Protocol Number: EE-301

Official Title: A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis

Document Date: 01 October 2019

NCT Number: NCT04124926

CLINICAL STUDY PROTOCOL

IND NUMBER: 79,212

EUDRACT: 2019-002579-33

A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis

PROTOCOL NO. EE-301

Sponsor:	Phathom Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, CA 94025
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Version of Protocol:	Version 3.0, Amendment 2
Date of Protocol:	01 Oct 2019
Previous Date and Version	22 Aug 2019, Version 2.0 (Amendment 1)

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6 R2: Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis
Protocol Number	EE-301
Protocol Date	01 Oct 2019

Protocol accepted and approved by:

Chief Operating Officer

[redacted]

Protocol Approval – Principal/Coordinating Investigator

Study Title	A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis
Protocol Number	EE-301
Protocol Date	01 Oct 2019

Protocol accepted and approved by:

Principal/Coordinating Investigator

[redacted]

Protocol Approval – Lead Statistician

Study Title	A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis
Protocol Number	EE-301
Protocol Date	01 Oct 2019

Protocol accepted and approved by:

Lead Statistician

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, Amendment 2, dated 01 Oct 2019, the International Council for Harmonisation harmonised tripartite guideline E6 R2: Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Phathom Pharmaceuticals, Inc. or implement protocol changes without Institutional Review Boards/Independent Ethics Committees approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a subinvestigator.

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

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

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

Summary of Changes

Protocol Amendment History and Reasons for Amendment

Version	Date	Reasons for Amendment
Version 1.0	05 Aug 2019	Original Protocol
Version 2.0 (Protocol Amendment 1)	22 Aug 2019	• To remove double-dummy and placebo from study drugs and other applicable sections • To change exclusion period for proton pump inhibitors and histamine H_2 receptor antagonists from 14 days prior to screening to 14 days prior to screening ^{13}C-UBT test • To update footnote (a) of Table 5-2 Excluded Medications and Treatments regarding prohibition period of medications that may interfere with ^{13}C-UBT test • To remove 'x' from dispense study drug at Maintenance Week 4 (Maintenance Day 29) in Table 13-1 Schedule of Events • To update a footnote to the Table 13-1 Schedule of Events to clarify that subjects may need to return for study drug administration after Week 2 and Week 8

Version	Date	Reasons for Amendment
Version 3.0 (Protocol Amendment 2)	01 Oct 2019	• To remove wording from Inclusion criterion #3 and throughout the document allowing a subject's legally acceptable representative to consent on their behalf. • To revise Exclusion criterion #1 to add wording allowable to extend endoscopy screening period to 10 days in rare instances with sponsor approval. Wording in Section 6.2.1 also updated to reflect changes to Exclusion criterion #1. • To add to exclude cytochrome P450 2C19 (CYP3A4) substrates with a narrow therapeutic index in Table 5-2. • To add overall study stopping criteria in Section 6.3.1.15. • To clarify requirements for informed consent process for pharmacogenetic sampling and analysis in Section 6.11. • To add smoking status and alcohol use in Table 13.1 Schedule of Events and to Section 7.6. • To update Section 13.3 Appendix 3: The Patient Assessment of Gastrointestinal Disorders-Symptoms Severity Index (PAGI-SYM) with most recent sample version.

For details of Amendments 1 and 2, see Appendix 7 (Section 13.7).

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Protocol Synopsis

Protocol Number:	EE-301
Title:	A Phase 3, Randomized, Double-Blind, Two-Phase, Multicenter Study to Evaluate the Efficacy and Safety of Vonoprazan 20 mg Compared to Lansoprazole 30 mg for Healing in Patients with Erosive Esophagitis and to Evaluate the Efficacy and Safety of Vonoprazan (10 mg and 20 mg) Compared to Lansoprazole 15 mg for the Maintenance of Healing in Patients with Healed Erosive Esophagitis
Sponsor:	Phathom Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, CA 94025
Study Phase:	3
Study Sites:	Approximately 150 sites in the US and Europe
Indication:	Patients with Erosive Esophagitis
Rationale:	In a Phase 2 dose-ranging study of vonoprazan (TAK-438) in subjects with erosive esophagitis (EE) (TAK-438/CCT-001), vonoprazan was noninferior to lansoprazole 30 mg in healing at all doses tested (5 mg, 10 mg, 20 mg, and 40 mg), with good tolerability. The study demonstrated a dose response relationship with vonoprazan. Furthermore, the rate of endoscopic healing of EE in subjects with more severe disease (Los Angeles Classification [LA classification] grades C/D) was 96% or higher with vonoprazan at doses 20 mg or higher compared to 87% with lansoprazole 30 mg. Based on the results, 20 mg of vonoprazan was selected as the dose for the Japan Phase 3 EE healing study (TAK-438/CCT-002). Study TAK-438/CCT-002 confirmed the noninferiority and superiority (post-hoc) of vonoprazan 20 mg to lansoprazole 30 mg for the healing of EE. Study TAK-438/CCT-003 confirmed the noninferiority and superiority (post-hoc) of vonoprazan 10 and 20 mg to lansoprazole 15 mg for the maintenance of healed EE. Study EE-301 will further examine the effectiveness and safety of vonoprazan in subjects in the US and Europe in the healing and maintenance of healed EE.
Objectives:	**Healing Phase** Primary • To assess the efficacy of vonoprazan (20 mg once daily [QD]) compared to lansoprazole (30 mg QD) in healing of EE over 8 weeks in subjects with endoscopically proven EE.

- To assess the safety of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in subjects with endoscopically proven EE.

Secondary

- To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE over 2 weeks in subjects with endoscopically proven EE.
- To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE in subjects with endoscopically proven EE LA Classification Grades C or D over 2 weeks and 8 weeks.
- To assess relief of heartburn of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in subjects with endoscopically proven EE over 8 weeks and within the first 3 days of treatment.

Maintenance Phase

Primary

- To assess the efficacy in maintenance of healing of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE.
- To assess the safety of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE.

Secondary

- To assess the efficacy in maintenance of healing of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE with baseline LA Classification Grades C or D.
- To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subject symptoms by subject daily diary.

Study Population: Subjects aged 18 years of age or older with endoscopically confirmed EE of LA classification Grades A to D during the Screening Period as assessed by a central adjudicator.

Study Design: This is a Phase 3, 2-phase multi-center, double-blind, noninferiority study of vonoprazan versus lansoprazole for the healing of all grades of EE and relief of heartburn and the maintenance of healing of all grades of EE and relief of heartburn. Subjects with EE (LA classification Grade A/B or C/D serving as a stratification at randomization) will be randomized to receive vonoprazan 20 mg or lansoprazole 30 mg QD for up to 8 weeks for the healing of EE. All subjects with endoscopic healing of EE at 2 or 8 weeks after the start of the study will enter a continuous 24-week Maintenance Phase. Subjects will be rerandomized to receive either vonoprazan 10 mg,

vonoprazan 20 mg, or lansoprazole 15 mg for 24 weeks. The subjects without confirmed endoscopic healing of EE at Week 8 will not be allowed to enter the Maintenance Phase. Subjects will complete an electronic diary twice daily to record the presence and maximum severity of daytime and nighttime heartburn symptoms throughout the study.

The study will include 4 main phases:

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

Healing Phase (Healing Day -1 to Healing Day 15 or 57): Subjects with EE whose eligibility is confirmed will be randomized to receive vonoprazan 20 mg or lansoprazole 30 mg QD for up to 8 weeks. The date of the first dosing is defined as Day 1. An endoscopy will be performed at Week 2. If endoscopic healing of EE is confirmed at Week 2, the subject will enter the Maintenance Phase. If endoscopic healing is not confirmed, the subject will continue to receive randomized treatment until Week 8. If endoscopic healing is confirmed at Week 8, the subject will enter the Maintenance Phase. During the Healing Phase, if the investigator deems that an additional endoscopy is warranted based on the subject's symptoms prior to the window of the subject's next scheduled per-protocol endoscopy, an unscheduled endoscopy will be permitted whenever required as part of routine clinical care. If the subject's EE is found to have healed at this unscheduled endoscopy visit, the subject will be considered to have completed the Healing Phase and will undergo randomization for entry into the Maintenance Phase. If the subject is found to still have EE (of any grade) at the unscheduled endoscopy visit, the subject will be allowed to continue in the study within the Healing Phase and will undergo their subsequent per-protocol endoscopy. If endoscopic healing of EE is not confirmed at Week 8, the subject will discontinue the study without entering the Maintenance Phase and be considered as completed for the Healing Phase. Healing will be defined as endoscopically confirmed healed.

Maintenance Phase (Maintenance Day 1 to Maintenance Day 169): Subjects with EE who have confirmed endoscopic healing of EE either at Week 2 or at Week 8 of the Healing Phase (or during an unscheduled endoscopy) will enter the Maintenance Phase. Subjects will be rerandomized to receive either vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg daily for 24 weeks. Maintenance of healing will be assessed by endoscopy at Week 24 of the Maintenance Phase. If during the 24-week Maintenance Phase the investigator deems that an endoscopy is warranted, based on subject symptoms, an unscheduled endoscopy will be

permitted whenever required. If the subject's EE is found to have relapsed at this unscheduled endoscopy visit, the subject will be discontinued from the Maintenance Phase of the study, considered a treatment failure, and will enter the Follow-up Phase. If the subject is found to have maintained healing of EE at the unscheduled endoscopy visit, the subject will be allowed to continue in the study until Week 24.

Follow-up Phase: A safety follow-up visit is planned at 4 weeks after the last dose of study drug to assess adverse events (AEs) and the serum gastrin level. Subjects who do not have EE healing at Week 8 and therefore discontinue the study after the Healing Phase will undergo the safety follow-up period.

Estimated Study Duration: The total duration of the study is up to 41 weeks. Screening Period is up to 35 days, Healing Phase is up to 2 or 8 weeks depending on the healing of EE, Maintenance Phase is up to 24 weeks, and safety follow-up is at 4 weeks after last study drug administration.

Efficacy Assessments:

Healing Phase

Primary

- The percentage of subjects who have complete healing of EE by Week 8 as assessed by endoscopy

Secondary

- The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy
- The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
- The percentage of subjects who have complete healing of EE by Week 8 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
- The percentage of 24-hour heartburn-free days over the Healing Phase as assessed by the daily diary
- The percentage of subjects with onset of sustained resolution of heartburn by Day 3 (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary)

Maintenance Phase

Primary

- The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy

Secondary

- The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy for subjects with baseline LA Classification Grades C or D.
- The percentage of 24-hour heartburn-free days over the Maintenance Phase as assessed by the daily diary.

Safety Assessments:

Safety will be assessed by:

- Adverse events
- Laboratory test values (hematology, serum chemistry, urinalysis); serum gastrin and pepsinogen I/II levels
- Gastric biopsy
- Electrocardiogram (for Maintenance Phase only)
- Vital signs

Study Drug, Dosage, and Route of Administration:

Healing Phase:

Blinded study drug (vonoprazan 20 mg QD or lansoprazole 30 mg QD) to be taken orally for up to 8 weeks.

Maintenance Phase:

Blinded study drug (vonoprazan 10 mg QD, vonoprazan 20 mg QD, or lansoprazole 15 mg QD) to be taken orally for 24 weeks.

Sample Size:

Healing Phase

A sample size of 500 subjects per treatment group provides at least 90% power to achieve noninferiority using a Farrington Manning test with a noninferiority margin of 10%, assuming EE healing rates by Week 8 of 80% and 80% for vonoprazan and lansoprazole, respectively.

Maintenance Phase

All subjects who have complete healing of EE during the Healing Phase will enter the Maintenance Phase. It is expected that approximately 800 subjects will enter the Maintenance Phase, but the actual number of subjects who enter will depend on the observed healing rates during the Healing Phase. During the study if less than 800 subjects are projected to enroll into the Maintenance Phase, additional subjects may be enrolled to ensure that a sufficient number of subjects enter the Maintenance Phase. For the maintenance of EE healing after 24 weeks, a sample size of 265 subjects per treatment group provides at least 90% power to achieve noninferiority with a noninferiority margin of 10% and at least 90% power to achieve superiority using the Farrington Manning test, assuming maintenance of EE healing rates of 82% and 70% for vonoprazan and lansoprazole, respectively.

Statistical Methods:

Analysis of Primary Efficacy Endpoint

Healing Phase: The EE healing rate by Week 8 will be calculated along with 2-sided 95% CIs for each treatment group. A subject will be considered to have "complete healing of EE by Week 8" if the subject demonstrates healing at the Week 2 or Week 8 endoscopy.

The noninferiority of vonoprazan to lansoprazole will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in EE rates between treatments (vonoprazan minus lansoprazole). The point estimate and 2-sided 95% CI of the difference in endoscopic healing rate between vonoprazan and lansoprazole will be calculated via the Miettinen and Nurminen method.

