Phathom Pharmaceuticals, Inc.

NERD-301

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

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Statistical Analysis Plan

Version 1.0

Prepared by:

Signature Page

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

Protocol Number: NERD-301

Approved by:

[redacted]

[redacted]

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
CI	Confidence interval
CTMS	Clinical Trial Management System
ECG	Electrocardiogram
eCRF	Electronic case report form
EE	Erosive esophagitis
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
H2RA	Histamine-2 receptor antagonist
IRT	Interactive response technology
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NERD	Symptomatic non-erosive gastroesophageal reflux disease
N-GSSIQ	Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index
PAGI-QoL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PPI	Proton pump inhibitor
PSQI	Pittsburgh Sleep Quality Index Questionnaire
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event

1. INTRODUCTION

Vonoprazan belongs to a new class of acid-inhibitory agents called potassium-competitive acid blockers. In addition to the treatment of heartburn in patients with symptomatic non-erosive gastroesophageal reflux disease (NERD), vonoprazan is being developed for healing of all grades of erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *Helicobacter pylori* infection.

Study NERD-301 will evaluate the safety and effectiveness of vonoprazan (10 mg and 20 mg) to treat heartburn in subjects with NERD.

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the Protocol Version 3.0, dated 25-April-2022.

2. OBJECTIVES AND ESTIMANDS

The primary objective of this study is as follows:

Table 1. Primary Objective, Endpoint, and Estimand

Objective	**Endpoint and Estimand with *Summary Measure and Endpoint***
Primary Efficacy: Placebo-controlled Treatment Period	
• To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in relief of heartburn over 4 weeks in subjects with NERD.	• Endpoint: The percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary. • Primary Estimand: Difference in the *mean percentage of days without daytime or nighttime heartburn over the 4-week Placebo-controlled Treatment Period* between each dose of vonoprazan and placebo (10 mg QD – placebo and 20 mg QD – placebo) in subjects with NERD, where a heartburn-free day is a day for which all entries are heartburn-free with no use of rescue antacid, H2RAs, and PPIs and assuming the percentage of heartburn-free days after treatment discontinuation is the percentage of heartburn-free days during the screening period, irrespective of rescue antacid, H2RAs, and PPIs used after treatment discontinuation. • Supportive Estimand: Difference in the *mean percentage of days without daytime or nighttime heartburn over the 4 week Placebo-controlled Treatment Period* as assessed by the daily diary between each dose of vonoprazan and placebo (10 mg QD – placebo and 20 mg QD - placebo) in subjects with NERD whose

	response to treatment is of interest only while on study drug, i.e., prior to study drug discontinuation due to any reason and irrespective of excluded/rescue medications and treatments.

The safety objectives are as follows:

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

The secondary objective is as follows:

Table 2. Secondary Objective, Endpoint, and Estimand

Objective	**Endpoint and Estimand with *Summary Measure and Endpoint***
Secondary Efficacy: Placebo-controlled Treatment Period	
• To assess the use of rescue antacid with vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.	• Difference in the *percentage of days without rescue antacid use over the 4-week Placebo-controlled Treatment Period* as assessed by the daily diary between each dose of vonoprazan and placebo (10 mg QD – placebo and 20 mg QD – placebo) in subjects with NERD whose response to treatment is of interest only while on study drug, i.e., prior to study drug discontinuation due to any reason and irrespective of excluded (non-rescue) medications and treatments.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

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

The study will include four periods:

Screening Period (Day -35 to Day -2): Subjects will provide informed consent and undergo screening assessments to determine study eligibility, and baseline assessment will

be performed. Subjects will complete the electronic diary twice daily during the Screening Period. If all eligibility criteria are met, the subject will enter the study.

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

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

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

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

3.2. Study Endpoints

The primary efficacy endpoint of this study is as follows:

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

The secondary endpoint of this study is as follows:

- The percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary.

