligibility criteria are to undergo all applicable Week 4 Run-In Period assessments (Table 13-1-Schedule of Events).

### 4.1.3 Lifestyle Considerations

Subjects should be instructed as follows:

- 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.
- 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 1 week after completing the On-Demand Treatment Period.

### 4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time (eg, Run-In Period, On-Demand Treatment Period) and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. The primary reason for discontinuation or withdrawal of the subject from the study drug or the study should be recorded in the electronic case report form (eCRF). For screen failure subjects, refer to Section 4.1.1.3. For Run-In failure subjects, refer to Section 4.1.2.2.

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 Appendix 3 (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 (subjects who discontinue from the Run-In Period will undergo all Week 4 Run-In Period assessments). Subjects who fail to return for final assessments will be contacted by the site to make every attempt to comply with the protocol.

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

See the SoE in Appendix 1 (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 Run-In Period or On-Demand Treatment 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:

- 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.
- 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.
- 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

Subjects who meet all of the inclusion criteria and none of the exclusion criteria and have symptomatic NERD will initially be dosed during an open-label Run-In Period with vonoprazan 20 mg QD for 4 weeks.

Subjects with stable disease (as defined by those who have no heartburn on the last 7 consecutive days of the Run-In Period) and are compliant with the diary and study medication will be randomized using a 1:1:1:1 allocation ratio to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo during the 6-week On-Demand Treatment Period. Subjects will be provided study medication on Day -1 of the On-Demand Treatment Period and instructed to take their first dose of study medication after experiencing the first heartburn episode.

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

## 5.2 Treatments Administered

### 5.2.1 Run-In Period

- Open-label study drug (vonoprazan 20 mg QD) to be taken orally for 4 weeks.
- Subjects should be instructed as follows:

  To take study drugs with approximately 240 mL (8 oz) water at about the same time each day.

### 5.2.2 On-Demand Treatment Period

- Blinded study drug (vonoprazan 10 mg, vonoprazan 20 mg, vonoprazan 40 mg, or placebo) to be taken orally On-Demand for treatment of episodic heartburn. Study drug should only be taken once in a 24-hour period. The diary will confirm if

24 hours has elapsed since the last dose of study drug. The On-Demand Treatment Period will be 6 weeks.

- Subjects should be instructed as follows:

  To take study drug On-Demand with approximately 240 mL (8 oz) water.

## 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 Period, Run-In Period, On-Demand Treatment Period, and Safety Follow-up Period.
- During the On-Demand Period, rescue antacid should not be taken until 3 hours after study drug administration.

## 5.4 Identity of Investigational Product and Rescue Antacid

### 5.4.1 Vonoprazan and Placebo

Vonoprazan study medication will be supplied as 10-mg, 20-mg, and 40-mg capsules. The tablet drug product will be over-encapsulated into Swedish Orange DB-AAel capsules containing microcrystalline cellulose at the contract manufacturing organization, [redacted] Rockford, IL, USA. The 40-mg capsule is composed of two 20-mg tablets in one Swedish Orange DB-AAel capsule. [redacted] manufactures the vonoprazan drug substance and tablet drug product.

The over-encapsulated vonoprazan 10-mg, 20-mg, and 40-mg dose strengths and placebo will be identical in appearance. They will be packaged in bottles.

### 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 Run-In, On-Demand Treatment, and Safety 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 bottles and shipped by [redacted].

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

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.

### 5.5.2 Test Article and Rescue Antacid Accountability

The investigator will maintain accurate records of receipt of all test articles, 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 study drug is dispensed in the 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 will be maintained using the IRT.

A double-blind design is employed so that both the investigators and the subjects will be unaware of the treatment assignment during the On-Demand Treatment Period. 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. 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.

### 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 at home, compliance with study drug is to be assessed at each visit. Compliance will be assessed by direct questioning and counting returned capsules during the 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 be recorded in the eCRF.

Noncompliance during the Run-In Period 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 during the Run-In Period or On-Demand Treatment Period is defined as completing less than 80% of study diary entries. Subjects exhibiting poor compliance as assessed by diary entries should be counseled on the importance of good compliance to the study assessments.

## 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 enrollment (or has received within 30 days before the time of enrollment) 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

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 $H_2$RAs 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 Background Medications

Subjects who are being treated with these medications before signing the informed consent, who have no endoscopic evidence of a gastric or duodenal ulcer (see Section 4.1.1.2) during the Screening Period, and who are compliant with the dosage as instructed by the medication package insert are permitted to continue, but the dose and administration method are not permitted to change. Switching between QD and once-weekly regimens is permitted for drugs containing the same active ingredient:

- Bisphosphonates
- Antiplatelets (includes low-dose aspirin)
- Anticoagulants
- Psychotropics
- Antidepressants
- Methotrexate
- Nonsteroidal anti-inflammatory drugs

Corticosteroids are permitted for the subjects who are using them before signing the ICF at start of the Screening Period, but the dose and administration will not be changed during the study.

### 5.9.2 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 |
| $H_2$RAs | Screening Period | Follow-up Visit |
| PPIs | Screening Period | Follow-up Visit |
| Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin) | 14 days prior to Run-In Period Day 1 | End of On-Demand treatment |
| CYP3A4 substrates with a narrow therapeutic index | 14 days prior to Run-In Period Day 1 | End of On-Demand treatment |
| Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy) | 30 days prior to Run-In Period 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 Run-In Period Day 1 | Follow-up Visit |
| Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan) | 5 days prior to Run-In Period Day 1 | Follow-up Visit |

Abbreviations: CYP, cytochrome P450 isoenzyme; $H_2$RA, histamine-$_2$ receptor antagonist; PPI, proton pump inhibitor.

# 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. Protocol waivers or exemptions are not allowed. 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

During the Screening Period, an endoscopy will be performed on all subjects to document the absence of EE. The screening endoscopy should be performed after the subject has fulfilled all other admission criteria (including diary) and will be assessed by the investigator. Any endoscopic confirmation performed in a routine clinical setting within 7 days before signing the informed consent is acceptable to use for the purpose of fulfilling the screening requirement.