If noninferiority is shown, superiority will also be assessed via the Farrington and Manning test of the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

Maintenance Phase: The maintenance of healing rate during the 24-week Maintenance Phase will be calculated along with 2-sided 95% CIs for each treatment group. The noninferiority of each dose group of vonoprazan to lansoprazole will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in maintenance of healing rates between treatments (vonoprazan minus lansoprazole). The point estimate and 2-sided 95% CI of the difference in the maintenance of healing rate between each dose group of vonoprazan and lansoprazole will be calculated via the Miettinen and Nurminen method.

If noninferiority is shown for a vonoprazan dose group, superiority of that dose group compared to lansoprazole will also be assessed via the Farrington and Manning test of the null hypothesis difference ≤0 versus the alternative hypothesis difference >0. An additional comparison will be made for superiority between the vonoprazan dose groups with no adjustment to the alpha level.

Analysis of Secondary Efficacy Endpoint

Healing Phase: The percentage of subjects who complete healing of EE at Week 2, who complete healing of EE at Week 2 for subjects with baseline LA Classification Grades C or D, and who complete healing of EE by Week 8 for subjects with baseline LA Classification Grades C or D will be analyzed for superiority of vonoprazan compared to lansoprazole similarly to the primary endpoint.

For the percentage of 24-hour heartburn-free days over the Healing Phase as assessed by daily diary, a 2-sided 95% CI will be calculated for the difference between the treatment groups in the mean percentage of 24-hour heartburn-free days (vonoprazan minus lansoprazole). If the lower

bound of this CI is greater than -15%, noninferiority will be concluded. If noninferiority is shown, the percentage of 24-hour heartburn-free days over the Healing Phase will also be compared between treatment groups using a Wilcoxon rank-sum test.

The percentage of subjects with onset of sustained resolution of heartburn by Day 3 will be analyzed for superiority of vonoprazan compared to lansoprazole similarly to the primary endpoint. Sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary.

Maintenance Phase: The percentage of subjects who maintain complete healing of EE after 24 weeks for subjects with baseline LA Classification Grades C or D will be analyzed for superiority of each vonoprazan dose group compared to lansoprazole similarly to the primary endpoint.

For the secondary endpoint of the percentage of 24-hour heartburn-free days over the Maintenance Phase as assessed by daily diary, a 2-sided 95% CI will be calculated for the difference between each vonoprazan dose group and the lansoprazole group in the mean percentage of 24-hour heartburn-free days (vonoprazan minus lansoprazole). If the lower bound of this CI is greater than -15%, noninferiority will be concluded. If noninferiority is shown for a vonoprazan dose group, superiority of that dose group compared to lansoprazole will also be assessed using a Wilcoxon rank-sum test.

Safety Analyses

For each phase, safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I/II levels, and vital signs.

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

Clinical laboratory tests, 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.

Version and Date of Protocol: Version 3.0, Amendment 2; 01 Oct 2019

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CYP2C19	cytochrome P450 2C19
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
EQ-5D-5L	EuroQoL-5 Dimensions-5 Levels
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
HbsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HP	*Helicobacter pylori*
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	interactive response technology
LA classification	Los Angeles Classification
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
PAGI-QoL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index
PPI	proton pump inhibitor
PPS	per-protocol set

Abbreviation	Definition
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 reactions
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

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 and maintenance of healing of all grades of EE and relief of heartburn.

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

In a Phase 2 dose-ranging study of vonoprazan (TAK-438) in subjects with EE (TAK-438/CCT-001), vonoprazan was noninferior to lansoprazole 30 mg in healing at all doses tested (5 mg, 10 mg, 20 mg, and 40 mg), with good tolerability. The study demonstrated a dose response relationship with vonoprazan. Furthermore, the rate of endoscopic healing of EE in subjects with more severe disease (Los Angeles Classification [LA classification] grades C/D) was 96% or higher with vonoprazan at doses 20 mg or higher compared to 87% with lansoprazole 30 mg. Based on the results, 20 mg of vonoprazan was selected as the dose for the Japan Phase 3 EE healing study (TAK-438/CCT-002).
Study TAK-438/CCT-002 confirmed the noninferiority and superiority (post-hoc) of vonoprazan 20 mg to lansoprazole 30 mg for the healing of EE. Study TAK-438/CCT-003 confirmed the noninferiority and superiority (post-hoc) of vonoprazan 10 and 20 mg to lansoprazole 15 mg for the maintenance of healed EE. Study EE-301 will further examine the effectiveness and safety of vonoprazan in subjects in the US and Europe in the healing and maintenance of healed EE.

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 endoscopy-negative GERD, EE, and Barrett’s esophagus. When defining GERD as the presence of at least weekly heartburn and/or regurgitation, epidemiological studies reported

prevalence estimates 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). Up to 50% of adults with GERD may develop EE (Fennerty 1997). Erosive esophagitis is one of the typical acid-related disorders caused by reflux of gastric acid into the esophagus. The endoscopic classification of EE, the LA Classification proposed in 1994, introduced the concept of a mucosal break, which is defined as "an area of slough or erythema with a sharp line of demarcation from adjacent normal mucosa." EE may be graded from A to D, according to the extent of mucosal break. 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).

Failure to effectively control acid reflux in patients with EE has been correlated with an increased morbidity leading to complications such as bleeding and strictures (Fennerty et al 1996). In addition, studies have shown that nighttime reflux is associated with a longer duration of esophageal exposure to gastric acid, leading to more severe esophageal and supra-esophageal injury (McGuigan et al 2004).

Despite the availability of PPIs and other anti-secretory agents, an unmet need remains in the management of GERD, and up to 40% of patients report suboptimal response to once daily (QD) PPI therapy (Fass 2009). Therefore, a significant number of patients are prescribed twice daily doses of PPIs even though this dosing regimen has not been thoroughly evaluated and is not labeled for any PPI for use in GERD. Furthermore, patients with moderate and severe EE (Grades C or D, based on the LA Classification) have shown sub-optimal healing rates of 62% to 84% after 8 weeks of treatment (Hunt 2005). Maintenance of healing rates are also suboptimal, with maintenance rates for lansoprazole 15 mg ranging from 72% to 81% after 6 months of therapy (PREVACID PI 2018 and Robinson et al 1996).

Vonoprazan has been shown to effectively address these areas of unmet need in the healing and maintenance of EE (Sugano 2018).

Vonoprazan is a potassium-competitive acid blocker, a novel class of orally active small molecule anti-secretory agent. It was developed by [redacted] Pharmaceutical Company Limited ([redacted]). Phathom Pharmaceuticals, Inc. (Phathom) has licensed the exclusive rights from [redacted] to develop and commercialize vonoprazan in the US, Europe, and Canada. Vonoprazan is shown not only to inhibit the H+, K+ -ATPase enzyme in the final step of acid

secretion, as the PPIs do, but does not require the presence of acid for its activation and competitively inhibits the binding of potassium ions to H+, K+ -ATPase enzyme. Furthermore, in contrast to the PPIs which take 3 to 5 days to produce their maximum acid-inhibitory effects, vonoprazan is expected to produce its maximum acid-inhibitory effect after absorption with the first dose and has the potential to produce better outcomes with its potent and sustained acid-inhibitory effects (Sakurai et al 2015).

1.3 Justification for Dose

Selection of the vonoprazan 20 mg dose for the Healing Phase and both the vonoprazan 10-mg and 20-mg doses for the Maintenance Phase of Study EE-301 is based on the data generated from the [redacted] Japan development program as well as the [redacted]Asian Phase 3 studies.

[redacted] conducted an 8-week, Phase 2 dose-ranging study evaluating healing of EE at vonoprazan doses of 5, 10, 20, and 40 mg. While Week 4 healing rates for subjects with LA Classification A or B were comparable across the groups (91.5% to 97.6%), those with LA Classification C or D had improved healing rates at the higher doses of 20 mg and 40 mg (5 mg: 87.3% and 10 mg: 86.4%, versus 20 mg: 100% and 40 mg: 96.0%). The vonoprazan 20 mg dose was subsequently selected for evaluation in the Phase 3 EE healing studies.

Phase 3 [redacted]EE healing Studies TAK-438/CCT-002 (Japan) and TAK-438-303 (Asia) demonstrated noninferiority of vonoprazan 20 mg to lansoprazole 30 mg for healing of EE. In a post hoc analysis, vonoprazan was superior to lansoprazole at Week 8 in the study conducted in Japan. The 20 mg dose is now approved for healing of EE in Japan and other markets and is the dose selected for healing of EE in Study EE-301.

For the PPIs, a frequently used approach for maintenance of healed EE is to step down to a lower dose than the dose used for healing. Several comparative EE maintenance studies have demonstrated that subjects with more severe grades of EE at baseline have high relapse rates (21% to 56%) after 6 months of treatment with lower maintenance doses (Lauritsen et al 2003, Labenz et al 2005, DeVault 2006). The clinical benefit of greater acid suppression in maintenance of healed EE is supported by data from a 2004 Cochrane review, which reported a higher maintenance rate in subjects who continued with healing doses of PPIs compared with subjects who were stepped down to a lower maintenance dose (advantage of 11.5 percentage points) in trials of 24 to 52 weeks duration (Hunt 2005).

In both the [redacted] Japan (TAK-438/CCT-003) and Asia (TAK-438-305, preliminary data) EE maintenance studies, vonoprazan 10 and 20 mg were compared with the approved step-down dose of lansoprazole 15 mg. In both studies, vonoprazan 10 and 20 mg were superior to lansoprazole 15 mg in post hoc analyses in maintenance of healing of all grades of EE. The 20-mg vonoprazan dose demonstrated a numerically greater improvement in maintenance of healing rate in subjects with LA Classification C or D than the 10-mg vonoprazan dose.

The safety profile of vonoprazan in Phase 3 studies showed there was no evidence of a dose-related increase in adverse effects with vonoprazan, and the safety profile of vonoprazan was similar to that of lansoprazole.

Therefore, based on the results of completed Japanese and Asian studies in the maintenance of EE, the vonoprazan 10 mg and 20 mg doses have been selected for maintenance of healed EE in Study EE-301.

The regulatory approved doses of lansoprazole 30 mg and 15 mg have been selected for the Healing and Maintenance Phase, respectively, as these are approved therapeutic doses in the US and Europe.

2 Study Objectives and Endpoints

Table 2-1 Objectives and Endpoints

Objectives	Endpoints
Healing Phase	
Primary	
• To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE over 8 weeks in subjects with endoscopically proven EE.	• The percentage of subjects who have complete healing of EE by Week 8 as assessed by endoscopy
• To assess the safety of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in subjects with endoscopically proven EE.	• Safety will be assessed by the following: o Adverse events o Laboratory test values (hematology, serum chemistry, urinalysis); serum gastrin and pepsinogen I/II levels o Vital signs
Secondary	
• To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE over 2 weeks in subjects with endoscopically proven EE.	• The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy
• To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in healing of EE in subjects with endoscopically proven EE LA Classification Grades C or D over 2 weeks and 8 weeks.	• The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D • The percentage of subjects who have complete healing of EE by Week 8 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
• To assess relief of heartburn of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in subjects with endoscopically proven EE over 8 weeks and within the first 3 days of treatment.	• The percentage of 24-hour heartburn-free days over the Healing Phase as assessed by the daily diary • The percentage of subjects with onset of sustained resolution of heartburn by Day 3 (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary)

Objectives	Endpoints
Exploratory	
• To assess the efficacy of vonoprazan (20 mg QD) compared to lansoprazole (30 mg QD) in subject symptoms by subject daily diary.	• The percentage of days without daytime heartburn over the Healing Phase as assessed by the daily diary • The percentage of days without nighttime heartburn over the Healing Phase as assessed by the daily diary • The mean severity of daytime and nighttime heartburn over the Healing Phase as assessed by the daily diary • The mean severity of daytime heartburn over the Healing Phase as assessed by the daily diary • The mean severity of nighttime heartburn over the Healing Phase as assessed by the daily diary • The time to sustained resolution of heartburn (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary) • The change from baseline to the end of the Healing Phase for each subscale and the total score of the PAGI-SYM questionnaire • The change from baseline to the end of the Healing Phase for each subscale and the total score of the PAGI-QoL questionnaire • The change from baseline to the end of the Healing Phase for the EQ-5D-5L
Maintenance Phase	
Primary	
• To assess the efficacy in maintenance of healing of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE. • To assess the safety of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE.	• The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy • Safety will be assessed by the following: o AEs o Laboratory test values (hematology, serum chemistry, urinalysis); serum gastrin and pepsinogen I/II levels o Gastric biopsy o Electrocardiogram o Vital signs