The safety endpoints of this study are as follows:

- Adverse Events (AEs)
- Laboratory test values (hematology, serum chemistry, urinalysis)
- Serum gastrin and pepsinogen I/II levels
- Electrocardiograms (ECGs)
- Vital signs

The exploratory endpoints for the Placebo-controlled Treatment Period are as follows:

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

- The percentage of days without daytime or nighttime heartburn over the last 7 days of the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of daytime and nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of daytime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The time to sustained resolution of heartburn during the Placebo-controlled Treatment Period (sustained resolution is defined as at least 7 consecutive days with no daytime or nighttime heartburn as assessed by the daily diary)
- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) questionnaire
- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life (PAGI-QoL) questionnaire
- The change from baseline to the end of the Placebo-controlled Treatment Period for the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L)
- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Nocturnal Gastroesophageal Reflux Disease Symptom Severity and Impact Questionnaire (N-GSSIQ)
- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the Pittsburgh Sleep Quality Index (PSQI) questionnaire

The exploratory endpoints for the Extension Period are as follows:

- The percentage of days without daytime or nighttime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without nighttime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without daytime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without daytime or nighttime heartburn from Week 4 to Week 8 in subjects re-randomized at Week 4 from placebo to either vonoprazan 10 mg or 20 mg
- The mean severity of daytime and nighttime heartburn over the Extension Period as assessed by the daily diary
- The mean severity of daytime heartburn over the Extension Period as assessed by the daily diary
- The mean severity of nighttime heartburn over the Extension Period as assessed by the daily diary

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

Exploratory endpoints for the Follow-up Period include:

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

3.3. Treatments

3.3.1. Placebo-controlled Treatment Period

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

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

3.3.2. Extension Period

Following completion of the Placebo-controlled Treatment Period at Week 4, all subjects will be assigned study drug for the Extension Period by the IRT system:

- Subjects randomized to placebo during the Placebo-controlled Treatment Period will be re-randomized to receive vonoprazan 10 mg or vonoprazan 20 mg QD for the 20-week Extension Period.
- Subjects randomized to 1 of the 2 vonoprazan treatment groups during the Placebo-controlled Treatment Period will continue to receive the same vonoprazan dose during the Extension Period.

3.4. Dose Adjustment/Modifications

No dose adjustments or modifications are allowed for this study.

4. GENERAL STATISTICAL CONSIDERATIONS

In general, descriptive statistics will be presented by treatment group and by visit, as applicable.

Data collected during the Placebo-controlled Treatment Period will be summarized by the following treatment groups:

- Placebo
- Vonoprazan 10 mg
- Vonoprazan 20 mg

Data collected during the Extension and Follow-up Periods will be summarized by the following treatment groups:

- Placebo – Vonoprazan 10 mg
- Placebo – Vonoprazan 20 mg
- Vonoprazan 10 mg – Vonoprazan 10 mg
- Vonoprazan 20 mg – Vonoprazan 20 mg

Selected data will be summarized over both treatment periods for patients who received vonoprazan throughout the study, that is, only subjects who were randomized to the vonoprazan groups during the Placebo-controlled Treatment period will be included in these summaries. These summaries will use the following treatment groups:

- Vonoprazan 10 mg
- Vonoprazan 20 mg

For continuous variables, summary statistics for the raw value and change from baseline at each time-point will include the number of subjects (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum.

Categorical variables will be summarized using subject counts and percentages. Percentages will be calculated using the total subjects per treatment unless otherwise specified.

Change from baseline in absolute terms is defined as the baseline value subtracted from the post-baseline value.

The efficacy analyses will be conducted on the Intent-to-Treat Set using the planned treatment. See Section 4.4.3 for the Intent-to-Treat Set definition.

The safety analyses will be conducted on the Safety Set using the actual treatment the subject received. If a subject receives more than one type of study drug during a period, the planned treatment will be assigned as the actual treatment for the subject in the safety summary tables for this period. Meanwhile, if a subject receives only one type of study drug during a period but the study drug type is different than the planned treatment, the actual treatment received will be assigned as the actual treatment for this subject in the safety summary tables for this period. See Section 4.4.4 for the Safety Set definition.

Statistical tests will be two-sided and will be conducted at the assigned α significance level. P-values will be reported to 4 decimal places, with p-values less than 0.0001 reported as "<0.0001".

SAS® Version 9.4 or higher will be used to perform all statistical analyses or procedures.

4.1. Sample Size

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

4.2. Randomization, Stratification, and Blinding

An IRT system will be used to administer the randomization schedule.

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

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

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

Biostatistics will generate the randomization schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IRT, which will link sequential subject randomization numbers to treatment codes. The randomization will also use an appropriate block size, which will not be revealed. The biostatistician generating the schedule will not be involved in study conduct or have access to efficacy and/or safety data while the study is ongoing.