## 6.2 Efficacy Assessments

### 6.2.1 Electronic Diary

Subjects will be given an electronic diary on the first day of the Screening Period. During the Screening, Run-In, and Safety Follow-up Periods subjects will complete the morning and evening Heartburn Diary and Rescue Antacid Diary. During the On-Demand Treatment Period, subjects will complete the heartburn episode diary, including the Timed Heartburn Assessments and Rescue Antacid Diary. Subjects must bring the electronic diary device to each site visit for the investigator to verify Run-In and On-Demand diary eligibility criteria and to move the subject to the appropriate period within the electronic diary device, as noted

in the eDiary Vendor User Manual. Subjects must return the devices that have been assigned to them upon completion/termination from the study.

#### 6.2.1.1 Morning and Evening Heartburn Diary

During the Screening Period, Run-In Period, and Safety Follow-up Period, subjects will document the presence and severity of daytime and nighttime heartburn symptoms twice daily in their diary. If the subject experiences no heartburn on any given day, they should also provide this information. The electronic diary should be completed every morning upon waking (to record the previous evening's heartburn episode and severity rating) and every evening before bedtime (to record that day's heartburn episode and severity rating).

#### 6.2.1.2 Rescue Antacid Diary

During all periods of the study, subjects will record the use of rescue antacid, including the time and number of tablets taken.

#### 6.2.1.3 On-Demand Heartburn Episode Diary

During the On-Demand Treatment Period, subjects will document episodes of heartburn experienced and the use of On-Demand study medication as they occur. On days that a subject has not reported an episode of heartburn, subjects will also be reminded every morning and every evening to record any unrecorded heartburn episodes (no longer than the prior day) OR to document that they have not had any heartburn episodes.

#### 6.2.1.4 On-Demand Heartburn Timed Assessments

Once heartburn is reported and the subject is eligible to take study medication (ie, 24 hours since the last administration), the diary will be programmed to collect the heartburn episode assessments for 3 hours in order to assess when heartburn relief occurs. The diary will prompt responses 30 minutes after study drug administration is reported and then 1, 1.5, 2, and 3 hours after study drug treatment. On rare occasions, when required, subjects may opt out of the timed assessments.

#### 6.2.1.5 Severity Definitions

The severity of heartburn will be graded by the subject according to the definitions outlined in Table 6-1 for the Screening, Run-In, and Safety Follow-up Periods.

**Table 6-1 Definitions of Heartburn Severity (Daytime/Nighttime) for the Screening, Run-In, and Safety 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 |

The severity of heartburn will be graded by the subject according to the definitions outlined in Table 6-2 for the On-Demand Treatment Period.

**Table 6-2 Definitions of Heartburn Severity for the On-Demand Treatment Period**

| |
|---|
| Mild - Heartburn is present but can be ignored, does not influence daily routine or sleep |
| Moderate - Heartburn cannot be ignored and/or occasionally influences daily routine or sleep |
| Severe - Heartburn regularly influences daily routine or sleep |
| Very Severe - Heartburn markedly influences daily routine or sleep |

### 6.2.2 PAGI-SYM Questionnaire

During the start of the Run-In Period (Day -1), at the end of the Run-In Period, and at the end of the On-Demand Treatment Period, each subject will self-administer a paper version of the Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) questionnaire.

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.

### 6.2.3 PAGI-QoL Questionnaire

During the start of the Run-In Period (Day -1), at the end of the Run-In Period, and at the end of the On-Demand Treatment Period, each subject will self-administer a paper version of the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL) questionnaire.

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.

### 6.2.4 Patient Global Impression of Change Questionnaire

At the end of the Run-In Period and at the end of the On-Demand Treatment Period, each subject will self-administer a paper version of the Patient Global Impression of Change.

Subjects will record their responses directly on each questionnaire. The data from the questionnaire will be entered into the eCRF, and the originals will remain at the site as source documentation.

### 6.2.5 Patient Global Impression of Severity Questionnaire

At the end of the Run-In Period and at the end of the On-Demand Treatment Period, each subject will self-administer a paper version of the Patient Global Impression of Severity.

Subjects will record their responses directly on each questionnaire. The data from the questionnaire will be entered into the eCRF, and the originals will remain at the site as source documentation.

### 6.2.6 Patient Preference Questionnaire

At the end of the On-Demand Treatment Period, each subject will self-administer a paper version of the Patient Preference Questionnaire.

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.

## 6.3 Safety Assessments

### 6.3.1 Pretreatment Events and Adverse Events

#### 6.3.1.1 Definitions

##### 6.3.1.1.1 Definitions of Pretreatment Adverse Events

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

A treatment-emergent adverse event (TEAE) is defined as any event that occurs after the first dose of study drug or any event at baseline that worsens in either intensity or frequency after the first dose of study drug 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 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 Appendix 3, 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 |
| *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 (ie, 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 cardiovascular accident but with some persisting paresis).
- Fatal: The AEs/PTEs are considered the cause of death.
- Unknown: The course of the AE/PTE cannot be followed up due to a hospital change or residence change at the end of the subject's participation in the study.

### 6.3.1.3 Time Period and Frequency for Collecting AE and SAE Information

#### 6.3.1.3.1 Collection and Reporting of Adverse Events

Collection of PTEs will commence from the time the 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:

1. Event term
2. Start and stop date
3. Severity
4. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs)
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
6. Action concerning study drug (not applicable for PTEs)
7. Outcome of event
8. Seriousness

#### 6.3.1.3.2 Collection and Reporting of Serious Adverse Events

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

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

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number

- Investigator's name
- Name of the study drug(s)
- Causality assessment

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

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

[redacted]

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 (contract research organization) will be delegated the responsibility for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), 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 products.

### 6.3.1.4 Regulatory Reporting Requirements for SAEs

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

The sponsor/sponsor designee has a legal responsibility to notify 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<br>• RBC count<br>• Hemoglobin<br>• Hematocrit<br>• RBC indices: MCV, MCH<br>• %Reticulocytes<br>• WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils |
| Clinical chemistry(a) | • Blood urea nitrogen<br>• Creatinine<br>• Total and direct bilirubin<br>• ALT/SGPT<br>• AST/SGOT<br>• Alkaline phosphatase<br>• Total protein<br>• Potassium<br>• Sodium<br>• Calcium<br>• Glucose (fasting)(e)<br>• GGT |
| Routine urinalysis | • Specific gravity, appearance, color<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase<br>• Microscopic examination (if blood or protein is abnormal) |
| Other screening tests | • FSH if menopause is suspected(b)<br>• Urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine<br>• Serum hCG pregnancy test(c) at Screening Visit 1<br>• Urine hCG pregnancy test(c) at Run-In Period Visit 2, randomization Visit 3, and final visit for On-Demand Treatment Period Visit 5<br>• Serology (HIV antibody, HBsAg, and HCV antibody; hepatitis C, viral load RNA(d) [qualitative])<br>• Serum gastrin (fasting 12 hours) and serum pepsinogen I and II levels will also be evaluated as safety/PD biomarkers at Day -1 of Run-In Period; Week 4 of Run-In Period; Week 6 of On-Demand Treatment Period; and safety follow-up visit. Day -1 baseline gastrin levels will not be blinded. Gastrin at the Week 4 Run-In, Week 6 On-Demand treatment, and Safety Follow-up visits 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. |

Abbreviations: 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; PD, pharmacodynamics; RBC, red blood cell; 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) Required only for confirmation of postmenopausal females as defined in Section 13.2 (Appendix 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.