Objectives	Endpoints
Secondary	
• To assess the efficacy in maintenance of healing of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subjects with healed EE with baseline LA Classification Grades C or D. • To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subject symptoms by subject daily diary.	• The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy for subjects with baseline LA Classification Grades C or D • The percentage of 24-hour heartburn-free days over the Maintenance Phase as assessed by the daily diary
Exploratory	
To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to lansoprazole (15 mg QD) in subject symptoms by subject daily diary.	• The percentage of days without daytime heartburn over the Maintenance Phase as assessed by the daily diary • The percentage of days without nighttime heartburn over the Maintenance Phase as assessed by the daily diary • The mean severity of daytime and nighttime heartburn over the Maintenance Phase as assessed by the daily diary • The mean severity of daytime heartburn over the Maintenance Phase as assessed by daily diary • The mean severity of nighttime heartburn over the Maintenance Phase as assessed by the daily diary • The percentage of 24-hour heartburn-free days during the Follow-up Phase as assessed by the daily diary • The change from maintenance baseline to the end of the Maintenance Phase for each subscale and the total score of the PAGI-SYM questionnaire • The change from maintenance baseline to the end of the Maintenance Phase for each subscale and the total score of the PAGI-QoL questionnaire • The change from baseline to the end of the Maintenance Phase for the EQ-5D-5L

Abbreviations: EE, erosive esophagitis; EQ-5D-5L, EuroQoL-5 Dimensions-5 Levels; LA classification, Los Angeles Classification; PAGI-SYM, Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index; PAGI-QoL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; QD, once a day

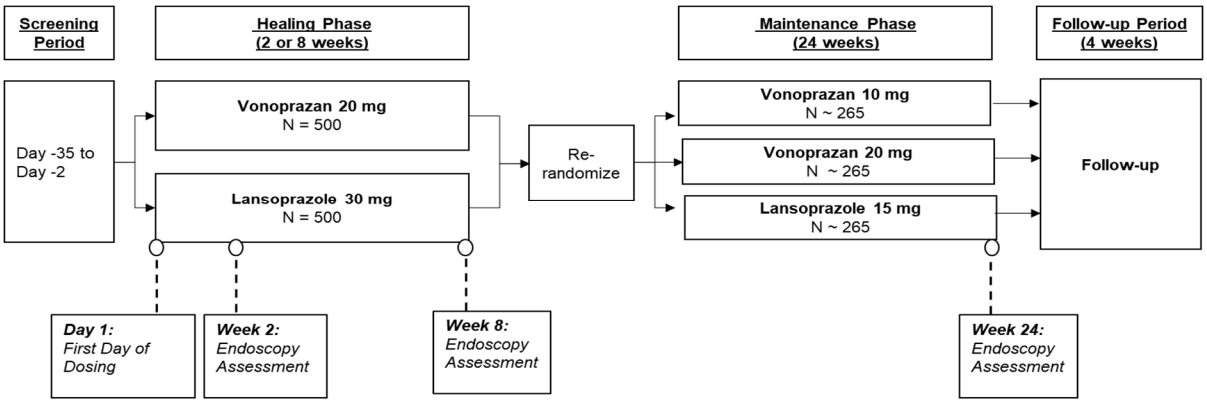
3 Investigational Plan

3.1 Study Design

This is a Phase 3, 2-phase multi-center, double-blind, noninferiority study of vonoprazan versus lansoprazole for the healing of all grades of EE and relief of heartburn and the maintenance of healing of all grades of EE and relief of heartburn. Subjects with EE with the LA classification Grade A/B or C/D serving as a stratification at randomization (see Table 6-1 for LA Classification definitions) will be randomized to receive vonoprazan 20 mg or lansoprazole 30 mg given QD for up to 8 weeks for the healing of EE. All subjects with endoscopic healing of EE at 2 or 8 weeks after the start of the study will enter a continuous 24-week Maintenance Phase. Subjects will be rerandomized to receive either vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg for 24 weeks. The subjects without confirmed endoscopic healing of EE at Week 8 will not be allowed to enter the Maintenance Phase. Subjects will complete the Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM), Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL), and the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) during each site visit and an electronic diary twice daily to record the presence and maximum severity of daytime and nighttime heartburn symptoms throughout the study.

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

Figure 3-1 Study Scheme



In Healing Phase, if endoscopic healing of EE is confirmed at Week 2, the subject will enter the Maintenance Phase. If endoscopic healing is not confirmed at Week 2 then the subject will continue to receive treatment until Week 8.

The study will include 4 main phases:

1. Screening Phase (Day -35 to Day -2): Subjects will provide informed consent and undergo screening assessments as noted in Table 13-1 to determine study eligibility, and baseline assessment will be performed. If all eligibility criteria are met, the subject will enter the study.
2. Healing Phase (Healing Day -1 to Healing Day 15 or 57): Subjects with EE whose eligibility is confirmed will be randomized to receive vonoprazan 20 mg or lansoprazole 30 mg QD for up to 8 weeks. The date of the first dosing is defined as Day 1. An endoscopy will be performed at Week 2. If endoscopic healing of EE is confirmed at Week 2, the subject will enter the Maintenance Phase. If endoscopic healing is not confirmed, the subject will continue to receive randomized treatment until Week 8. If endoscopic healing is confirmed at Week 8, the subject will enter the Maintenance Phase. During the Healing Phase, if the investigator deems that an additional endoscopy is warranted based on the subject's symptoms prior to the window of the subject's next scheduled per-protocol endoscopy, an unscheduled endoscopy will be permitted whenever required as part of routine clinical care. If the subject's EE is found to have healed at this unscheduled endoscopy visit, the subject will be considered to have completed the Healing Phase and will undergo randomization for entry into the Maintenance Phase. If the subject is found to still have EE (of any grade) at the unscheduled endoscopy visit, the subject will be allowed to continue in the study within the Healing Phase and will undergo their subsequent per-protocol endoscopy. If endoscopic healing of EE is not confirmed at Week 8, the subject will discontinue the study without entering the Maintenance Phase and be considered as completed for the Healing Phase. Healing will be defined as endoscopically confirmed healed.

3. Maintenance Phase (Maintenance Day 1 to Maintenance Day 169): Subjects with EE who have confirmed endoscopic healing of EE either at Week 2 or at Week 8 of the Healing Phase (or during an unscheduled endoscopy) will enter the Maintenance Phase. Subjects will be rerandomized to receive either vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg daily for 24 weeks. Maintenance of healing will be assessed by endoscopy at Week 24 of the Maintenance Phase. If during the 24-week Maintenance Phase the investigator deems that an endoscopy is warranted, based on subject symptoms, an unscheduled endoscopy will be permitted whenever required. If the subject's EE is found to have relapsed at this unscheduled endoscopy visit, the subject will be discontinued from the Maintenance Phase of the study, considered a treatment failure, and will enter the Follow-up Phase. If the subject is found to have maintained healing of EE at the unscheduled endoscopy visit, the subject will be allowed to continue in the study until Week 24.
4. Follow-up Phase: A safety follow-up visit is planned at 4 weeks after the last dose of study drug to assess adverse events (AEs) and the serum gastrin level. Subjects who do not have EE healing at Week 8 and therefore discontinue the study after the Healing Phase will undergo the safety follow-up period.

End-of-study definition: 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

This study is designed as a randomized, double-blind, active-control comparison of vonoprazan versus the PPI lansoprazole. The objective is to demonstrate the noninferiority of vonoprazan to lansoprazole for the healing and the maintenance of healing of EE. Lansoprazole was chosen as the active control as it is well established and used globally. In a Phase 2 dose-ranging study and a Phase 3 study in Japan, a higher rate of healing for vonoprazan compared with lansoprazole was demonstrated in subjects with more severe EE (baseline LA classification grades C or D). Therefore, the present study is planned to enrich the C or D population to 30% of subjects to further assess the potential benefit of vonoprazan in treating subjects with more severe EE. Healing will be assessed at Week 2 and Week 8 based on the results of the Japanese as well as an Asian Phase 3 healing study, which demonstrate that a large majority of vonoprazan- and lansoprazole-treated subjects heal by Week 2, and a greater percentage heal by Week 8.

The 6-month Maintenance Phase is consistent with the treatment duration for PPIs. The Phase 3 study in Japan reported 6-month maintenance rates of 94.9% and 98.0% for vonoprazan 10 mg and 20 mg, respectively, compared with 83.2% for lansoprazole 15 mg. Therefore, endoscopies will only be performed at Week 24 or at study termination to reduce the burden of these procedures on subjects. If deemed clinically necessary by the investigator, an additional endoscopy can be conducted earlier during the 24-week Maintenance Phase whenever required.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

This study will be conducted at approximately 150 sites in the US and Europe with an estimated total of 1000 randomized subjects (500 subjects in each treatment group during the Healing Phase). The target number of subjects with LA classification Grade C or-D will be approximately 30% of the total number of subjects (300 total). Enrollment of EE subjects with Grade A or B will be stopped when 700 or 70% of the total planned subjects with Grade A or B EE are enrolled.

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 Inclusion Criteria

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

1. The subject is ≥18 years of age at the time of informed consent signing.
2. In the opinion of the investigator or subinvestigators, the subject is capable of understanding and complying with protocol requirements.
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 is found to have endoscopically confirmed EE of LA Classification Grades A to D during the Screening Period (Visit 1) as assessed by a central adjudicator. The target number of subjects with LA classification Grade C or D will be approximately 30% of the total number of subjects (300 total). Enrollment of EE subjects with Grade A or B will end when the number of subjects with Grade A or B EE is approximately 700 or 70% of the total planned number of subjects. Given the invasive nature of an endoscopy, any endoscopic confirmation performed in a routine clinical setting before signing the informed consent will be acceptable to use for the purpose of fulfilling the screening requirement if all of the following apply:
(1) appropriate endoscopy pictures were taken; (2) appropriate gastric biopsy samples were taken; (3) the endoscopy pictures can be sent to the central adjudicator via the adjudication systems; and (4) all screening procedures (including the completion of adjudication) AND randomization can be completed within a 7-day period after the date of the endoscopy.
5. 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.

4.1.2 Exclusion Criteria

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

1. The subject's endoscopic examination for entering this study fails to confirm EE within 7 days (no later than 10 days on rare occasion with sponsor approval) prior to randomization.
2. The subject is determined to be positive for *Helicobacter pylori* (HP) or has had an HP infection within 45 days of randomization.
3. The subject has endoscopic Barrett's esophagus (>1 cm of columnar-lined esophagus) and/or definite dysplastic changes in the esophagus.

4. The subject has any other 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) are eligible to participate.
5. The subject has scleroderma (systemic sclerosis).
6. 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).
7. The subject has an active gastric or duodenal ulcer at the start of the Screening Period. Additionally, subjects with gastric or duodenal erosions are permitted to participate.
8. The subject has received any 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.
9. 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.
10. The subject has cutaneous lupus erythematosus or systemic lupus erythematosus.
11. The subject has had clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to randomization.
12. The subject has Zollinger-Ellison syndrome or other gastric acid hypersecretory conditions.

13. 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), PPIs, or any excipients used in the ^{13}C-urea breath test: mannitol, citric acid, or aspartame. Skin testing may be performed according to local standard practice to confirm hypersensitivity.
14. The subject has a history of alcohol abuse, illegal drug use, or drug addiction within the 12 months prior to screening, or regularly consumes >21 units of alcohol (1 unit = 12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine) per week based on self-report. Subjects must have a negative urine drug screen at screening.
15. The subject is taking any excluded medications or treatments listed in the protocol (Section 5.8.2).
16. 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.
17. 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.
18. 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.
19. 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 cured cutaneous basal cell carcinoma or cervical carcinoma in situ).
20. The subject has acquired immunodeficiency syndrome (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.

21. 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

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.

4.1.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in 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, and any serious AE (SAE).

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.

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

The duration of the study is defined for each subject as the date signed written informed consent is provided through the last follow-up visit performed 4 weeks after the last dose of study drug.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time 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 or study drug should be recorded in the electronic case report form

(eCRF). For screen failure subjects, refer to Section 4.1.4. A subject may be withdrawn from the study for any of the following reasons:

1. Adverse event or SAE: The subject has experienced a pretreatment adverse event (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.

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 6 (Section 13.6) 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 (IRB)/Independent Ethics Committees (IEC), 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 6.5 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 or study drug 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 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 schedule of events (SoE) (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 repeatedly fails to return for 3 scheduled visits 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 will be randomized at the baseline/randomization visit (Visit 2; Day -1) to receive vonoprazan 20 mg QD or lansoprazole 30 mg QD using a 1:1 allocation ratio in the Healing Phase of the study.

Upon verification of healing, subjects will be randomized to receive either vonoprazan 10 mg QD, vonoprazan 20 mg QD, or lansoprazole 15 mg QD for 24 weeks in the Maintenance Phase of the study using a 1:1:1 allocation ratio.