The study treatment blind during the Placebo-controlled Treatment Period and the Extension Period will be maintained using the IRT. A double-blind design is employed for the Placebo-controlled Treatment Period so that both the investigators and the subjects will be unaware of the treatment assignment. Moreover, study center staff involved in study drug administration and study endpoint assessments, PPD personnel, and the Phathom team, including the study statistician, will be blinded to the treatment received during the Placebo-controlled Treatment Period.

During the Extension Period, both investigators and subjects will remain blinded to the subject's individual treatment assignment through the Extension Period. Following the interim analysis (if performed; see Section 10), Phathom and PPD would be unblinded to the treatment assignment of individual subjects during the Placebo-controlled Treatment Period.

4.3. Assessment Windows

4.3.1. Study Day

For this study, randomization is to occur on Day -1 while the date of first dose of study drug is defined as Day 1 for both the Placebo-controlled Treatment Period and Extension Period. There is no Day 0 defined for this study. For analysis purposes, study day is calculated as:

Date of assessment – Day 1 +1, for assessments done after first dose of study drug

Date of assessment – Day 1, for assessments done before the first dose of study drug

4.3.2. Analysis Visit Windows

Analysis visit windows will be defined for analysis purposes and for summary tables presented by visit. Data (such as AEs and concomitant medications) that are not collected by visit and will not be summarized by visit will not use visit windows. Both scheduled and unscheduled assessments will be considered as valid assessments for analysis. Analysis visit labels will be assigned to each post-baseline record based on the study day windows relative to the date of first dose of study drug (Day 1). For the Placebo-controlled Treatment Period, if an assessment on Day -1 is missing, the closest visit with non-missing assessment on or before the date of first dose of study drug will be used as baseline. For the Extension Period, the closest visit in the Placebo-controlled Treatment Period with non-missing assessment on or before the date of first dose of study treatment during Extension Period will be used as baseline. All by-visit summary and analysis will be based on the analysis visit windows presented below.

Table 3. Analysis Visit Windows

Period	Nominal Visit (recorded on eCRF)	Analysis Visit	Target Study Day of Visit	Analysis Visit Window
Placebo-controlled Treatment	Visit 1 Screening	Screening	NA	Date of informed consent to the day prior to first dose of study drug
Placebo-controlled Treatment	Visit 2 Day -1	Baseline	-1	Day prior to first dose of study drug

Placebo-controlled Treatment	Visit 4 Week 4	Week 4	28	2 to 42 days and prior to starting treatment during the Extension Period
Extension	Visit 6 Week 12	Week 12	85	57 to 127 days
Extension	Visit 9 Week 24 Final	Week 24	169	128 days or greater and within 6 days after the last dose of study drug in the Extension Period
Follow-up	Visit 10 Week 28 Follow-up	Week 28	197	7 or more days after the last dose of study drug in the Extension Period

Unscheduled assessments will also be assigned to analysis visits based on the analysis visit window defined in Table 3 above. When data is summarized by assigned analysis visit based on study day, visits will be referenced in summary tables by analysis visits only. Listings will present both nominal visits as recorded on the electronic case report form (eCRF) and the analysis visits. After all the records have been assigned to an analysis visit, if there are multiple valid records for an assessment within an assigned analysis visit, only one of these records will be used for summary statistics and analyses. The record to be used is determined based on the following hierarchy (in descending order):

For safety assessments, including laboratory tests, ECG and vital signs:

1. the record closest to the target visit day
2. the record on the latest visit in the analysis visit window

For data handling purposes, the following visit window definitions will be used for the Placebo-controlled Treatment Period, Extension Period, Follow-up Period, and Overall study duration summaries:

- Placebo-controlled Treatment Period: from the date of first dose of study drug to the date of last dose of study drug in the Placebo-controlled Treatment Period. If the date of first dose of study drug is missing, then it will be imputed as the date of randomization + 1. If the date of last dose of study drug is missing, then the earliest of the following available dates will be used as the date of the end of the Placebo-controlled Treatment Period:
    - Date of Week 4 visit
    - Date of treatment discontinuation
    - Date of study discontinuation

  - Date the patient is expected to run out of study drug based on the kit dispensed at randomization

- Extension Period: from the date of first dose of study drug in the Extension Period to the date of last dose of study drug in the Extension Period. If the date of first dose of study drug is missing, then it will be imputed as the date of the end of Placebo-controlled Treatment Period + 1. If the date of last dose of study drug is missing, then the earliest of the following available dates will be used as the date of the end of the Extension Period:
  - Date of Week 24 visit
  - Date of treatment discontinuation
  - Date of study discontinuation
  - Date the patient is expected to run out of study drug based on the kit(s) dispensed at the latest of Week 4 or Week 12 visit
- Follow-up Period: from the date of the end of Extension Period + 1 to the date of completion/withdrawal/last contact.
- Overall study duration: from the date of the start of Placebo-controlled Treatment Period to the date of completion/withdrawal/last contact.