(c) As needed for women of childbearing potential. During the Run-In Period and On-Demand Treatment Period, serum pregnancy test will be performed if the urine pregnancy test is positive.

(d) Reflex - if hepatitis C positive.

(e) 8 hours fasting at Screening Visit 1.

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 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, lungs, cardiovascular system, and abdomen (liver and spleen).

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, QTcF (derived) and QRS interval. 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

Not applicable.

# 7 Statistical and Analytical Plan

This section describes the statistical and analytical methods to be used for the study. A statistical analysis plan (SAP) 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 SAP will be finalized before database lock.

## 7.1 Sample Size Calculations

The sample size for the On-Demand Treatment Period is calculated based on the following assumptions:

- Subjects will be randomized to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo with a randomization ratio of 1:1:1:1.
- Each subject experiences at least 4 evaluable heartburn episodes.
- Comparison between each dose of vonoprazan to placebo will be performed using the Fisher's Exact test.
- A clinically relevant difference of 15% between each dose of vonoprazan and placebo in the proportion of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug.

Based on these assumptions, a sample size of 200 heartburn episodes per treatment group (or 50 subjects with at least 4 heartburn episodes per treatment group) provides at least 80% statistical power at the significance level of 0.05. During the study if less than 200 subjects are projected to enroll into the On-Demand Treatment Period, additional subjects may be enrolled into the Run-In Period to ensure that a sufficient number of subjects enroll into the On-Demand Treatment Period.

Assuming 60% of subjects at the end of the Run-In Period do not meet the eligibility criteria for the On-Demand Treatment Period, a total of approximately 500 subjects will be enrolled into the Run-In Period to achieve 200 subjects for the On-Demand Treatment Period.

The hypothesis testing is as follows:

Null Hypothesis $H_{0:}\ P_{vono} = P_{placebo}$

Alternative Hypothesis $H_{a:}\ P_{vono} \neq P_{placebo}$

where P is the proportion of heartburn episodes.

## 7.2 Analysis Sets

The following analysis sets will be used in the statistical analysis.

### 7.2.1 All Subjects Set

All Subjects set consists of all eligible subjects who enrolled into the Run-In Period.

### 7.2.2 Safety Sets

All safety endpoints will be reported for the Run-In and On-Demand Treatment Periods separately using the Safety set of each period. For the Run-In Period, the primary and secondary endpoints will be reported for the Safety Run-In set.

**Safety Run-In Set**

The Safety Run-In set includes subjects in the All Subjects set who received at least one dose of study drug (vonoprazan 20 mg) during the Run-In Period.

**Safety On-Demand Set**

The Safety On-Demand set includes all subjects in the Safety Run-In set who were randomized and treated at least one heartburn episode with randomized treatment during the On-Demand Treatment Period.

### 7.2.3 Intent-to-Treat Set

All efficacy endpoints (primary, secondary, and exploratory) will be analyzed for the On-Demand Treatment Period for the Intent-to-Treat (ITT) On-Demand set.

**Intent-to-Treat On-Demand Set**

The ITT On-Demand set includes all subjects in the Safety Run-In set who were randomized and completed at least one heartburn episode diary during the On-Demand Treatment Period.

## 7.3 Description of Subgroups

The primary endpoint, the percentage of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug, will be analyzed by subgroup using the primary analysis method.

The subgroups are:

- age category, years (<45, ≥45 - <65, ≥65 - <75, ≥75)
- sex (male, female)
- baseline body mass index (BMI) category, $kg/m^2$ (<25, ≥25 - <30, ≥30)
- mean heartburn severity during the Screening Period (mild, moderate, severe, very severe)

## 7.4 Statistical Analysis Methodology

For the On-Demand Treatment Period, each treatment comparison of vonoprazan 10 mg, 20 mg, and 40 mg to placebo will be tested at the 0.05 significance level.

An evaluable heartburn episode is an episode for which study drug was taken and for which the subject completed at least one entry in the heartburn episode diary. For a heartburn episode to be considered completely relieved, a subject must not have taken rescue antacid within 3 hours of taking study drug.

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 of all endpoints, primary, secondary, and exploratory, will be described in detail in the SAP. Statistical analysis will be performed using SAS software Version 9.4 or later.

No adjustments will be made for multiple comparisons given the exploratory nature of this study.

### 7.4.1 Efficacy Analyses

#### 7.4.1.1 Primary Efficacy Endpoint

The primary endpoint of the percentage of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug will be compared between each dose of vonoprazan and placebo using Fisher's Exact test for the ITT On-Demand set.

A sensitivity analysis of the primary endpoint will be performed by including heartburn episodes with rescue antacid use within 3 hours after taking study drug as completely relieved.

#### 7.4.1.2 Secondary Efficacy Endpoint

All secondary endpoints will be analyzed for the ITT On-Demand set and compared for each dose of vonoprazan to placebo.

The following secondary endpoints will be compared for each dose of vonoprazan to placebo using Fisher's Exact test.

- The percentage of evaluable heartburn episodes completely relieved within 3 hours after taking study drug.
- The percentage of subjects with complete relief of heartburn within 3 hours after the first episode and with no further heartburn reported for 24 hours after taking study drug.

The following secondary endpoints will be compared for each dose of vonoprazan to placebo using a Wilcoxon rank-sum test.

- The percentage of evaluable heartburn episodes for each subject that are completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug.