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 for both the Healing and Maintenance Phases will be stratified by baseline LA classification (Grades A/B and Grades C/D; see Table 6-1 for LA Classification definitions). The randomization will also use an appropriate block size, which will not be revealed.

5.2 Treatments Administered

Healing Phase:

Blinded study drug (vonoprazan 20 mg QD or lansoprazole 30 mg QD) to be taken orally for up to 8 weeks.

Maintenance Phase:

Blinded study drug (vonoprazan 10 mg QD, vonoprazan 20 mg QD, or lansoprazole 15 mg QD) to be taken orally for 24 weeks.

Study drug administration will be as presented in Table 5-1.

Table 5-1 Study Drugs

Study Drugs	Treatment arm				
	Vonoprazan Healing	Lansoprazole Healing	Vonoprazan Maintenance		Lansoprazole Maintenance
Vonoprazan 20 mg	X		X		
Vonoprazan 10 mg				X	
Lansoprazole 30 mg		X			
Lansoprazole 15 mg					X

Subjects should be instructed as follows:

- To take study drugs with approximately 240 mL (8 oz) water 30 minutes before morning meal at about the same time each day.
- To present to the clinic in a fasting state when he/she is scheduled for laboratory tests and/or an endoscopy. On such study visit days, subjects will be instructed to take their dose of study drugs (if appropriate) after study procedures are completed.

5.3 Identity of Investigational Product

Vonoprazan

Vonoprazan study medication will be supplied as 10-mg and 20-mg capsules. The tablet drug product will be over-encapsulated into Swedish Orange DB-AAel capsules containing microcrystalline cellulose at the contract manufacturing organization, [redacted], Rockford, IL, USA.[redacted] Pharmaceutical Company, Ltd, Hikari, Japan manufactures the vonoprazan drug substance and tablet drug product.

The over-encapsulated vonoprazan 10-mg and 20-mg strengths will be identical in appearance. They will be packaged in a blister card.

Lansoprazole

Commercially available 15 mg and 30 mg lansoprazole capsules will be supplied by [redacted] Novaro, Cerano, Italy, in plain white capsules. The capsule product will be over-encapsulated into Swedish Orange DB-AAel capsules containing microcrystalline cellulose at the contract manufacturing organization, [redacted], Rockford, IL.

The over-encapsulated lansoprazole 15 mg and 30 mg will be packaged in a blister card.

Each blister card will bear a label that includes the pertinent study information and local regulatory requirements. Labels will be in the appropriate language for the area in which the study drug is dispensed.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Over-encapsulated vonoprazan and over-encapsulated lansoprazole will be prepared as blister cards and shipped by [redacted]. Each blister card will contain a (randomized) dosage for 1 subject and a sufficient quantity for dispensing during the Healing and Maintenance Phases of the study.

Study supplies must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at a controlled room temperature (20°-25°C [68°-77°F]; excursions allowed between 15°-30°C [59°- 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.

5.4.2 Test Article 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.

5.4.3 Other Supplies

An electronic diary will be provided to each subject to record the presence and maximum severity of daytime and nighttime heartburn twice daily (in the morning to capture heartburn during the night and in the evening to capture heartburn during the day).

5.5 Overdose Management

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

Cases of overdose without manifested signs or symptoms are not considered AEs. Adverse events associated with an overdose will be documented on AE eCRF(s) according to Section 6.3.1.14.1. The SAEs associated with overdose should be reported according to the procedure outlined in Section 6.3.1.14.2.

5.5.1 Treatment of Overdose

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

5.6 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 whole study. 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, database is locked, and the study is unblinded.

5.6.1 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, investigational drug must be stopped immediately, and the subject must be withdrawn from the study.

5.7 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. Subject treatment compliance assessment results should be recorded in the 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, including dates for delays and/or dose reductions will also be recorded in the eCRF.

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

5.8 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.

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

5.8.1 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 4.1.2) 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 that 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.

5.8.2 Excluded Medications

A list of excluded medications is provided in Table 5-2.

Table 5-2 Excluded Medications and Treatments

Excluded Medications and Treatments	Beginning of Exclusion	End of Exclusion
Medications for gastrointestinal tract		
Proton pump inhibitors	14 days prior to screening ^{13}C-UBT	End of the study
Histamine H_2 receptor antagonists	14 days prior to screening ^{13}C-UBT	End of treatment
Muscarinic antagonists (eg, hyoscyamine), gastrointestinal motility stimulants, oral anticholinergic drugs, prostaglandins, sucralfate	Start of the Screening Period	End of the study
Bismuth	30 days prior to screening ^{13}C-UBT	End of the study
Medications that may interfere with ^{13}C-UBT(a)	14 days prior to screening ^{13}C-UBT	End of Screening Period
Antibiotics	30 days prior to screening ^{13}C-UBT	End of Screening Period
Strong inhibitors or inducers of CYP2C19 (eg, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampicin, ritonavir)	14 days prior to study treatment	End of treatment
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	4 days prior to study treatment	End of treatment
CYP3A4 substrates with a narrow therapeutic index	4 days prior to study treatment	End of treatment
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	End of the study
Surgical or endoscopic treatment of EE (eg, fundoplication, LINX procedure)	Start of the Screening Period	End of the study
Any upper gastrointestinal tract surgery except for endoscopic removal of benign gastric polyps.	Start of the Screening Period	End of the study
Other investigational products	30 days before the start of the Screening Period	End of the study

Abbreviations: CYP2C19, cytochrome P450 2C19; CYP3A4, cytochrome P450 3A4; EE, erosive esophagitis; UBT, urea breath test

(a) Prohibited period is 14 days prior to any ^{13}C-UBT or as otherwise stated in the package insert for the ^{13}C urea breath testing kit package to be used. The exclusion period is not applicable to proton pump inhibitors and antibiotics; they have a separate exclusion period.

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 ^{13}C Urea Breath Test

To establish HP infection status, a ^{13}C urea breath test will be performed during the Screening Phase.

Medications such as PPIs are to be stopped at least 14 days before taking the ^{13}C-urea breath test in order to exclude false negative results. Antibiotics (particularly those with antihelicobacter action, and bismuth preparations) are to be stopped 30 days before taking the test. See Table 5-2.

Exhaled air samples will be taken in accordance with instructions for use of centrally provided testing kits for HP infection status determination and protocol eligibility.

6.2 Efficacy Assessments

6.2.1 Endoscopy

During the Screening Period, at the Week 2 visit, and at the Week 8 visit (if a subject's EE has not healed at Week 2), an endoscopy will be performed on all subjects to document the presence/absence of EE. The screening endoscopy should be performed after the subject has fulfilled all other admission criteria and within 7 days (no later than 10 days on rare occasion with sponsor approval) prior to randomization. (Given the invasive nature of an endoscopy,

any endoscopic confirmation performed in a routine clinical setting before signing the informed consent will be acceptable to use for the purpose of fulfilling the screening requirement if all of the following apply: (1) appropriate endoscopy pictures were taken; (2) appropriate gastric biopsy samples were taken; (3) the endoscopy pictures can be sent to the central adjudicator via the adjudication systems; and (4) all screening procedures (including the completion of adjudication) AND randomization can be completed within a 7-day period after the date of the endoscopy). During the Healing Phase, if the investigator deems that an additional endoscopy is warranted based on subject symptoms prior to the window of the subject's next scheduled per-protocol endoscopy, an unscheduled endoscopy will be permitted whenever required as part of routine clinical care. If the subject's EE is found to have healed at this unscheduled endoscopy visit, the subject will be considered to have completed the Healing Phase and will be randomized for entry into the Maintenance Phase.

During the Maintenance Phase an endoscopy will be performed at the Maintenance Week 24 visit to document the presence/absence of healed EE. If deemed clinically necessary by the investigator, an additional endoscopy can be conducted earlier or whenever required during the 24-week Maintenance Phase. If an unscheduled endoscopy conducted earlier documents the recurrence of EE, the subject will be considered to have recurrence of EE and will enter the Follow-up Phase.

Esophagitis will be graded according to the LA Classification of Esophagitis Grading Scale as defined in Table 6-1.

Table 6-1 LA Grade Classification

Grade A	One or more mucosal breaks with a length of no longer than 5 mm that does not extend between the tops of 2 mucosal folds
Grade B	One or more mucosal breaks with a length of longer than 5 mm that does not extend between the tops of 2 mucosal folds
Grade C	One or more mucosal breaks that are continuous between the tops of 2 or more mucosal folds, which involves less than 75% of the circumference
Grade D	One or more mucosal breaks, which involves at least 75% of the circumference

A mucosal break is defined as "an area of slough or erythema with a sharp line of demarcation from adjacent normal mucosa"

6.2.2 Adjudication of EE Grading

Adjudication Process

A central adjudication committee will assess the subject's screening endoscopy in order to determine whether the subject meets the LA grade eligibility criterion. Additionally, the central adjudicator will review images from all other study-related endoscopies. The adjudicators will be composed of independent experts who are highly experienced in endoscopic grading of EE.

During the screening endoscopy procedure, the investigator/endoscopist will take pictures of the lower third of the esophagus (to ensure inclusion of the proximal extent of the EE) documenting the investigator's/endoscopist's visual assessment of the subject's EE LA grade. These pictures will then be sent via the adjudication vendors electronic system to a blinded central adjudicator for an independent standardized review of the endoscope pictures. Given the invasive nature of an endoscopy, any endoscopic confirmation performed in a routine clinical setting before signing the informed consent will be acceptable for entrance criteria if all of the following apply: (1) appropriate endoscopy pictures were taken; (2) appropriate gastric biopsy samples were taken; (3) the endoscopy pictures can be sent to the central adjudicator via the adjudication systems; and (4) all screening procedures (including the completion of adjudication) AND randomization can be completed within a 7-day period after the date of the endoscopy.

The adjudicator will have up to 2 business days to review the endoscopic pictures and provide their assessment. If the adjudicator's rating agrees with the investigator, the subject will be enrolled, based on their rating. If the adjudicator and investigator assessments are misaligned, a second blinded adjudicator will review the endoscopic pictures within another 2 business days. The subject will be enrolled, based on the 2 matching LA grade ratings. If there are 3 different ratings across the 2 adjudicators and the investigator, the 2 adjudicators will discuss their assessments and reach alignment on the LA grade rating. If the adjudicators are unable to reach consensus, the primary adjudicator's assessment will be used to determine the subject's eligibility. Once the adjudication process has been completed, the results will be communicated to the investigator via the central adjudication system. The investigator should not change his/her initial grading if the final assessment is different from the initial assessment. Both the investigator's and adjudicator's assessment will be entered into the

clinical database. The central adjudication system will allocate all of an individual subject's future endoscope pictures to the same adjudicator.

All other study-related endoscopies will be evaluated in a similar manner as described above with both the investigator's and adjudicator's assessments documented in the eCRF. The central adjudicator's assessment will be used to determine whether the subject's EE has healed during the Healing Phase or recurred during the Maintenance Phase.

6.2.3 Symptom Diary

Subjects will download an electronic diary application on his/her own phone during the Screening Period. For subjects who do not have a phone or whose phone does not support the electronic diary application, the sponsor will provide a device with the electronic diary downloaded on it. Throughout the Screening Period (at least 7 days), Healing Phase, Maintenance Phase, and Follow-up Phase, subjects will document the presence and maximum 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 severity rating) and every evening before bedtime (to record that day's heartburn severity rating). The last entry that the subject will make to their electronic diary should be on the morning of the Safety Follow-up Visit, prior to their site visit.

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

Table 6-2 Definitions of Heartburn Severity (Daytime/Nighttime)

Definitions of Daytime Heartburn Severity (Daytime=Awake Time)
None - No heartburn
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)
None - No heartburn
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

In the Follow-up Phase, the use of antacid and H_2 receptor antagonist medications will also be collected in the electronic diary.

6.2.4 PAGI SYM Questionnaire

On Study Day -1, Week 2, and Week 8 (unless the subject is healed at Week 2) of the Healing Phase and Week 4, 12, and 24 of the Maintenance Phase (or upon premature termination), each subject will self-administer a paper version of the PAGI-SYM.

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. Refer to Section 13.3 for samples of the questionnaire.

6.2.5 PAGI QoL Questionnaire

On Study Day -1, Week 2, and Week 8 (unless the subject is healed at Week 2) of the Healing Phase and Weeks 4, 12, and 24 of the Maintenance Phase (or upon premature termination), each subject will self-administer a paper version of the PAGI-QoL.

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. Refer to Section 13.4 for samples of the questionnaire.

6.2.6 EQ-5D-5L

On Study Day -1, Week 2, and 8 (unless the subject is healed at Week 2) of Healing Phase, Week 4, 12, and 24 of Maintenance Phase (or upon premature termination), each subject will self-administer a paper version of the EQ-5D-5L.

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. Refer to Section 13.5 for samples of the questionnaire.