4.4. Analysis Set

4.4.1. Screened Set

The screened set will be defined as all subjects who signed the informed consent form before entering the Placebo-controlled Treatment Period of the study. Screen failures are defined as subjects who were not randomized into the Placebo-controlled Treatment Period of the study.

4.4.2. Randomized Set

For the Placebo-controlled Treatment Period, the randomized set will be defined as all subjects randomly assigned to receive study drug regardless of whether they received a dose of study drug or not during the Placebo-controlled Treatment Period.

For the Extension Period, the randomized set will be defined as all subjects randomly assigned to receive study drug regardless of whether they received a dose of study drug or not during the Extension Period.

4.4.3. Intent-to-Treat (ITT) Set

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

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

Analyses will be conducted on the ITT set using the planned treatment.

4.4.4. Safety Set

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

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

Analyses will be conducted on the safety set using the actual treatment the subject received.

4.5. Intercurrent Event Types

The intercurrent events defined for this study are as follows:

Table 4. Intercurrent Event types

Label	Intercurrent Event Type
IcEv1 (Discontinuation)	Discontinuation of treatment over the 4-week Placebo-controlled Treatment Period due to any reason
IcEv2 (Excluded antisecretory (non-rescue) medications)	Use of PPIs or H2Ras
IcEv3 (Rescue medication)	Use of rescue medication (sponsor-provided antacid)

Abbreviation: IcEV=intercurrent event; H2RA: histamine-2 receptor antagonist; PPI: proton pump inhibitor

4.6. Estimand Specifications

The estimand specifications for the primary and secondary efficacy endpoints are as follows:

Table 5. Primary Objective(s) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To assess the efficacy of vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) in relief of heartburn over 4 weeks in subjects with NERD
Estimand Label	Estimand 1 (Primary)
Estimand Description	Difference in the *mean percentage of days without daytime or nighttime heartburn over the 4-week Placebo-controlled Treatment Period* between each dose of vonoprazan and placebo (10 mg QD – placebo and 20 mg QD – placebo) in subjects with NERD, where a heartburn-free day is a day for which all entries are heartburn-free with no use of rescue antacid, H2RAs, and PPIs and assuming the percentage of heartburn-free days after treatment discontinuation is the percentage of heartburn-free days during the screening period, irrespective of rescue antacid, H2RAs, and PPIs used after treatment discontinuation.
Target Population	Patients with NERD who would meet all the inclusion/exclusion criteria of the study
Endpoint	Percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period
Treatment Condition(s)	Experimental: Vonoprazan 10 mg, Vonoprazan 20 mg Comparator: Placebo
Population-Level Summary	Difference in the mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period
Intercurrent Event Strategy	
IcEv1 (Discontinuation)	Composite
IcEv2 (Excluded (non-rescue) medications)	Composite
IcEv3 (Rescue medication)	Composite
Rationale for Strategies	Composite strategy is utilized as treatment discontinuation may represent an unfavorable outcome. Composite strategy is utilized as use of rescue medication may indicate the subject experienced heartburn even if heartburn was not indicated in the diary. Composite strategy is utilized for use of rescue medication and prohibited medication (ie, H2RAs, PPIs) as use of other acid-reducing medications may confound efficacy results for heartburn.

Table 5. Primary Objective(s) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events (continued)

Estimand Label	Estimand 2 (Supportive)
Estimand Description	Difference in the *mean percentage of days without daytime or nighttime heartburn over the 4-week Placebo-controlled Treatment Period* as assessed by the daily diary between each dose of vonoprazan and placebo (10 mg QD – placebo and 20 mg QD - placebo) in subjects with NERD whose response to treatment is of interest only while on study drug, i.e., prior to study drug discontinuation due to any reason and irrespective of excluded/rescue medications and treatments
Target Population	Patients with NERD who would meet all the inclusion/exclusion criteria of the study
Endpoint	Percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period
Treatment Condition(s)	Experimental: Vonoprazan 10 mg, Vonoprazan 20 mg Comparator: Placebo
Population-Level Summary	Difference in the mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period
Intercurrent Event Strategy	
IcEv1 (Discontinuation)	While on Treatment
IcEv2 (Excluded (non-rescue) medications)	Treatment Policy
IcEv3 (Rescue medication)	Treatment Policy
Rationale for Strategies	Treatment Policy strategy is used to understand the treatment effect in the Placebo-controlled Treatment Period irrespective of the taken prohibited/rescue medications as these reflect what might happen in clinical practice. Every attempt is taken to measure the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period. While on treatment strategy is used when response to treatment before the discontinuation of the study drug is of interest and was selected due to the short (<24 hours) half-life of the drug.