- The percentage of days study drug was taken over the On-Demand Treatment Period.
- The mean number of tablets of rescue antacid taken per day over the On-Demand Treatment Period.
- The percentage of 24-hour heartburn-free days over the On-Demand Treatment Period.

#### 7.4.1.3 Exploratory Endpoints On-Demand Treatment Period

The exploratory endpoints will be analyzed for the ITT On-Demand set. The analysis of exploratory endpoints will be described in detail in the SAP. These endpoints are:

- The percentage of evaluable heartburn episodes completely relieved within 30 minutes or 1, 1.5, or 2 hours and with no further heartburn reported for 24 hours after taking study drug.
- The percentage of evaluable heartburn episodes that are completely relieved within 30 minutes or 1, 1.5, or 2 hours after taking study drug.
- The percentage of evaluable heartburn episodes that improved at 30 minutes or 1, 1.5, 2, or 3 hours after taking study drug.
- The percentage of episodes for which subjects continue to be heartburn-free after 24 or 48 hours of taking study drug.
- The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours with no further heartburn reported for 24 hours after taking study drug.
- The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours after taking study drug.
- The percentage of subjects with complete relief of the first episode of heartburn within 3 hours after taking study drug.
- The mean number of days between heartburn episodes.

- The percentage of days without daytime heartburn over the On-Demand Treatment Period.
- The percentage of days without nighttime heartburn over the On-Demand Treatment Period.
- The mean severity of daytime and nighttime heartburn over the On-Demand Treatment Period.
- The mean severity of nighttime heartburn over On-Demand Treatment Period.
- The mean severity of daytime heartburn over the On-Demand Treatment Period.
- The percentage of days without rescue antacid use over the On-Demand Treatment Period.
- The change from baseline to the end of the On-Demand Treatment Period for each subscale and the total score of the PAGI-SYM questionnaire.
- The change from baseline to the end of the On-Demand Treatment Period for each subscale and the total score of the PAGI-QoL questionnaire.
- The patient global impression of change in GERD symptoms at the end of the On-Demand Treatment Period.
- The patient global impression of severity in GERD symptoms over the last 7 days of the On-Demand Treatment Period.
- The percentage of subjects with each dosing preference.

#### 7.4.1.4 Exploratory Endpoints Run-In Period

The exploratory endpoints will be analyzed for the Safety Run-In set. The analysis of exploratory endpoints will be described in detail in the SAP. These endpoints are:

- The percentage of 24-hour heartburn-free days over the Run-In Period.
- The percentage of days without daytime heartburn over the Run-In Period.

- The percentage of days without nighttime heartburn over the Run-In Period.
- The mean severity of daytime and nighttime heartburn over the Run-In Period.
- The mean severity of nighttime heartburn over the Run-In Period.
- The mean severity of daytime heartburn over the Run-In Period.
- The percentage of days without rescue antacid use over the Run-In Period.
- The change from baseline to the end of the Run-In Period for each subscale and the total score of the PAGI-SYM questionnaire.
- The change from baseline to the end of the Run-In Period for each subscale and the total score of the PAGI-QoL questionnaire.
- The patient global impression of change in GERD symptoms at the end of the Run-In Period.
- The patient global impression of severity in GERD symptoms over the last 7 days of the Run-In Period.

### 7.4.2 Safety Analyses

Safety will be summarized separately for the Run-In Period and the On-Demand Treatment Period. For each period, safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I/II levels, ECGs and vital signs. For the Run-In Period, baseline will be the last assessment on or before the date of first dose of study drug in the Run-In Period. For the On-Demand Treatment Period, baseline will be the last assessment on or before the date of randomization.

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing TEAEs (see definition in Section 6.3.1.1.2) will be summarized by MedDRA system organ class (SOC) and preferred term (PT) overall, by severity, and by relationship to study drug for the Run-In and On-Demand Treatment Periods 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 an SOC, the subject will be counted only once for that SOC. In the tabulation of TEAE frequency by maximum intensity, a subject will be counted only once using the highest severity for each PT and SOC.

Clinical laboratory tests, pepsinogen I/II levels, gastrin levels, 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.

### 7.4.3 Other Analyses

For the Run-In Period, demographics and other baseline characteristics will be summarized overall and by treatment group using the Safety Run-In set. For the On-Demand Treatment Period, demographics and other baseline characteristics will be summarized overall and by treatment group using the ITT On-Demand and Safety On-Demand sets.

Summary statistics (N, 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, race).

### 7.4.4 Interim Analyses

No interim analyses will be performed.

# 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 diary cards, 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, removing 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 (WHODRUG).

After database lock, each study site will receive a CDROM containing all of their site-specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a CDROM copy 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 CDROM copy 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 US Food and Drug Administration (FDA) or any regulatory authority(ies), or the IRB/IEC.

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

## 10.2 Financial Disclosure and Obligations

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

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

## 10.3 Investigator Documentation

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

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

## 10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

## 10.5 Adherence to Protocol

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

## 10.6 Adverse Events and Study Report Requirements

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

## 10.7 Investigator's Final Report

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

## 10.8 Records Retention

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

## 10.9 Publications

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

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

# 11 Study Management

## 11.1 Monitoring

### 11.1.1 External Data Monitoring Committee

Not applicable.

### 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 and approval, 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 will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations 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.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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# 13 Appendices