6.3 Safety Assessments

6.3.1 Pretreatment Adverse Events and Adverse Events

6.3.1.1 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.

6.3.1.2 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 AE (TEAE) is defined as any event that occurs after the first dose of study drug in that phase or any event at baseline that worsens in either intensity or frequency after the first dose of study drug in that phase.

6.3.1.3 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 6-3)
   - Exposes the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization

Table 6-3 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 6.3.1.14.2 and Section 6.3.1.14.3).

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 6.3.1.14.2. 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 6.6 must also be performed. In addition, if the LFT increases are SAEs, a Liver Function Test Increase Form must be completed and transmitted (see Section 6.3.1.14.2).

6.3.1.4 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 the Table 6-4.

Table 6-4 Adverse Events of Special Interest List

Term
Hepatotoxicity
Severe cutaneous adverse reactions
Clostridioides difficile infections and pseudomembranous colitis
Hypergastrinemia
Bone fracture

For additional details on liver function monitoring see Section 13.6.

6.3.1.5 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 draw); 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. Baseline evaluations (eg, laboratory tests, ECG, 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.

6.3.1.6 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.

6.3.1.7 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.

6.3.1.8 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.

6.3.1.9 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.

6.3.1.10 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.

6.3.1.11 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.

6.3.1.12 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.

6.3.1.13 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 has almost disappeared; 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 which 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.

6.3.1.14 Time Period and Frequency for Collecting AE and SAE Information

6.3.1.14.1 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 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 to 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

6.3.1.14.2 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 form 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.

6.3.1.14.3 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 form 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.

6.3.1.14.4 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.

6.3.1.15 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 towards 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 SUSAR 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.

6.4 Safety Monitoring Committee

Not applicable.

6.5 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn, and any sponsor-supplied drug (vonoprazan active or lansoprazole active) should be immediately discontinued. If the pregnancy occurs during administration of active study drug, eg, after Visit 2 (Randomization) 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 6.3.1.14.2. 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 in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

6.6 Laboratory Analyses

See Table 6-5 for the list of clinical laboratory tests to be performed and to 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 case report form. 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 abnormal 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 6-5, 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 6-5 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices: MCV, MCH • %Reticulocytes • WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils
Clinical chemistry(a)	• Blood urea nitrogen • Creatinine • Total and direct bilirubin • ALT/SGPT • AST/SGOT • Alkaline phosphatase • Total protein • Potassium • Sodium • Calcium • Glucose (fasting) • GGT
Routine urinalysis	• Specific gravity, appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)
Other screening tests	• FSH if menopause is suspected(b) • Urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine(c) • Serum hCG pregnancy test(d) at Screening Visit 1 • Urine hCG pregnancy test(d) at randomization and all other study visits • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody; hepatitis C, Viral Load RNA(e) [Qualitative]) • Serum gastrin and serum pepsinogen I and II levels will also be evaluated as exploratory safety/PD biomarkers at screening; Weeks 2 and 8 (if not healed) during the Healing Phase; Weeks 4, 12, and 24 of the Maintenance Phase; and the safety follow-up visit. Gastrin and pepsinogen I and II results will not be reported to investigative sites or other blinded personnel until 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; HIV, human immunodeficiency virus; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PD, pharmacodynamics; RBC, red blood cells; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cells.

(a) See Section 13.4 for the appropriate guidance on reporting of abnormal liver function tests. For liver test monitoring, see Section 13.6.1. For temporary and permanent discontinuation of study drugs due to abnormal liver function tests, see Section 13.6.2 and Section 13.6.3, respectively.

(b) Follicle-stimulating hormone will be conducted at the investigator's discretion to determine the postmenopausal status of women whose duration of (consecutive) amenorrhea is borderline or open to doubt and where the investigator believes the subject to be menopausal by history.

(c) The central laboratory will confirm any positive drug screen results.

(d) As needed for women of childbearing potential. During the Healing Phase and Maintenance Phase, serum pregnancy test will be performed if the urine pregnancy test is positive.

(e) Reflex - if Hepatitis C positive.

Investigators must document their review of each laboratory safety report.

6.7 Physical Examinations

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.

6.8 Vital Signs

Vital signs will include body temperature (oral, temporal, or tympanic measurement), sitting blood pressure (resting more than 5 minutes), and pulse (beats per minute). When vital signs are scheduled at the same time as blood draws, the blood draw will take priority, and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

6.9 Electrocardiograms

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, QT interval, 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.

6.10 Gastric Mucosal Biopsy

Four biopsies (one each from the greater and lesser curvature of the body, and one each from the greater and lesser curvature of the antrum) will be taken during the baseline endoscopy of the Healing Phase, as well as the Week 24 /Final Visit of the Maintenance Phase for all subjects. In addition, gastric biopsies are to be done on any subject who prematurely terminates from the study at any time, including those subjects whose EE is not healed at the Week 8 Healing Phase endoscopy.

The biopsies will be placed in 10% buffered formalin and shipped to the central pathology laboratory for subsequent staining and analysis. All biopsies will be evaluated for the presence of active and chronic inflammation, atrophy, intestinal metaplasia, changes in endocrine cell density, and enterochromaffin-like (ECL) cell hyperplasia.

Detail on processes for collection and shipment of these samples can be found in the laboratory manual.

6.11 Pharmacogenetics

Collection for genotyping: Every subject must sign the informed consent/be consented in order to participate in the pharmacogenetic analysis. The informed consent can be part of the main consent or a separate consent for pharmacogenetics, depending on country-specific requirements. This sample is optional, but sites are encouraged to discuss the importance of sample collection with the subjects. During the study, a blood sample will be collected for cytochrome P450 2C19 (CYP2C19) genotype testing to determine the subject's metabolizer status, unless prohibited by local or ethical regulations. The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation in the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the clinical efficacy of lansoprazole.

In the event of an issue with the analysis for CYP2C19, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual.

7 Statistical and Analytical Plan

This section briefly 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 data. To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized before database lock.

7.1 Primary Efficacy Endpoints

Healing Phase:

The percentage of subjects who have complete healing of EE by Week 8 as assessed by endoscopy

Maintenance Phase:

The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy

7.2 Secondary Efficacy Endpoints

Healing Phase:

- The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy
- The percentage of subjects who have complete healing of EE at Week 2 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
- The percentage of subjects who have complete healing of EE by Week 8 as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
- The percentage of 24-hour heartburn–free days over the Healing Phase as assessed by the daily diary
- The percentage of subjects with onset of sustained resolution of heartburn by Day 3 (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary)

Maintenance Phase:

- The percentage of subjects who maintain complete healing of EE after 24 weeks as assessed by endoscopy for subjects with baseline LA Classification Grades C or D
- The percentage of 24-hour heartburn–free days over the Maintenance Phase as assessed by the daily diary

7.3 Exploratory Endpoints

Healing Phase:

- The percentage of days without daytime heartburn over the Healing Phase as assessed by the daily diary
- The percentage of days without nighttime heartburn over the Healing Phase as assessed by the daily diary
- The mean severity of daytime and nighttime heartburn over the Healing Phase as assessed by the daily diary
- The mean severity of daytime heartburn over the Healing Phase as assessed by the daily diary
- The mean severity of nighttime heartburn over the Healing Phase as assessed by the daily diary
- The time to sustained resolution of heartburn (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary)
- The change from baseline to the end of the Healing Phase for each subscale and the total score of the PAGI-SYM questionnaire
- The change from baseline to the end of the Healing Phase for each subscale and the total score of the PAGI-QoL questionnaire
- The change from baseline to the end of the Healing Phase for the EQ-5D-5L

Maintenance Phase:

- The percentage of days without daytime heartburn over the Maintenance Phase as assessed by the daily diary

- The percentage of days without nighttime heartburn over the Maintenance Phase as assessed by the daily diary
- The mean severity of daytime and nighttime heartburn over the Maintenance Phase as assessed by the daily diary
- The mean severity of daytime heartburn over the Maintenance Phase as assessed by the daily diary
- The mean severity of nighttime heartburn over the Maintenance Phase as assessed by the daily diary
- The percentage of 24-hour heartburn-free days over the Follow-up Phase as assessed by the daily diary
- The change from maintenance baseline to the end of the Maintenance Phase for each subscale and the total score of the PAGI-SYM questionnaire
- The change from maintenance baseline to the end of the Maintenance Phase for each subscale and the total score of the PAGI-QoL questionnaire
- The change from maintenance baseline to the end of the Maintenance Phase for the EQ-5D-5L

7.4 Sample Size Calculations

7.4.1 Healing Phase

A sample size of 500 subjects per treatment group provides at least 90% power to achieve noninferiority using a Farrington Manning test with a noninferiority margin of 10%, assuming EE healing rates by Week 8 of 80% and 80% for vonoprazan and lansoprazole, respectively.

A fixed noninferiority margin of -10% is justified based on historical results from 2 randomized, double-blind, placebo-controlled studies that evaluated EE healing rates after 8 weeks with lansoprazole, the active comparator in the current study. In these studies, the EE healing rates with placebo were compared to lansoprazole 15 mg, lansoprazole 30 mg, or lansoprazole 60 mg (Earnest et al 1998) or to lansoprazole 15 mg, lansoprazole 30 mg, or omeprazole 20 mg (Castell et al 1996). The difference in the EE healing rate between lansoprazole 30 mg and placebo reported by Earnest was 40% (87% vs 47%) and by Castell

was 55% (87% vs 32%) with lower limits of the 2-sided 95% confidence interval of 26% and 48%, respectively. Using the most conservative assumption of the lower bound of 26% as the estimate of the treatment effect of lansoprazole 30 mg compared to placebo, a -10% noninferiority margin would assure that vonoprazan retains at least 60% of the treatment effect of lansoprazole 30 mg.

The current study will enroll approximately 30% of subjects with more severe EE (Grade C or Grade D). The historical EE healing rates are from studies in which the percentage of subjects with more severe EE (Grade 3 or Grade 4) ranged from 35% (Castell et al 1996) to 63% (Earnest et al 1998). The grading scale used in the historical data was different but does provide information that the percentage of subjects with more severe EE that were enrolled in these studies is similar or higher than the 30% of Grade C or Grade D subjects planned for the current study. Therefore, these rates are considered relevant to informing the noninferiority margin for the primary endpoint for the Healing Phase and a fixed noninferiority margin of -10% is justified.

7.4.2 Maintenance Phase

All subjects who have complete healing of EE during the Healing Phase will enter the Maintenance Phase. It is expected that approximately 800 subjects will enter the Maintenance Phase, but the actual number of subjects who enter will depend on the observed healing rates during the Healing Phase. During the study if less than 800 subjects are projected to enroll into the Maintenance Phase, additional subjects may be enrolled to ensure that a sufficient number of subjects enter the Maintenance Phase.

For the maintenance of EE healing after 24 weeks, a sample size of 265 subjects per treatment group provides at least 90% power to achieve noninferiority with a noninferiority margin of 10% and at least 90% power to achieve superiority using the Farrington Manning test, assuming maintenance of EE healing rates of 82% and 70% for vonoprazan and lansoprazole, respectively.

Two randomized, double-blind studies were conducted that evaluated maintenance of EE healing after a 12-month maintenance treatment period with lansoprazole 15 mg QD, lansoprazole 30 mg QD, or placebo (PREVACID PI 2018). In these 2 studies, the differences in the Month 6 maintenance of EE healing rate between lansoprazole 15 mg and placebo were 54% (81% vs 27%) and 59% (72% vs 13%) with lower limits of the 2-sided 95%

confidence interval of 39% and 43%, respectively. Using the most conservative assumption of the lower bound of 39% as the estimate of the treatment effect of lansoprazole 15 mg compared to placebo, a -10% noninferiority margin would assure that vonoprazan retains at least 75% of the treatment effect of lansoprazole 15 mg. In these historical maintenance studies, the percentage of subjects with Grade 3 or Grade 4 EE was approximately 45% which is similar or higher than the 30% of subjects with Grade C or Grade D EE planned for the current study. Therefore, these rates are considered relevant to informing the noninferiority margin for the primary endpoint for the Maintenance Phase and a fixed noninferiority margin of -10% is justified.

7.5 Analysis Sets

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

The efficacy endpoints for each phase will be summarized using the modified intent-to-treat (MITT) analysis set defined for that phase. The primary endpoint for each phase will also be summarized using the per-protocol set defined for that phase. The MITT analysis set will be considered the primary population for efficacy analysis.

Modified Intent to Treat Analysis Set:

All analyses using the MITT set will group subjects according to the randomized treatment.

Healing Phase: The MITT set will be defined as all subjects randomized into the Healing Phase who have documented EE at baseline and receive at least 1 dose of study drug during the Healing Phase.

For the analyses of endpoints assessed by endoscopy, subjects who do not have a postbaseline endoscopy during the Healing Phase will be considered “not healed.”