Abbreviation: IcEV = intercurrent event; NERD = Non-Erosive Gastroesophageal Reflux Disease
Refer to Table 4 for specific intercurrent event definitions.

Table 6. Secondary Objective(s) and Estimand(s) with Rationale for Strategies to Address Intercurrent Events

Objective	To assess the use of rescue antacid with vonoprazan (10 mg and 20 mg QD) compared to placebo (QD) over 4 weeks in subjects with NERD.
Estimand Label	Estimand 3 (Secondary)
Estimand Description	Difference in the mean *percentage of days without rescue antacid use over the 4-week Placebo-controlled Treatment Period* as assessed by the daily diary between each dose of vonoprazan and placebo (10 mg QD – placebo and 20 mg QD - placebo) in subjects with NERD whose response to treatment is of interest only while on study drug, i.e., prior to study drug discontinuation due to any reason and irrespective of excluded (non-rescue) medications and treatments.
Target Population	Patients with NERD who would meet all the inclusion/exclusion criteria of the study
Endpoint	Percentage of days without rescue antacid use over the Placebo-controlled Treatment Period
Treatment Condition(s)	Experimental: Vonoprazan 10 mg, Vonoprazan 20 mg Comparator: Placebo
Population-Level Summary	Difference in the mean percentage of days without recue antacid use over the Placebo-controlled Treatment Period
Intercurrent Event Strategy	
IcEv1 (Discontinuation)	While on Treatment
IcEv2 (Excluded (non-rescue) medications)	Treatment Policy
IcEv3 (Rescue medication)	Composite
Rationale for Strategies	Treatment Policy strategy is used to understand the treatment effect in the Placebo-controlled Treatment Period irrespective of the taken prohibited/rescue medications as these reflect what might happen in clinical practice. Every attempt is taken to measure the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period. While on treatment strategy is used when response to treatment before the discontinuation of the study drug is of interest and was selected due to the short (<24 hours) half-life of the drug. Composite strategy is implied because the patients' outcome is incorporated into the definition of the endpoint.

Abbreviation: IcEV = intercurrent event; NERD = Non-Erosive Gastroesophageal Reflux Disease
Refer to Table 4 for specific intercurrent event definitions.

5. SUBJECT DISPOSITION

5.1. Disposition

5.1.1. Screened and Screen Failure Subjects

The following will be summarized and presented for overall subjects for the Screened Set:

- total number of screened subjects
- number and percentage of screen failures
- number and percentage of screen failures for each primary reason

Subjects who fail to satisfy all inclusion/exclusion criteria will be listed for the Screened Set.

5.1.2. Placebo-controlled Treatment Period Randomized Subjects

The following will be summarized and presented by treatment group and for overall subjects for the Randomized Set:

- number of randomized subjects
- number of subjects randomized but not treated
- number and percentage of subjects who completed the Placebo-controlled Treatment Period
- number and percentage of subjects who discontinued treatment during the Placebo-controlled Treatment Period
- number and percentage of subjects for each reason for discontinuing treatment during the Placebo-controlled Treatment Period
- number and percentage of subjects who entered the Extension Period
- number and percentage of subjects who did not enter the Extension Period
- number and percentage of subjects for each reason for not entering the Extension Period

Percentages will be based on the number of subjects in the Randomized Set. Subject disposition data will be listed for the Randomized Set. Additionally, the reason for discontinuation for subjects who discontinued during the Placebo-controlled Treatment Period will be listed separately for the Randomized Set.

5.1.3. Extension Period Randomized Subjects

The following will be summarized and presented by treatment group and for overall subjects for the Randomized Set:

- number of randomized subjects

- number of subjects randomized but not treated
- number and percentage of subjects who completed the Extension Period
- number and percentage of subjects who discontinued treatment during the Extension Period
- number and percentage of subjects for each reason for discontinuing treatment during the Extension Period
- number and percentage of subjects who completed the study
- number and percentage of subjects who did not complete the study
- number and percentage of subjects for each reason for not completing the study

Percentages will be based on the number of subjects in the Randomized Set. Subject disposition data will be listed for the Randomized Set. Additionally, the reason for discontinuation for subjects who discontinued during the Extension Period will be listed separately for the Randomized Set.