## 13.1 Appendix 1: Schedule of Events

## Table 13-1 Schedule of Events

| | Screening Period (a) | Run-In Period | | | On-Demand Treatment Period | | | | | Safety Follow-up | Unscheduled Visit (b) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Timing** | **Up To 5 Weeks** | **Day-1** | **Day 1 (c)** | **Week 4 (Day-1 of On-Demand Treatment Period) (c) Day 28** | **Day 1 (c)** | **Week 1 Day 7** | **Week 2 Day 14** | **Week 3 Day 21** | **Week 6 /Final Visit/EOS Visit Day 42** | **Day 49** | |
| **Visit Windows (Days)** | **Day -36 to -2** | | | **Day 26 to Day 35** | | **Day 5 to 9** | **Day 12 to 16** | **Day 19 to 25** | **Day 40 to 46** | **Day 49 to 60** | |
| **Visit Number:** | **1** | **2** | | **3** | | **TC1** | **TC2** | **4** | **5** | **6** | |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria for Run-In Period | X | X | | | | | | | | | |
| Inclusion/Exclusion Criteria for On-Demand Treatment Period | | | | X(d) (p) | | | | | | | |
| Demographic and medical history | X | | | | | | | | | | |
| Smoking status and alcohol use | X | | | | | | | | | | |
| Medication history | X | | | | | | | | | | |
| Physical examination(e) | X | X | | X (p) | | | | | X | X | X |
| Vital signs | X | X | | X(p) | | | | | X | X | X |
| Weight and height | X | | | | | | | | | | |
| Concomitant medications | X | X | | X(p) | | X | X | X | X | X | X |
| Concurrent medical conditions | X | | | | | | | | | | |
| FSH(f) | X | | | | | | | | | | |
| Hepatitis B and C; HIV | X | | | | | | | | | | |
| Urine drug screen | X | | | | | | | | | | |
| Clinical laboratory test including hematology, serum chemistry, and urinalysis(g) | X | | | X(p) | | | | | X | X | X |
| 12 hour Fasting serum gastrin/pepsinogen I/II levels(h) | | X (o) | | X(p) | | | | | X | X | |
| Pregnancy test (i) | X | X | | X(p) | | | | | X | | |
| Guidance on avoidance of pregnancy | X | X | | X(p) | | X | X | X | X | | |
| ECG | X | X | | | | | | | X | | |
| Endoscopy | X(j) | | | | | | | | | | |
| Subject's diary; distribute and/or review including safety and treatment compliance and/or collect diary device | X(k) | X | | X(p) | | X | X | X | X | X | |

| | Screening Period (a) | Run-In Period | | | On-Demand Treatment Period | | | | | Safety Follow-up | Unscheduled Visit (b) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Timing | Up To 5 Weeks | Day-1 | Day 1 (c) | Week 4 (Day-1 of On-Demand Treatment Period) (c) Day 28 | Day 1 (c) | Week 1 Day 7 | Week 2 Day 14 | Week 3 Day 21 | Week 6 /Final Visit/EOS Visit Day 42 | Day 49 | |
| Visit Windows (Days) | Day -36 to -2 | | | Day 26 to Day 35 | | Day 5 to 9 | Day 12 to 16 | Day 19 to 25 | Day 40 to 46 | Day 49 to 60 | |
| Visit Number: | 1 | 2 | | 3 | | TC1 | TC2 | 4 | 5 | 6 | |
| PAGI-SYM | | X | | X(p) | | | | | X | | |
| PAGI-QoL | | X | | X(p) | | | | | X | | |
| Patient Global Impression of Change | | | | X(p) | | | | | X | | |
| Patient Global Impression of Severity | | | | X(p) | | | | | X | | |
| Patient Preference Questionnaire | | | | | | | | | X | | |
| Enrollment (Run-In) | | X | | | | | | | | | |
| Randomization (On-Demand) | | | | X | | | | | | | |
| Dispense study drug | | X(l) | | X(l) | | | | | | | |
| Dispense rescue antacid | X | X(m) | | X(m) | | | | | X(m) | | |
| First day of open-label study drug administration | | | X | | | | | | | | |
| First day of possible blinded study drug administration | | | | | X | | | | | | |
| Drug return/accountability/ review treatment compliance (n) | | | | X(p) | | | | | X | X | |
| Telephone call to subject | | | | | | X | X | X | | | |
| AE/pretreatment event assessment | X | X | | X(p) | | X | X | X | X | X | X |

Abbreviations: AE, adverse event; ECG, electrocardiogram; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus, PAGI-SYM, Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index; PAGI-QoL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; TC, telephone contact

(a) Visit window is Day -36 to Day -2 for assessment of clinical laboratory assessments, ECG, and endoscopy in the Screening Period. Any endoscopic confirmation performed in a routine clinical setting within 7 days before signing the informed consent is acceptable to use for the purpose of fulfilling the screening requirement.

(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) The date of first dosing day is defined as Day 1 in both Run-In Period and On-Demand Treatment Period. The date of randomization is defined as Day -1 of On-Demand Treatment Period.

(d) Subjects should continue to meet inclusion criteria (Section 4.1.1.1) and exclusion criteria (Section 4.1.1.2), except Inclusion Criterion 4.

(e) Full physical examination is performed at Screening; a brief physical examination is performed at all other visits.

(f) Required only for confirmation of postmenopausal females as described in Section 13.2 (Appendix 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.

(g) See Section 6.3.3 and Table 6-4 for all required laboratory assessments.

(h) Gastrin Week 4 Run-In, Week 6 On-Demand treatment and Safety follow-up visits and pepsinogen I and II results will be blinded and will not be reported to investigative sites or other blinded personnel until the study blind is broken.

(i) Only female subjects with childbearing potential. Serum hCG at screening and urine hCG at all subsequent visits.

(j) The screening endoscopy can be performed any time during that period; however, it should be performed after the subject has fulfilled all other admission criteria. Any endoscopic confirmation performed in a routine clinical setting within 7 days before signing the informed consent is acceptable to use for the purpose of fulfilling the screening requirement.

(k) 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 Screening, Run-In and Follow-up Period. During the On-Demand Treatment Period, subjects will be instructed to complete the electronic diary to document heartburn episodes and study drug administration. Rescue antacid use should be reported during all periods.

(l) Subjects are to start dose administration from Day 1.

(m) Rescue antacid will be dispensed as needed after the Screening Period.

(n) Sites will document dispensing rescue antacid. Subjects do not need to return unused rescue antacid.

(o) Day -1 baseline gastrin levels will not be blinded.

(p) Run-In failure procedures.

## 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 nonsterilized male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

> *Females NOT of childbearing potential are defined as those who 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 an follicle-stimulating hormone (FSH) >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 (all subjects) | • ALT or AST >8 × ULN |
| Normal ALT and AST | • ALT or AST >5 × ULN and persists for more than 2 weeks<br>• 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<br>• 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%) |
| Elevated ALT or AST | • ALT or AST >5 × ULN **AND** persists for more than 2 weeks<br>• ALT or AST >5× ULN **AND** in conjunction with elevated total bilirubin >2 ULN or INR >1.5<br>• ALT or AST >5 × ULN **AND** appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) |

Abbreviations: 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:

### 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 for Functional Heartburn and Functional Dyspepsia

Rome IV criteria (2016) 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/esophogastric 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)*

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

AND

2. 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*

- Postprandial epigastric pain or burning, epigastric bloating, excessive belching, and nausea can also be present
- Vomiting warrants consideration of another disorder
- Heartburn is not a dyspeptic symptom but may often co-exist
- Symptoms that are relieved by evacuation of feces or gas should generally not be considered as part of dyspepsia
- 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

Changes to the protocol text

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 bold and deletions are shown in ~~strike through~~ text. Corrections of obvious typing errors or omissions are not highlighted.