Maintenance Phase: The MITT set will be defined as all subjects randomized into the Maintenance Phase who have healed EE and receive at least 1 dose of study drug during the Maintenance Phase.

For the analyses of endpoints assessed by endoscopy, subjects who do not have an endoscopy during the Maintenance Phase will be considered “recurred.”

Per-Protocol Set:

All analyses using the per-protocol set (PPS) will group subjects according to the randomized treatment.

Healing Phase: The PPS will consist of all MITT subjects who have been compliant with the protocol, including those subjects who are compliant with study treatment, have not taken PPIs or H2 receptor antagonist, did not have any major protocol deviations, and have results from endoscopy performed at the end of the Healing Phase unless the subject was a treatment failure.

Maintenance Phase: The PPS will consist of all MITT subjects who have been compliant with the protocol, including those subjects who are compliant with study treatment, have not taken any PPIs or H2 receptor antagonist, did not have any major protocol deviations, and have results from endoscopy performed at the end of the Maintenance Phase unless the subject was a treatment failure.

Safety Set:

All analyses using the safety set will group subjects according to the treatment actually received.

Healing Phase: The safety set will be defined as all randomized subjects who receive at least 1 dose of study drug during the Healing Phase.

Maintenance Phase: The safety set will be defined as all randomized subjects who receive at least 1 dose of study drug during the Maintenance Phase.

7.6 Description of Subgroups to be Analyzed

Subgroup analyses for the primary endpoint in each phase will be conducted for demographic and other relevant clinical variables, including age, sex, body mass index, smoking status, alcohol use, region, baseline EE grade (both separately A, B, C, and D and with Grades A or B and C or D combined), and CYP2C19 status (extensive metabolizer versus poor metabolizer). Subgroup analyses for the primary endpoint in the Maintenance Phase will also be conducted by Healing Phase treatment and by duration of Healing Phase treatment.

7.7 Statistical Analysis Methodology

Baseline for the Healing Phase will be the last visit prior to the first dose of study drug in the Healing Phase. Baseline for the Maintenance Phase will be the last visit during the Healing Phase prior to the first dose of study drug in the Maintenance Phase.

Efficacy endpoints assessed by results from endoscopy will be based on the assessment from the central adjudication.

7.7.1 Analysis of Primary Efficacy Endpoint

7.7.1.1 Healing Phase

The EE healing rate by Week 8 will be calculated along with 2-sided 95% CIs for each treatment group. A subject will be considered to have "complete healing of EE by Week 8" if the subject demonstrates healing at the Week 2 or Week 8 endoscopy.

The noninferiority of vonoprazan to lansoprazole will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in EE rates between treatments (vonoprazan minus lansoprazole). The point estimate and 2-sided 95% CI of the difference in endoscopic healing rate between vonoprazan and lansoprazole will be calculated via the Miettinen and Nurminen method.

If noninferiority is shown, superiority will also be assessed via the Farrington and Manning test of the null hypothesis difference ≤ 0 versus the alternative hypothesis difference >0.

7.7.1.2 Maintenance Phase

The maintenance of healing rate during the 24-week Maintenance Phase will be calculated along with 2-sided 95% CIs for each treatment group. The noninferiority of each dose group of vonoprazan to lansoprazole will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in maintenance of healing rates between treatments (vonoprazan minus lansoprazole). The point estimate and 2-sided 95% CI of the difference in the maintenance of healing rate between each dose group of vonoprazan and lansoprazole will be calculated via the Miettinen and Nurminen method.

If noninferiority is shown for a vonoprazan dose group, superiority of that dose group compared to lansoprazole will also be assessed via the Farrington and Manning test of the null hypothesis difference ≤0 versus the alternative hypothesis difference >0.

Methodology for control of type I error for the comparisons of each dose group of vonoprazan to lansoprazole will be addressed in the SAP. An additional comparison will be made for superiority between the vonoprazan dose groups with no adjustment to the alpha level.

7.7.2 Analysis of Secondary Efficacy Endpoint

7.7.2.1 Healing Phase

The percentage of subjects who complete healing of EE at Week 2, who complete healing of EE at Week 2 for subjects with baseline LA Classification Grades C or D, and who complete healing of EE by Week 8 for subjects with baseline LA Classification Grades C or D will be analyzed for superiority of vonoprazan compared to lansoprazole similarly to the primary endpoint.

For the secondary endpoint of the percentage of 24-hour heartburn–free days over the Healing Phase as assessed by daily diary, a 2-sided 95% CI will be calculated for the difference between the treatment groups in the mean percentage of 24-hour heartburn–free days (vonoprazan minus lansoprazole). If the lower bound of this CI is greater than -15%, noninferiority will be concluded. If noninferiority is shown, the percentage of 24-hour heartburn–free days over the Healing Phase will also be compared between treatment groups using a Wilcoxon rank-sum test.

A fixed noninferiority margin of -15% is justified based on results from a randomized, double-blind study in 1284 subjects that evaluated EE healing with placebo, lansoprazole 15 mg, lansoprazole 30 mg, or omeprazole 20 mg (Castell et al 1996). In this study, a twice daily patient diary was used to collect daytime and nighttime heartburn symptoms. The diary was very similar to the diary being used in the current study, except that it used a 4-point severity scale (none, mild, moderate, severe) rather than a 5-point severity scale (none, mild, moderate, severe, very severe). Given that the secondary endpoint is based on presence or absence of any degree of heartburn, these minor scale differences are not relevant for the purpose of establishing the noninferiority margin. The difference in the mean percentage of

24-hour heartburn–free days between lansoprazole 30 mg (72.6%) and placebo (31.6%) was 41.0%; the lower limit of the 2-sided 95% CI was 35.8%. Hence, even with a conservative assumption of this lower bound as the true treatment effect of lansoprazole 30 mg, a noninferiority margin of -15% assures that vonoprazan retains at least 58% of the treatment effect of lansoprazole 30 mg compared with placebo.

The percentage of subjects with onset of sustained resolution of heartburn by Day 3 will be analyzed for superiority of vonoprazan compared to lansoprazole similarly to the primary endpoint. Sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary.

Methodology for control of type I error for the secondary endpoints for the Healing Phase will be addressed in the SAP.

7.7.2.2 Maintenance Phase

The percentage of subjects who maintain complete healing of EE after 24 weeks for subjects with baseline LA Classification Grades C or D will be analyzed for superiority of each vonoprazan dose group compared to lansoprazole similarly to the primary endpoint.

For the secondary endpoint of the percentage of 24-hour heartburn–free days over the Maintenance Phase as assessed by daily diary, a 2-sided 95% CI will be calculated for the difference between each vonoprazan dose group and the lansoprazole group in the mean percentage of 24-hour heartburn–free days (vonoprazan minus lansoprazole). If the lower bound of this CI is greater than -15%, noninferiority will be concluded. If noninferiority is shown for a vonoprazan dose group, superiority of that dose group compared to lansoprazole will also be assessed using a Wilcoxon rank-sum test.

A fixed noninferiority margin of -15% is justified based on results from a randomized, double-blind study that evaluated maintenance of EE healing over 6 months with placebo, dexlansoprazole 30 mg QD, and dexlansoprazole 60 mg QD (Metz et al 2009). This study used the same twice daily patient diary to collect daytime and nighttime heartburn symptoms that will be used in the current study.

Data for the relief of heartburn based on a daily patient diary from a maintenance of EE healing study that compared the efficacy of lansoprazole 15 mg QD to placebo are not available, as the maintenance of EE healing studies for lansoprazole demonstrated superior

relief of symptoms including heartburn based on the investigator's assessment. However, data are available from a study comparing dexlansoprazole, the R-enantiomer of lansoprazole, to placebo, and results for the approved dexlansoprazole maintenance dose of 30 mg are considered relevant to inform the noninferiority margin for the approved lansoprazole maintenance dose of 15 mg.

The difference in the mean percentage of 24-hour heartburn–free days between dexlansoprazole 30 mg (83.3%) and placebo (36.0%) was 47.3%; the lower limit of the 2-sided 95% CI was 40.3%. Hence, even with a conservative assumption of this lower bound as the true treatment effect of lansoprazole 15 mg, a noninferiority margin of -15% assures that vonoprazan retains at least 62% of the treatment effect of lansoprazole 15 mg compared with placebo.

Methodology for control of type I error for the secondary endpoints for the Maintenance Phase will be addressed in the SAP. For each secondary endpoint, an additional comparison will be made for superiority between the vonoprazan dose groups with no adjustment to the alpha level.

7.7.3 Analysis of Exploratory Efficacy Endpoint

For the exploratory efficacy endpoints, all comparisons between treatment groups will be performed with no adjustment to the alpha level.

7.7.3.1 Healing Phase

The percentage of days without daytime heartburn, the percentage of days without nighttime heartburn, the mean severity of daytime and nighttime heartburn, the mean severity of daytime heartburn, the mean severity of nighttime heartburn, and the change from baseline to the end of the Healing Phase for the EQ-5D-5L and for each subscale and the total score of the PAGI-SYM and PAGI-QoL questionnaires will be compared between treatment groups using a Wilcoxon rank-sum test.

For analysis of the daytime and nighttime heartburn symptoms from the daily diary, the maximum severity of heartburn will be coded as 0=None, 1=Mild, 2=Moderate, 3=Severe, or 4=Very Severe.

The time to sustained resolution of heartburn (defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by daily diary) will be analyzed with a time-to-event analysis.

7.7.3.2 Maintenance Phase

The percentage of days without daytime heartburn, the percentage of days without nighttime heartburn, the mean severity of daytime and nighttime heartburn, the mean severity of daytime heartburn, the mean severity of nighttime heartburn, and the change from maintenance baseline (the last visit during the Healing Phase prior to the first dose of the study drug in the Maintenance Phase) to the end of the Maintenance Phase for the EQ-5D-5L and for each subscale and the total score of the PAGI-SYM and PAGI-QoL questionnaires will be compared between treatment groups using a Wilcoxon rank-sum test. Comparisons will be made between each dose group of vonoprazan and the lansoprazole treatment group as well as between the 2 vonoprazan dose groups.

The percentage of 24-hour heartburn-free days over the Follow-up Phase will also be summarized by maintenance treatment group.

7.7.4 Safety Analyses

For each phase, safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I/II levels, and vital signs.

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects experiencing TEAEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT) overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related AEs overall and by severity.

For tabulations of TEAE frequency, if a subject has more than 1 episode of the same event, the subject will be counted only once for that event. If a subject has more than 1 TEAE that is coded to the same PT, the subject will be counted only once for that PT. If a subject has more than 1 TEAE within a SOC, the subject will be counted only once for that SOC. In the tabulation of TEAE frequency by intensity, a subject will be counted only once using the highest severity for each PT and SOC.

Clinical laboratory tests, 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.

7.7.5 Other Analyses

For each phase, demographics and other baseline characteristics will be summarized overall and by treatment group using the MITT, PPS, and safety 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 and baseline EE grade).

7.7.6 Interim Analyses

An analysis of the Healing Phase data may be performed after all subjects have completed the Healing Phase. The data for the Healing Phase would be locked and the blind broken in order to perform this analysis. This analysis would be conducted after all subjects have been randomized into the Maintenance Phase, and no changes to the conduct of the Maintenance Phase of the study would be made based on the results from the Healing Phase.

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.

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 harmonised tripartite guideline E6: Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC 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 sub-investigator 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 time line 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 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.

12 Reference List

Castell DO, Richter JE, Robinson M, et al. Efficacy and safety of lansoprazole in the treatment of erosive reflux esophagitis. The Lansoprazole Group. Am J Gastroenterol. 1996;91(9):1749-57.

DeVault KR. Review article: the role of acid suppression in patients with non-erosive reflux disease or functional heartburn. Aliment Pharmacol Ther. 2006;23 Suppl 1:33-9.

Earnest DL, Dorsch E, Jones J, et al. A placebo-controlled dose-ranging study of lansoprazole in the management of reflux esophagitis. Am J Gastroenterol. 1998;93(2):238-43.

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

Fass R. Proton pump inhibitor failure--what are the therapeutic options? Am J Gastroenterol. 2009;104 Suppl 2:S33-8.

Fennerty MB, Castell D, Fendrick AM, et al. The diagnosis and treatment of gastroesophageal reflux disease in a managed care environment, Suggested disease management guidelines. Arch Intern Med 1996;156(5):477-84.

Fennerty MB. Medical treatment of gastroesophageal reflux disease in the managed care environment. Semin Gastrointest Dis. 1997;8(2):90-9.

Freston JW. Therapeutic choices in reflux disease: defining the criteria for selecting a proton pump inhibitor. Am J Med. 2004;117(Suppl 5A):14S-22S.