5.1.4. Placebo-controlled Treatment Period

The following will be summarized for the Placebo-controlled Treatment Period Safety Set:

- number and percentage of subjects in the Safety Set and ITT Set
- number and percentage of subjects for each reason for exclusion from the ITT Set
- number and percentage of subjects who completed the Placebo-controlled Treatment Period
- number and percentage of subjects who discontinued from the Placebo-controlled Treatment Period
- number and percentage of subjects for each reason for discontinuation of study drug during the Placebo-controlled Treatment Period

5.1.5. Extension Period

The following will be summarized for the Extension Period Safety Set:

- number and percentage of subjects in the Safety Set and ITT Set
- number and percentage of subjects for each reason for exclusion from the ITT Set
- number and percentage of subjects who completed the Extension Period
- number and percentage of subjects who discontinued from the Extension Period
- number and percentage of subjects for each reason for discontinuation of study drug during the Extension Period

5.2. Protocol Deviations

Protocol deviations will be recorded within the PPD Clinical Trial Management System (CTMS) and will undergo a blinded review prior to database lock and unblinding. Significant protocol deviations are defined as the subset of deviations which are considered to affect primary efficacy and safety assessments, the safety or mental integrity of a subject, or the scientific value of the trial.

The number and percentage of subjects with subject-specific significant protocol deviations will be summarized by CTMS activity subtype, treatment group, and overall for the Randomized Set separately for the Placebo-controlled Treatment Period and Extension Period.

Individual subject protocol deviations, both significant and non-significant, will be listed in a by-treatment, by-subject data listing separately for the Placebo-controlled Treatment Period and Extension Period using the Randomized Set.

6. DEMOGRGAPHICS AND BASELINE CHARACTERISTICS

6.1. Demographics

Demographic variables collected at Baseline, such as age (years), sex, race, ethnicity, height (cm), weight (kg), and body mass index (BMI) will be summarized using the Randomized and ITT Sets.

Continuous variables, including age, BMI, weight, and height, will be summarized using descriptive statistics for each treatment group and overall. Categorical variables will be summarized by reporting the number and percentage of subjects in each category for each treatment group and overall.

- Age group 1 at Baseline (<45, ≥45 - <65, ≥65 - <75, ≥75)
- Age group 2 at Baseline (≥18 - ≤64, ≥65 - ≤84, ≥85)
- Sex (Female, Male)
- Fertility Status (Sterile, Post-Menopausal, Potentially Able to Bear Children, N/A)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown, Ethnicity Not Reported)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other Race, Unknown Race, Race Not Reported)
- Smoking Status (Never smoked, Current smoker, Ex-smoker)
- Alcohol Use (Drink Everyday, Drink a Couple of Days per Week, Drink a Couple of Days per Month, Never Drink)
- BMI category (<25, ≥25 - <30, ≥30)

At baseline, the mean severity of heartburn and the number of days with heartburn will be summarized based on the daytime and nighttime heartburn symptoms reported in the daily diary during the last 7 days prior to Day -1, i.e, Days -8 to -2, inclusive. Only days with at

least 1 morning or evening diary entry during the specified days will be included in these summaries. In addition, the mean severity of heartburn and number of days with heartburn will be summarized using the following categories:

- Number of days with:
  - Daytime or nighttime heartburn (0, 1-3, 4-5, 6-7)
  - Daytime heartburn (0, 1-3, 4-5, 6-7)
  - Nighttime heartburn (0, 1-3, 4-5, 6-7)
- Mean severity of
  - Daytime or nighttime heartburn (0, >0 - ≤ 1, > 1 - ≤ 2, > 2 - ≤ 3, >3 – 4)
  - Daytime heartburn (0, >0 - ≤ 1, > 1 - ≤ 2, > 2 - ≤ 3, >3 – 4)
  - Nighttime heartburn (0, >0 - ≤ 1, > 1 - ≤ 2, > 2 - ≤ 3, >3 – 4)

In addition, the percentage of heartburn-free days during the screening period, calculated using all available diary data prior to randomization, will also be summarized using the same data handling rules as for the percentage of heartburn-free days during the Placebo-controlled Treatment Period (See Section 8.1.2).