### 13.5.1 Protocol Amendment 1

#### *Protocol Synopsis*

Study Population:

Main Exclusion Criteria:

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

On-Demand Treatment Period (Main Inclusion Criteria):

- The subject has **stable disease, ie,** no heartburn in the last 7 days of the Run-In Period.
- The subject completes the Run-In Period and continues to ~~meet~~**fulfill** all ~~of the inclusion and exclusion~~**eligibility** criteria for the Run-In Period (except heartburn inclusion criteria).

Study Design:

On-Demand Treatment Period:
Subjects who have stable disease (ie, no heartburn on the last 7 days of the Run-In Period) **and are compliant with the diary and study medication** will be randomized to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo On-Demand (but no more than 1 dose within 24 hours) for 6 weeks to treat episodic heartburn. Study-supplied rescue antacid will be allowed 3 hours after taking study medication if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid. In addition, a more detailed diary will also document time of study drug administration and when heartburn relief occurs. **Subjects will be contacted by phone weekly during the first 3 weeks to assess their understanding of diary instructions and On-Demand dosing and to emphasize the importance of completing the diary assessments.**

Sample Size:

Based on these assumptions, a sample size of 200 heartburn episodes per treatment group (or 50 subjects with at least 4 heartburn episodes per treatment group) provides at least 80% statistical

power at the 0.05 significance level. **During the study if less than 200 subjects are projected to enroll into the On-Demand Treatment Period, additional subjects may be enrolled into the Run-In Period to ensure that a sufficient number of subjects enroll into the On-Demand Treatment Period.**

Assuming ~~40~~**60**% of subjects at the end of the Run-In Period do not meet the eligibility criteria for the On-Demand Treatment Period, ~~a total of 334~~**approximately 500** subjects will be enrolled into the Run-In Period to achieve 200 subjects for the On-Demand Treatment Period.

## *Study Design (Section 3.1)*

Figure 3-1 was updated to reflect the subject number changes and the addition of new telephone contacts.

On-Demand Treatment Period:

Subjects who have stable disease (ie, no heartburn on the last 7 days of the Run-In Period**) and are compliant with the Diary and study medication** will be randomized to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo On-Demand for 6 weeks to treat episodic heartburn. Study drug should only be taken once in a 24-hour period. Study-supplied rescue antacid will be allowed 3 hours after taking study medication if needed. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid. In addition, a more detailed diary will also document time of study drug administration and when heartburn relief occurs. **Subjects will be contacted by phone weekly during the first 3 weeks to assess their understanding of diary instructions and On-Demand dosing and to emphasize the importance of completing the diary assessments.**

## *Selection of Study Population (Section 4.1)*

This study will be conducted at approximately 65 sites in the United States and will enroll approximately ~~334~~**500** subjects in the Run-In Period to allow randomization of approximately 200 subjects (approximately 50 subjects per arm) in the On-Demand Treatment Period.

## *Exclusion Criteria for Run-In Period (Section 4.1.1.2)*

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

6. 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.

11. The subject has received ~~any~~**vonoprazan in a clinical trial at any time or any other** investigational compound (including those in post-marketing studies) within 30 days prior to the start of the Screening Period. 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.

14. The subject has had clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to ~~randomization~~**Screening**.

17. The subject has a history of alcohol abuse, illegal drug use, drug addiction, 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 within the 12 months prior to screening. Subjects must have a negative urine drug screen for cannabinoids/tetrahydrocannabinol and non-prescribed medications at screening. Subjects taking prescription drugs **(except prescription cannabinoids/tetrahydrocannabinol)** will be allowed.

### *Inclusion Criteria for On-Demand Treatment Period (Section 4.1.2.1)*

2. The subject has **stable disease, ie,** no heartburn the last 7 days of the Run-In Period.

3. The subject continues to ~~meet the inclusion and exclusion~~**fulfill all eligibility** criteria for the Run-In Period (except Inclusion Criteria 4).

### *Run-In Failures (Section 4.1.2.2)*

Run-In failures refer to instances when subjects consent to participate in the clinical study, are subsequently entered in the Run-In Period of the study, and do not meet the eligibility criteria for the On-Demand Treatment Period. Run-In failures may also include those subjects who withdraw from the study drug or the study (Section 4.2) during the Run-In Period. **Run-In failures who do not meet On-Demand entrance eligibility criteria are to undergo all applicable Week 4 Run-In Period assessments (Table 13-1-Schedule of Events).**

### *Handling of Withdrawals (Section 4.2.2)*

Subjects who discontinue study drug or active participation in the study will no longer receive study drug. When a subject withdraws from the study drug or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will undergo all end-of-study assessments~~.~~ **(subjects who discontinue from the Run-In Period will undergo all Week 4 Run-In Period assessments).** Subjects who fail to

return for final assessments will be contacted by the site to make every attempt to comply with the protocol.

### *Method of Assigning Subjects to Treatment Groups (Section 5.1)*

Subjects with stable disease (as defined by those who have no heartburn on the last 7 consecutive days of the Run-In Period) **and are compliant with the diary and study medication** will be randomized using a 1:1:1:1 allocation ratio to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo during the 6-week On-Demand Treatment Period. Subjects will be provided study medication on Day -1 of the On-Demand Treatment Period and instructed to take their first dose of study medication after experiencing the first heartburn episode.

### *Treatment Compliance (Section 5.8.1)*

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~~, including dates for delays and/or dose reductions,~~ will~~also~~ be recorded in the eCRF.

### *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 |
| $H_2$RAs | Screening Period | Follow-up Visit |
| PPIs | Screening Period | Follow-up Visit |
| Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin) | 14 days prior to **Run-In Period** Day 1 | End of **On-Demand** treatment |
| CYP3A4 substrates with a narrow therapeutic index | 14 days prior to **Run-In Period** Day 1 | End of **On-Demand** treatment |
| Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy) | 30 days prior to **Run-In Period** 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 **Run-In Period** Day 1 | Follow-up Visit |
| Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan) | 5 days prior to **Run-In Period** Day 1 | Follow-up Visit |

| Excluded Medications and Treatments | Beginning of Exclusion | End of Exclusion |
|---|---|---|

Abbreviations: CYP, cytochrome P450 isoenzyme; $H_2RA$, histamine-$_2$ receptor antagonist; PPI, proton pump inhibitor.