Hunt RH. Review article: the unmet needs in delayed-release proton-pump inhibitor therapy in 2005. Aliment Pharmacol Ther. 2005;22(Suppl 3):10-9.

Labenz J, Armstrong D, Lauritsen K, et al. Esomeprazole 20 mg vs. pantoprazole 20 mg for maintenance therapy of healed erosive oesophagitis: results from the EXPO study. Aliment Pharmacol Ther. 2005;22(9):803-11.

Lauritsen K, Devière J, Bigard MA, et al. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther. 2003;17(3):333-41.

McGuigan JE, Belafsky PC, Fromer L, et al. Review article: diagnosis and management of night-time reflux. Aliment Pharmacol Ther. 2004;20 (Suppl 9):57-72.

Metz DC, Howden CW, Perez MC, et al. Clinical trial: dexlansoprazole MR, a proton pump inhibitor with dual delayed-release technology, effectively controls symptoms and prevents relapse in patients with healed erosive oesophagitis. Aliment Pharmacol Ther. 2009;29(7):742-54.

PREVACID (lansoprazole) delayed-release Capsules, PREVACID SoluTab (lansoprazole) delayed-release orally disintegrating tablets. Full Prescribing Information including Medication Guide. Deerfield, IL: [redacted] Pharmaceuticals America, Inc., Revised Jun 2018.

Robinson M, Lanza F, Avner D, et al. Effective maintenance treatment of reflux esophagitis with low-dose lansoprazole. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1996;124(10):859-67.

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

Sugano K. Vonoprazan fumarate, a novel potassium-competitive acid blocker, in the management of gastroesophageal reflux disease: safety and clinical evidence to date. Therap Adv Gastroenterol. 2018;11.

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

13 Appendices

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events

	Screening Period (a)	Healing Phase					Maintenance Phase					Safety F/U (e)	Un-sched-uled Visit (f)
Timing		**Healing Day -1 (b)**	**Healing Day 1(b)**	**Week 2 (c) Healing Day 15**	**Week 8 (c,m) Healing Day 57**		**Main Week 4 Main Day 29**	**Main Week 12 Main Day 85**	**Main Week 16 Main Day 113**	**Main Week 20 Main Day 141**	**Main Week 24 Main Day 169 Final Visit/ET (d)**		
Visit Windows (Days)	**Day-35 to -2**	**-**		**12 to 18**	**54 to 60**		**26 to 36**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**-**	**-**
Visit Number:	**1**	**2**		**3**	**4**		**M1**	**M2**	**M3**	**M4**	**M5**	**F/U**	**-**
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X											
Demographic and medical history	X												
Smoking status and alcohol use	X												
Medication history	X												
Physical examination(g)	X	X		X	X		X	X			X	X	X
Vital signs	X	X		X	X		X	X			X	X	X
Weight and height	X												
Concomitant medications	X	X		X	X		X	X			X	X	X
Concurrent medical conditions	X												
FSH(h)	X												
Hepatitis B and C; HIV	X												
Urine drug screen	X												
Clinical laboratory test including hematology, serum chemistry, and urinalysis(i)	X			X	X		X	X			X		
^{13}C-UBT Breath Test	X												
CYP2C19 genotyping test				X									
Serum gastrin/pepsinogen I/II levels(j)	X			X	X		X	X			X	X	
Pregnancy test (serum HCG)(k)	X												
Pregnancy test (urine HCG)(k)		X		X	X		X	X			X		
Guidance on avoidance of pregnancy	X	X		X	X		X	X					
ECG	X										X		

	Screening Period (a)	Healing Phase					Maintenance Phase					Safety F/U (e)	Un-sched-uled Visit (f)
Timing		**Healing Day -1 (b)**	**Healing Day 1(b)**	**Week 2 (c) Healing Day 15**	**Week 8 (c,m) Healing Day 57**		**Main Week 4 Main Day 29**	**Main Week 12 Main Day 85**	**Main Week 16 Main Day 113**	**Main Week 20 Main Day 141**	**Main Week 24 Main Day 169 Final Visit/ET (d)**		
Visit Windows (Days)	**Day-35 to -2**	**-**		**12 to 18**	**54 to 60**		**26 to 36**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**-**	**-**
Visit Number:	**1**	**2**		**3**	**4**		**M1**	**M2**	**M3**	**M4**	**M5**	**F/U**	**-**
Subject's diary; distribute and/or review(l)	X(r)	X		X	X		X	X			X	X	
PAGI-SYM		X		X	X		X	X			X		
PAGI-QoL		X		X	X		X	X			X		
EQ-5D-5L		X		X	X		X	X			X		
Endoscopy	X			X	X						X		
Gastric biopsy(n)	X				X(s)						X		
Randomization		X		X(o)	X(o)								
Dispense study drug		X(p)		X(q)	X(q)			X					
First day of study drug administration			X										
Drug return/accountability/ review treatment compliance(q)				X	X		X	X			X		
Phone call to subject									X	X			
AE/pretreatment event assessment	X	X		X	X		X	X	X	X	X	X	X

Abbreviations: AE, adverse events; CYP2C19, cytochrome P450 2C19; ECG, electrocardiogram; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FSH, follicle-stimulating hormone; F/U, follow-up; HCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; Main, maintenance; PAGI-SYM, Patient Assessment of Gastrointestinal Disorders-Symptoms Severity Index; PAGI-QoL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life; UBT, urea breath test

(a) Visit window is Day -35 to Day -2 for assessment of *Helicobacter pylori*, serum gastrin and pepsinogen I/II values, ECG, and endoscopy in the Screening Period. However, given the invasive nature of an endoscopy, any endoscopic confirmation performed in a routine clinical setting before informed consent signing which would have included standard of care gastric mucosa sampling, endoscopy images available for adjudication and done within 7 days of randomization/dosing is acceptable to use for the purpose of fulfilling the Screening requirement, and repeat endoscopic examination during the Screening Period will not be required.

(b) The date of randomization is defined as Day -1. The date of first dosing day is defined as Day 1 for both the Healing and Maintenance Phases.

(c) If the subject is confirmed as healed and rerandomized to the Maintenance Phase, this visit is considered the baseline visit for the Maintenance Phase, and subjects who prematurely discontinue from the Healing Phase or who are not healed at Week 8 should undergo Maintenance Phase Week 24/Final Visit/ET procedures (including gastric biopsy).
(d) For early discontinuations, the assessments mentioned for Week 24 are required to be performed.
(e) A safety follow-up visit is to be scheduled 4 weeks after the last dose of study drug administration. Subjects whose healing is not confirmed after Week 8 and who discontinued the study after the Healing Phase will undergo a safety follow-up visit 4 weeks after the last dose of study drug administration.
(f) 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, and adverse event assessment. If the visit results in premature termination, then all procedures outlined for Maintenance Phase Week 24 /Final visit should be performed.
(g) Full physical examination is performed at baseline; a brief physical examination is performed at all other visits.
(h) If menopause is suspected.
(i) See Section 6.6 for all protocol-required laboratory assessments.
(j) Gastrin and pepsinogen I and II results will not be reported to investigative sites or other blinded personnel until the study blind is broken.
(k) Only female subjects with childbearing potential.
(l) Subjects should be instructed to complete the electronic diary every morning upon waking (for nighttime symptoms) and every evening before bedtime (for daytime symptoms) on each day of the study.
(m) Visit to be performed if not healed at Week 2.
(n) Four gastric mucosal biopsies (1 each from the greater and lesser curvature of the body and 1 each from the greater and lesser curvature of the antrum) should be obtained at each time point a gastric biopsy is done.
(o) Subjects with confirmed endoscopic healing at Week 2 or Week 8 will be rerandomized to the Maintenance Phase.
(p) Subjects are to start dose administration from Day 1.
(q) Subjects are to visit the study site without taking the study drug at Week 2 and Week 8 visits. For subjects without confirmed endoscopic healing of erosive esophagitis at Week 2, the daily dose of the study drug is to be administered after completion of assessments scheduled on that day. Subjects may need to return to the site a few days after Week 2 and Week 8 visits to receive a new allotment of study drug. No study procedures will be performed.
(r) Complete at least 7 days of diary during screening period
(s) only if EE not healed (follow Week 24 Final Visit/ET 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 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 (IUDs)

- 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, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential, and 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: The Patient Assessment of Gastrointestinal Disorders-Symptoms Severity Index (PAGI-SYM)

PAGI-SYM

This questionnaire asks you about the severity of symptoms you may have related to your gastrointestinal problem. There are no right or wrong answers. Please answer each question as accurately as possible.

For each symptom, please *circle the number* that best describes how *severe* the symptom has been during the past 2 weeks. If you have not experienced this symptom, circle 0. If the symptom has been very mild, circle 1. If the symptom has been mild, circle 2. If it has been moderate, circle 3. If it has been severe, circle 4. If it has been very severe, circle 5. Please be sure to answer every question.

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
1. nausea (feeling sick to your stomach as if you were going to vomit or throw up)	0	1	2	3	4	5
2. retching (heaving as if to vomit, but nothing comes up)	0	1	2	3	4	5
3. vomiting	0	1	2	3	4	5
4. stomach fullness	0	1	2	3	4	5
5. not able to finish a normal-sized meal	0	1	2	3	4	5
6. feeling excessively full after meals	0	1	2	3	4	5
7. loss of appetite	0	1	2	3	4	5
8. bloating (feeling like you need to loosen your clothes)	0	1	2	3	4	5
9. stomach or belly visibly larger	0	1	2	3	4	5
10. upper abdominal (above the navel) pain	0	1	2	3	4	5

1

PAGI-SYM (Standard) - United States/English - Original version - Mapi
ID037341 / PAGI_SYM_AU2.1_standard_eng-USori.doc

Please rate the severity of the following symptoms during the past 2 weeks.

	None	Very Mild	Mild	Moderate	Severe	Very Severe
11. upper abdominal (above the navel) discomfort	0	1	2	3	4	5
12. lower abdominal (below the navel) pain	0	1	2	3	4	5
13. lower abdominal (below the navel) discomfort	0	1	2	3	4	5
14. heartburn (burning pain rising in your chest or throat) during the day	0	1	2	3	4	5
15. heartburn (burning pain rising in your chest or throat) when lying down	0	1	2	3	4	5
16. feeling of discomfort inside your chest during the day	0	1	2	3	4	5
17. feeling of discomfort inside your chest at night (during sleep time)	0	1	2	3	4	5
18. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) during the day	0	1	2	3	4	5
19. regurgitation or reflux (fluid or liquid from your stomach coming up into your throat) when lying down	0	1	2	3	4	5
20. bitter, acid or sour taste in your mouth	0	1	2	3	4	5

2

PAGI-SYM (Standard) - United States/English - Original version - Mapi
ID037341 / PAGI_SYM_AU2.1_standard_eng-USori.doc

13.4 Appendix 4: The Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL) - Sample Copy

PAGI-QoL

The following questions ask about how some of the gastrointestinal problems you may be experiencing (such as pain, discomfort or other problems) may have affected your overall quality of life and well-being in the past 2 weeks.

Please answer every question by *circling the number* that best represents your opinion. There are no right or wrong answers.