Demographic and baseline characteristics data will be listed by treatment and subject using the Randomized Set.

6.2. Medical History

6.2.1. General Medical History

Medical history will be coded using Version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with medical history coded to each MedDRA SOC and PT will be summarized by treatment group and overall using the Safety Set.

Medical history will be listed by treatment and subject using the Randomized Set.

7. TREATMENTS AND MEDICATIONS

7.1. Prior and Concomitant Medications

Any prior and concomitant medication used during the study will be recorded and coded using WHODRUG Version B3-March 2019. Summaries of all medications by drug class (ATC Level 4 coding) and preferred term will be provided separately for prior medications and concomitant medications for each treatment group and overall. Medications with missing ATC Level 4 terms will be summarized using the highest-level term that is available. All summaries will be performed using the Safety Set.

For the Placebo-controlled Treatment Period, prior medications are those with the start and stop dates prior to the first dose of study drug in the Placebo-controlled Treatment Period. Concomitant medications are those:

- with start dates prior to the first dose of study drug in the Placebo-controlled Treatment Period and continuing after the first dose of study drug in the Placebo-controlled Treatment Period, or
- with start dates between the first dose of study drug in the Placebo-controlled Treatment Period but on or before the last dose of study drug in the Placebo-controlled Treatment Period.

Prior and concomitant medications for the Placebo-controlled Treatment Period will be summarized separately by treatment group and overall.

For the Extension Period, concomitant medications are those with:

- start dates prior to the first dose of study drug in the Extension Period and continuing after the first dose of study drug in the Extension Period, or
- with start dates after the first dose of study drug in the Extension Period but before the last dose of study drug in the Extension period

The concomitant medications for the Extension Period will be summarized by treatment group and overall.

In instances where a medication start date is incomplete, it will be conservatively imputed to determine whether or not the medication was prior or concomitant. If the start date is missing, then it will be assumed to be concomitant. Imputation details for missing concomitant medication start and end date are presented in Appendix Section 12.2.

All prior and concomitant medications will be listed by treatment and subject for the Safety Set.

7.2. Study Treatments

7.2.1. Extent of Exposure

Study drug exposure will be calculated as the number of days from the first to last dose date of each period:

Exposure = Date of last dose – Date of first dose + 1.

If the date of first/last dose is missing, it will be imputed using the start/end date of the corresponding analysis window as described in Section 4.3.2.

Descriptive summary statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum for the study drug exposure (days) will be presented by treatment group and overall for the Safety Set for each period, and overall (i.e., across periods).

Subject counts and percentages for the duration of study drug exposure for the Placebo-controlled Treatment Period will be summarized cumulatively and for the following categories: ≥1 to ≤14 days, >14 to ≤28 days, >28 days. Similarly, subject counts and percentages for the duration of study drug exposure for the Extension Period will be summarized cumulatively and for the following categories: ≥1 to ≤14 days, >14 to ≤28 days, >28 to ≤56 days, >56 to ≤84 days, >84 to ≤112 days, >112 to ≤140 days, >140 days. Lastly, subject counts and percentages for the duration of study drug exposure over both treatment periods will be summarized cumulatively and for the following categories: ≥1 to ≤14 days, >14 to ≤28 days, >28 to ≤56 days, >56 to ≤84 days, >84 to ≤112 days, >112 to ≤140 days, >140 days to ≤168 days, >168 days.

All study drug exposure data will be listed using the Safety Set.

7.2.2. Treatment Compliance

Treatment compliance for each period will be calculated as follows:

$Compliance\ (\%) = \frac{total\ capsules\ taken}{total\ capsules\ expected} \times 100$, where

total expected capsules = (date of last dose for the period – date of first dose for the period) +1

total capsules taken = total number of capsules dispensed for the period – total number of capsules returned

For each period, if a subject has at least one kit not returned, the following imputation will be utilized:

- if all dispensed kits are not returned, the compliance is imputed as 100% for the period
- if only partial kits are returned, the missing capsules returned will be treated as 0 and the compliance will be computed consequently
- if a subject has a returned amount imputed for at least one kit which results to a treatment compliance of >120%, then the treatment compliance will be set to 100% instead for the period

Each subject will be categorized as either compliant (compliance of ≥80% and ≤120%) or non-compliant (compliance of <80% or >120%).