### *Electronic Diary (Section 6.2.1)*

Subjects will be given an electronic diary on the first day of the Screening Period. During the Screening, Run-In, and Safety Follow-up Periods subjects will complete the morning and evening Heartburn Diary and Rescue Antacid Diary. During the On-Demand Treatment Period, subjects will complete the heartburn episode diary, including the Timed Heartburn Assessments and Rescue Antacid Diary. **Subjects must bring the electronic diary device to each site visit for the investigator to verify Run-In and On-Demand diary eligibility criteria and to move the subject to the appropriate period within the electronic diary device, as noted in the eDiary Vendor User Manual. Subjects must return the devices that have been assigned to them upon completion/termination from the study.**

### *On-Demand Heartburn Episode Diary (Section 6.2.1.3*

During the On-Demand Treatment Period, subjects will document episodes of heartburn experienced and the use of ~~on-demand~~ **On-Demand** study medication as they occur. **On days that a subject has not reported an episode of heartburn, s**~~S~~ubjects will also be ~~expected to complete the diary in the~~**reminded every** morning and **every** evening to ~~document~~**record any unrecorded heartburn episodes (no longer than the prior day) OR to document that they** ~~if they have or~~ have not had **any** heartburn **episodes**.

### *On-Demand Heartburn Timed Assessments (Section 6.2.1.4)*

Once heartburn is reported and the subject is eligible to take study medication (ie, 24 hours since the last administration), the diary will be programmed to collect the heartburn episode assessments for 3 hours in order to assess when heartburn relief occurs. The diary will prompt responses 30 minutes after study drug administration is reported and then 1, 1.5, 2, and 3 hours after study drug treatment. ~~Subjects will be allowed to~~**On rare occasions, when required, subjects may** opt out of the timed assessments.

## *Table 6-4 Protocol-Required Safety Laboratory Assessments*

| Laboratory Assessments | Parameters |
|---|---|
| Hematology | • Platelet count<br>• RBC count<br>• Hemoglobin<br>• Hematocrit<br>• RBC indices: MCV, MCH<br>• %Reticulocytes<br>• WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils |
| Clinical chemistry(a) | • Blood urea nitrogen<br>• Creatinine<br>• Total and direct bilirubin<br>• ALT/SGPT<br>• AST/SGOT<br>• Alkaline phosphatase<br>• Total protein<br>• Potassium<br>• Sodium<br>• Calcium<br>• Glucose (fasting)**(e)**<br>• GGT |
| Routine urinalysis | • Specific gravity, appearance, color<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase<br>• Microscopic examination (if blood or protein is abnormal) |
| Other screening tests | • FSH if menopause is suspected(b)<br>• Urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine<br>• Serum hCG pregnancy test(c) at Screening Visit 1<br>• Urine hCG pregnancy test(c) at Run-In Period Visit 2, randomization Visit 3, and final visit for On-Demand Treatment Period Visit ~~5~~**7**<br>• Serology (HIV antibody, HBsAg, and HCV antibody; hepatitis C, viral load RNA(d) [qualitative])<br>• Serum gastrin **(fasting 12 hours)** and serum pepsinogen I and II levels will also be evaluated as safety/PD biomarkers at Day -1 **of Run-In Period**; Week 4 of Run-In Period; Week 6 of On-Demand Treatment Period; and safety follow-up visit. **Day -1 baseline gastrin levels will not be blinded.** Gastrin **at the Week 4 Run-In, Week 6 On-Demand treatment,** and **Safety Follow-up visits** 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. |

| Laboratory Assessments | Parameters |
|---|---|

Abbreviations: 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; PD, pharmacodynamics; RBC, red blood cell; 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) ~~Follicle-stimulating hormone will be conducted at the investigator's discretion to determine the postmenopausal status of women~~**Required only for confirmation of postmenopausal females as defined in Section 13.2 (Appendix 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**.

(c) As needed for women of childbearing potential. During the Run-In Period and On-Demand Treatment Period, serum pregnancy test will be performed if the urine pregnancy test is positive.

(d) Reflex - if hepatitis C positive.

**(e) 8 hours fasting at Screening Visit 1.**

## *Vital Signs (Section 6.3.5)*

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). ~~When vital signs are scheduled at the same time as blood collections, the blood collections will take priority.~~

## *Electrocardiograms (Section 6.3.6)*

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, **QTcF (derived)** and QRS interval. 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.

## *Sample Size Calculations (Section 7.1)*

Based on these assumptions, a sample size of 200 heartburn episodes per treatment group (or 50 subjects with at least 4 heartburn episodes per treatment group) provides at least 80% statistical power at the significance level of 0.05. **During the study if less than 200 subjects are projected to enroll into the On-Demand Treatment Period, additional subjects may be**

**enrolled into the Run-In Period to ensure that a sufficient number of subjects enroll into the On-Demand Treatment Period.**

Assuming ~~40~~**60**% of subjects at the end of the Run-In Period do not meet the eligibility criteria for the On-Demand Treatment Period, a total of ~~334~~ **approximately 500** subjects will be enrolled into the Run-In Period to achieve 200 subjects for the On-Demand Treatment Period.

### *Intent-to-Treat Set (Section 7.2.3)*

The ITT On-Demand set includes all subjects in the Safety ~~On-Demand~~**Run-In** set who **were randomized and** completed at least one heartburn episode diary during the On-Demand Treatment Period.