During the past 2 weeks, because of your gastrointestinal problems, how often...	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1. have you had to depend on others to do your daily activities?	0	1	2	3	4	5
2. have you avoided performing your daily activities?	0	1	2	3	4	5
3. have you had difficulty concentrating?	0	1	2	3	4	5
4. has it taken you longer than usual to perform your daily activities?	0	1	2	3	4	5
5. have you felt tired?	0	1	2	3	4	5
6. have you lost the desire to participate in social activities such as visiting friends or relatives?	0	1	2	3	4	5
7. have you been worried about having stomach symptoms in public?	0	1	2	3	4	5
8. have you avoided performing physical activities or sports?	0	1	2	3	4	5
9. have you avoided traveling?	0	1	2	3	4	5
10. have you felt frustrated about not being able to do what you wanted to do?	0	1	2	3	4	5

1

During the past 2 weeks, because of your gastrointestinal problems, how often...	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
11. have you felt constricted in the clothes you wear?	0	1	2	3	4	5
12. have you felt frustrated about not being able to dress as you wanted to?	0	1	2	3	4	5
13. have you felt concerned about what you can and cannot eat?	0	1	2	3	4	5
14. have you avoided certain types of foods?	0	1	2	3	4	5
15. have you restricted eating at restaurant or at someone's home?	0	1	2	3	4	5
16. have you felt less enjoyment in food than usual?	0	1	2	3	4	5
17. have you felt concerned that a change in your food habits could trigger your symptoms?	0	1	2	3	4	5
18. have you felt frustrated about not being able to choose the food you wanted to?	0	1	2	3	4	5
19. have you felt frustrated about not being able to choose the type of beverage you wanted to?	0	1	2	3	4	5
20. has your relationship with your spouse or partner been disturbed?	0	1	2	3	4	5
21. has your relationship with your children or relatives been disturbed?	0	1	2	3	4	5
22. has your relationship with your friends been disturbed?	0	1	2	3	4	5
23. have you been in a bad mood?	0	1	2	3	4	5
24. have you felt depressed?	0	1	2	3	4	5

During the past 2 weeks, because of your gastrointestinal problems, how often...	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
25. have you felt anxious?	0	1	2	3	4	5
26 have you felt angry?	0	1	2	3	4	5
27. have you felt irritable?	0	1	2	3	4	5
28. have you felt discouraged?	0	1	2	3	4	5
29. have you been stressed?	0	1	2	3	4	5
30. have you felt helpless?	0	1	2	3	4	5

13.5 Appendix 5: EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) - Sample Copy

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

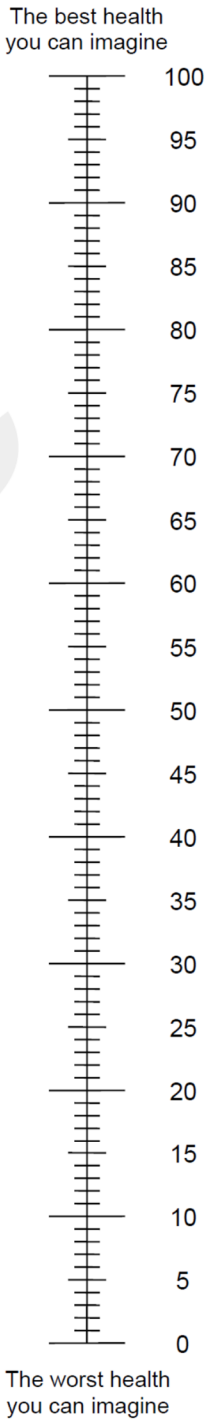
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



13.6 Appendix 6: Liver Function Tests

13.6.1 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, g-glutamyl transferase, 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, γ-glutamyl transferase, 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, γ-glutamyl transferase, and INR) should be repeated within a maximum of 48 hours after the abnormality was found.

13.6.2 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 occurs 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.

13.6.3 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 • ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value in conjunction with elevated total bilirubin >2 × ULN **or** INR >1.5 • ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
Elevated ALT or AST	• ALT or AST >5 × ULN **AND** persists for more than 2 weeks • ALT or AST >5× ULN **AND** in conjunction with elevated total bilirubin >2 ULN or INR >1.5 • 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:

[redacted]

[redacted]

13.6.4 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.

13.7 Appendix 7: 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.

13.7.1 Protocol Amendment 1

Protocol Synopsis

Study Drug, Dosage, and Route of Administration:

Healing Phase:
Blinded study drug (vonoprazan 20 mg QD or lansoprazole 30 mg QD) to be taken orally for up to 8 weeks.
~~To maintain study treatment blind, subject will also receive a placebo dose to match the treatment arm to which they are not assigned.~~
Maintenance Phase:
Blinded study drug (vonoprazan 10 mg QD, vonoprazan 20 mg QD, or lansoprazole 15 mg QD) to be taken orally for 24 weeks.
~~To maintain study treatment blind, subject will also receive a placebo dose to match the treatment arm to which they are not assigned.~~

Exclusion Criteria (Section 4.1.2)

Numbering of exclusion criteria was corrected.

Treatment Administered (Section 5.2)

Study drug administration will be ~~To maintain the study treatment blind, a double-dummy approach will be used, ie, the subject will also receive a placebo dose to match the treatment arm to which they are not assigned~~ as presented in Table 5-1.

Table 5-1 Study Drugs

Study Drugs	**Treatment arm**				
	Vonoprazan Healing	**Lansoprazole Healing**	**Vonoprazan Maintenance**		**Lansoprazole Maintenance**
Vonoprazan 20 mg	X		X		
Vonoprazan 10 mg				X	
Lansoprazole 30 mg		X			
Lansoprazole 15 mg					X
~~Placebo to match vonoprazan~~		~~X~~			~~X~~
~~Placebo to match lansoprazole 30 mg~~	~~X~~				
~~Placebo to match lansoprazole 15 mg~~			~~X~~	~~X~~	

Identity of Investigational Product (Section 5.3)

Vonoprazan

Vonoprazan study medication will be supplied as 10-mg and 20-mg capsules. The tablet drug product will be over-encapsulated into Swedish Orange DB-AA**el** capsules containing microcrystalline cellulose at the contract manufacturing organization, [redacted]**, Rockford, IL,** [redacted]~~, Sauderton, PA~~ USA. [redacted] Pharmaceutical Company, Ltd, Hikari, Japan manufactures the vonoprazan drug substance and tablet drug product.

The over-encapsulated vonoprazan 10-mg and 20-mg strengths ~~and placebo for vonoprazan~~ will be identical in appearance. They will be packaged in a ~~7-count~~ blister **card**~~strip~~.

Lansoprazole

Commercially available 15 mg and 30 mg lansoprazole capsules will be supplied by [redacted] Novaro, Cerano, Italy in plain white capsules. **The capsule product will be over-encapsulated into Swedish Orange DB-AAel capsules containing microcrystalline cellulose at the contract manufacturing organization,** [redacted]**, Rockford, IL.**[redacted]~~,~~ ~~Sauderton, PA USA will manufacture matching plain white placebo capsules.~~

The **over-encapsulated** lansoprazole ~~and placebo will be white hard gelatin capsules size #3 for~~ 15 mg and ~~size # 1 for~~ 30 mg~~, and they~~ will be packaged in a ~~7-count~~ blister **card**~~strip~~.

~~**Subject Kits**~~

~~A 7-count blister strip of vonoprazan 10 mg or 20 mg and a 7-count blister strip of placebo for lansoprazole 15 mg or 30 mg will be packaged in a single child-resistant wallet. Additionally, a 7-count blister strip of lansoprazole 15 mg or 30 mg and a 7-count blister strip of placebo for vonoprazan will be packaged in a single child-resistant wallet.~~

~~Dosing consists of 1 active capsule plus 1 placebo capsule daily. Cartons of either 3, 7, or 13 wallets will be supplied at study visits.~~

Each **blister card**~~wallet~~ will bear a label that includes the pertinent study information and local regulatory requirements. Labels will be in the appropriate language for the area in which the study drug is dispensed.

Study Drug Packaging and Storage (Section 5.4.1)

Over-encapsulated vonoprazan and **over-encapsulated** lansoprazole~~, and matching placebos~~ will be prepared ~~in kits (cartons) containing walleted~~ **as** blister **cards**~~strips~~ and shipped by [redacted]. Each ~~kit~~ **blister card** will contain a (randomized) dosage for 1 subject and a sufficient quantity for dispensing during the Healing and Maintenance Phases of the study.

Blinding (Section 5.6)

A ~~double-dummy and~~ double-blind design is employed so that both the investigators and the subjects will be unaware of the treatment assignment during the whole study.

Table 5-2 Excluded Medications and Treatments

Excluded Medications and Treatments	Beginning of Exclusion	End of Exclusion
Medications for gastrointestinal tract		
Proton pump inhibitors	14 days prior to ~~start of the~~ **screening ^{13}C-UBT**~~Screening Period~~	End of the study
Histamine H_2 receptor antagonists	14 days prior to ~~start of the~~ **screening ^{13}C-UBT**~~Screening Period~~	End of treatment
Muscarinic antagonists (eg, hyoscyamine), gastrointestinal motility stimulants, oral anticholinergic drugs, prostaglandins, sucralfate	Start of the Screening Period	End of the study
Medications that may interfere with ^{13}C-UBT(a)	14 days prior to screening ^{13}C-UBT	End of Screening Period

(a) **Prohibited period is 14 days prior to any 13C-UBT or as otherwise stated in the package insert for the ^{13}C urea breath testing kit package to be used.** The exclusion period is not applicable to proton pump inhibitors and antibiotics; they have a separate exclusion period.

Pregnancy (Section 6.5)

If any subject is found to be pregnant during the study she should be withdrawn, and any sponsor-supplied drug (vonoprazan active **or** lansoprazole active~~, and matching placebo~~) should be immediately discontinued.

Table 13-1 Schedule of Events

- 'x' is removed for study drug dispensing at Maintenance Week 4 visit (Maintenance Day 29)

- Footnote (q) Subjects are to visit the study site without taking the study drug at Week 2 and Week 8 visits. For subjects without confirmed endoscopic healing of erosive esophagitis at Week 2, the daily dose of the study drug is to be administered after completion of assessments scheduled on that day. **Subjects may need to return to the site a few days after Week 2 and Week 8 visits to receive a new allotment of study drug. No study procedures will be performed.**

13.7.2 Protocol Amendment 2

Inclusion Criteria (Section 4.1.1)

3. The subject ~~or, when applicable, the subject's legally acceptable representative,~~ signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures. The subject ~~(or legally acceptable representative, if applicable)~~ 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.

This change also affected the Protocol Synopsis, Section 3.1 (Study Design), Section 4.2.1 (Reasons for Withdrawal/Discontinuation), Section 9.1 (Independent Ethics Committee or Institutional Review Board), Section 9.3 (Subject Information and Consent), Section 10.1 (Confidentiality), and Section 10.3 (Investigator Documentation).

Exclusion Criteria (Section 4.1.2)

1. The subject's endoscopic examination for entering this study fails to confirm EE within 7 days **(no later than 10 days on rare occasion with sponsor approval)** prior to randomization.

This change also affected Section 6.2.1 (Endoscopy).

Table 5-2 Excluded Medications and Treatments

Excluded Medications and Treatments	Beginning of Exclusion	End of Exclusion
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	4 days prior to study treatment	End of treatment
CYP3A4 substrates with a narrow therapeutic index	**4 days prior to study treatment**	**End of treatment**
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	End of the study

Endoscopy (Section 6.2.1)

During the Screening Period, at the Week 2 visit, and at the Week 8 visit (if a subject's EE has not healed at Week 2), an endoscopy will be performed on all subjects to document the

presence/absence of EE. The screening endoscopy should be performed after the subject has fulfilled all other admission criteria and within 7 days **(no later than 10 days on rare occasion with sponsor approval)** prior to **randomization** ~~dosing~~.

Regulatory Reporting Requirements for SAEs (Section 6.3.1.15)

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.

Pharmacogenetics (Section 6.11)

Collection for genotyping: Every subject must sign the informed consent/**be consented** in order to participate in **the pharmacogenetic analysis** ~~this study~~. **The informed consent can be part of the main consent or a separate consent for pharmacogenetics, depending on country-specific requirements. The sample is optional, but sites are encouraged to discuss the importance of sample collection with the subjects.** During the study, a blood sample will be collected for cytochrome P450 2C19 (CYP2C19) genotype testing to determine the subject's metabolizer status, unless prohibited by local or ethical regulations. The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation in the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the clinical efficacy of lansoprazole.

In the event of **an issue with the analysis for CYP2C19** ~~DNA extraction failure~~, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Description of Subgroups to be Analyzed (Section 7.6)

Subgroup analyses for the primary endpoint in each phase will be conducted for demographic and other relevant clinical variables, including age, sex, body mass index, **smoking status,**

alcohol use, region, baseline EE grade (both separately A, B, C, and D and with Grades A or B and C or D combined), and CYP2C19 status (extensive metabolizer versus poor metabolizer). Subgroup analyses for the primary endpoint in the Maintenance Phase will also be conducted by Healing Phase treatment and by duration of Healing Phase treatment.

Table 13-1 Schedule of Events

	Screening Period (a)	Healing Phase					Maintenance Phase						
Timing		**Healing Day -1 (b)**	**Healing Day 1(b)**	**Week 2 (c) Healing Day 15**	**Week 8 (c,m) Healing Day 57**		**Main Week 4 Main Day 29**	**Main Week 12 Main Day 85**	**Main Week 16 Main Day 113**	**Main Week 20 Main Day 141**	**Main Week 24 Main Day 169 Final Visit/ET (d)**	**Safety F/U (e)**	**Un-sched-uled Visit (f)**
Visit Windows (Days)	**Day-35 to -2**	**-**		**12 to 18**	**54 to 60**		**26 to 36**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**-**	**-**
Visit Number:	**1**	**2**		**3**	**4**		**M1**	**M2**	**M3**	**M4**	**M5**	**F/U**	**-**
Informed Consent	X												
Inclusion/Exclusion Criteria	X	X											
Demographic and medical history	X												
Smoking status and alcohol use	**X**												
Medication history	X												

Appendix 3: The Patient Assessment of Gastrointestinal Disorders-Symptoms Severity Index (PAGI-SYM) (Section 13.3)

The sample copy of the PAGI-SYM questionnaire was replaced with an updated version.

Appendix 6: Liver Function Tests (Section 13.6)

Permanent Discontinuation of Study Drug (Section 13.6.3)

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** ~~AE~~.