### *Description of Subgroups (Section 7.3)*

- mean heartburn severity during the ~~Run-In~~**Screening** Period (mild, moderate, severe, very severe)

## *Table 13-1 Schedule of Events*

| | Screening Period (a) | Run-In Period | | | On-Demand Treatment Period | | | | | Safety Follow-up | Unscheduled Visit (b) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Timing | Up To 5 Weeks | Day-1 | Day 1 (c) | Week 4 (Day-1 of On-Demand Treatment Period) (c) Day 28 | Day 1 (c) | **Week 1 Day 7** | **Week 2 Day 14** | Week 3 Day 21 | Week 6 /Final Visit/EOS Visit Day 42 | Day 49 | |
| Visit Windows (Days) | Day -36 to -2 | | | Day 26 to Day 35 | | **Day 5 to 9** | **Day 12 to 16** | Day 19 to 25 | Day 40 to 46 | Day 49 to 60 | |
| Visit Number: | 1 | 2 | | 3 | | **TC1** | **TC2** | 4 | 5 | 6 | |
| Informed Consent | X | | | | | | | | | | |
| Inclusion/Exclusion Criteria for Run-In Period | X | X | | | | | | | | | |
| Inclusion/Exclusion Criteria for On-Demand Treatment Period | | | | X(d) **(p)** | | | | | | | |
| Demographic and medical history | X | | | | | | | | | | |
| Smoking status and alcohol use | X | | | | | | | | | | |
| Medication history | X | | | | | | | | | | |
| Physical examination(e) | X | X | | X **(p)** | | | | | X | X | X |
| Vital signs | X | X | | X**(p)** | | | | | X | X | X |
| Weight and height | X | | | | | | | | | | |
| Concomitant medications | X | **X** | | X**(p)** | | **X** | **X** | X | X | X | X |
| Concurrent medical conditions | X | | | | | | | | | | |
| FSH(f) | X | | | | | | | | | | |
| Hepatitis B and C; HIV | X | | | | | | | | | | |
| Urine drug screen | X | | | | | | | | | | |
| Clinical laboratory test including hematology, serum chemistry, and urinalysis(g) | X | | | X**(p)** | | | | | X | X | X |
| 12 **hour** Fasting serum gastrin/pepsinogen I/II levels(h) | | X **(o)** | | X**(p)** | | | | | X | X | |
| Pregnancy test (i) | X | X | | X**(p)** | | | | | X | | |
| Guidance on avoidance of pregnancy | X | X | | X**(p)** | | **X** | **X** | X | X | | |
| ECG | X | X | | | | | | | X | | |

| | Screening Period (a) | Run-In Period | | | On-Demand Treatment Period | | | | | Safety Follow-up | Unscheduled Visit (b) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Timing | Up To 5 Weeks | Day-1 | Day 1 (c) | Week 4 (Day-1 of On-Demand Treatment Period) (c) Day 28 | Day 1 (c) | **Week 1 Day 7** | **Week 2 Day 14** | Week 3 Day 21 | Week 6 /Final Visit/EOS Visit Day 42 | Day 49 | |
| Visit Windows (Days) | Day -36 to -2 | | | Day 26 to Day 35 | | **Day 5 to 9** | **Day 12 to 16** | Day 19 to 25 | Day 40 to 46 | Day 49 to 60 | |
| Visit Number: | 1 | 2 | | 3 | | **TC1** | **TC2** | 4 | 5 | 6 | |
| Endoscopy | X(j) | | | | | | | | | | |
| Subject's diary; distribute and/or review including safety and treatment compliance **and/or collect diary device** | X(k) | X | | X**(p)** | | **X** | **X** | X | X | X | |
| PAGI-SYM | | X | | X**(p)** | | | | | X | | |
| PAGI-QoL | | X | | X**(p)** | | | | | X | | |
| Patient Global Impression of Change | | | | X**(p)** | | | | | X | | |
| Patient Global Impression of Severity | | | | X**(p)** | | | | | X | | |
| Patient Preference Questionnaire | | | | | | | | | X | | |
| Enrollment (Run-In) | | X | | | | | | | | | |
| Randomization (On-Demand) | | | | X | | | | | | | |
| Dispense study drug | | X(l) | | X(l) | | | | | | | |
| Dispense rescue antacid | X | X(m) | | X(m) | | | | | X(m) | | |
| First day of open-label study drug administration | | | X | | | | | | | | |
| First day of possible blinded study drug administration | | | | | X | | | | | | |
| Drug return/accountability/ review treatment compliance (n) | | | | X**(p)** | | | | | X | X | |
| Telephone call to subject | | | | | | **X** | **X** | X | | | |
| AE/pretreatment event assessment | X | X | ~~X~~ | X**(p)** | ~~X~~ | **X** | **X** | X | X | X | X |

Abbreviations: AE, adverse event; ECG, electrocardiogram; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus, PAGI-SYM, Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index; PAGI-QoL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; **TC, telephone contact**

(a) Visit window is Day -36 to Day -2 for assessment of clinical laboratory assessments, ECG, and endoscopy in the Screening Period. Any endoscopic confirmation performed in a routine clinical setting within 7 days before signing the informed consent is acceptable to use for the purpose of fulfilling the screening requirement.

(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~~ **final** visit should be performed.

(c) The date of first dosing day is defined as Day 1 in both Run-In Period and On-Demand Treatment Period. The date of randomization is defined as Day -1 of On-Demand Treatment Period.

(d) Subjects should continue to meet inclusion criteria (Section 4.1.1.1) and exclusion criteria (Section 4.1.1.2), except Inclusion ~~Criteria~~**Criterion** 4.

~~(e)~~ Full physical examination is performed at Screening~~Period~~; a brief physical examination is performed at all other visits.

(f) Required only for confirmation of postmenopausal **females as described in Section 13.2 (Appendix 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**.

(g) See Section 6.3.3 **and Table 6-4** for all required laboratory assessments.

(h) Gastrin **Week 4 Run-In, Week 6 On-Demand treatment and Safety follow-up** visits and pepsinogen I and II results **will be blinded and** will not be reported to investigative sites or other blinded personnel until the study blind is broken.

(i) Only female subjects with childbearing potential. Serum hCG at screening and urine hCG at all subsequent visits.

(j) The screening endoscopy can be performed any time during that period; however, it should be performed after the subject has fulfilled all other admission criteria. Any endoscopic confirmation performed in a routine clinical setting within 7 days before signing the informed consent is acceptable to use for the purpose of fulfilling the screening requirement.

(k) 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 Screening, Run-In and Follow-up Period. During the On-Demand Treatment Period, subjects will be instructed to complete the electronic diary to document heartburn episodes and study drug administration. Rescue antacid use should be reported during all periods.

(l) Subjects are to start dose administration from Day 1.

(m) Rescue antacid will be dispensed as needed after the Screening Period.

(n) Sites will document dispensing rescue antacid. Subjects do not need to return unused rescue antacid.

**(o) Day -1 baseline gastrin levels will not be blinded.**

**(p) Run-In failure procedures.**