Compliance rate will be summarized by treatment group and overall for each period. Moreover, subject counts and percentages for the following compliance intervals (<80, ≥80 - ≤100, >100 - ≤120, >120) will be summarized by treatment group and overall for each period.

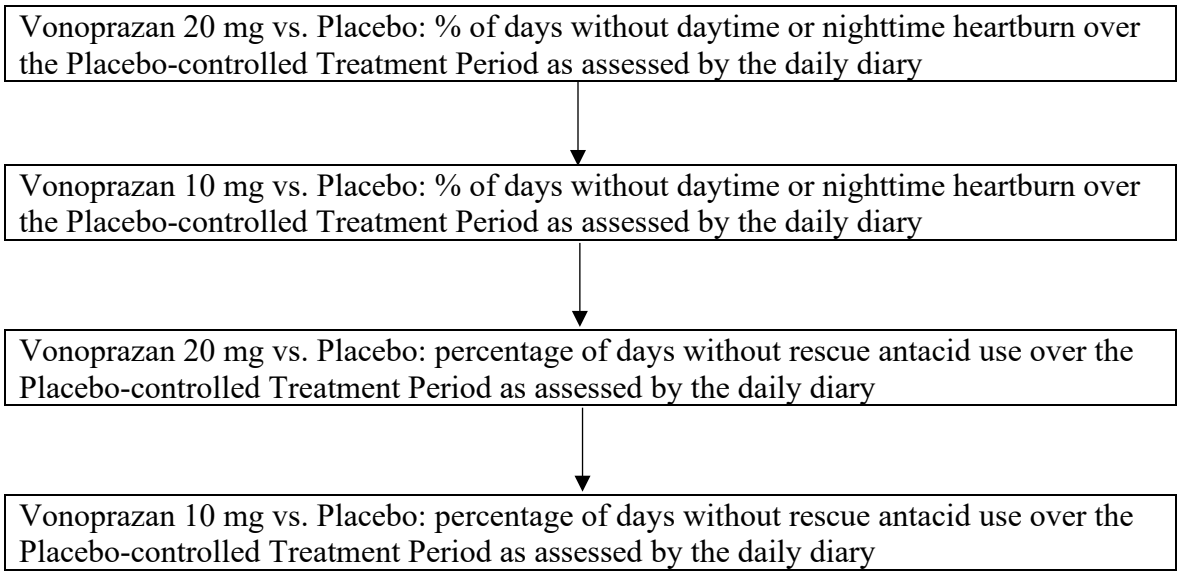
All compliance data will be listed using the Safety Set.

7.2.3. Diary Compliance

A summary of the percentage of missing diaries in each period will be summarized by treatment group. A study day with no diary entry will be counted as two missing diary entries. A study day with only either the daytime or nighttime diary entry will be counted as one missing diary entry. The percentage will be calculated based on expected number of diary entries in the period, that is, the treatment duration in the period times two.

8. EFFICACY ANALYSIS

The overall type 1 error rate will be controlled at alpha=0.05 by utilizing a fixed sequence testing procedure. The comparisons will be performed in the following order until a test is not significant. Tests that are not significant based on this testing procedure for the primary and secondary endpoints will be considered purely nominal.



No multiplicity adjustment will be performed for the exploratory endpoints. Each exploratory endpoint will be tested independently at an alpha level of 0.05.

Comparisons will also be made between the vonoprazan dose groups for all endpoints with no multiplicity adjustment.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint of the Estimand 1 (primary) is the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary.

8.1.1. Primary Analysis

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

The severity and frequency of heartburn at baseline will be summarized as the mean severity and the number of days, respectively, from the daytime and nighttime heartburn symptoms reported in the daily diary during the last 7 days prior to Day -1 of the Placebo-controlled Treatment Period.

Descriptive summary statistics including the number of subjects, mean, standard deviation, median, Q1, Q3, minimum, and maximum percentage of days without daytime or nighttime heartburn will be presented. For each comparison of vonoprazan treatment group to placebo, the LS mean difference, 2-sided 95% CI, and p-value will also be presented.

The percentage of subjects without daytime or nighttime heartburn by study day during the Placebo-controlled Treatment Period will be presented by treatment group in a figure.

All efficacy data will be listed using the ITT Set.

8.1.2. Derivation of the Primary Endpoint

A diary day will be included in the denominator for the calculation of a subject's percentage of days without daytime or nighttime heartburn if the following conditions are satisfied:

- both the morning and evening diary for that day were completed
- or if only one diary entry for that day was completed and this diary entry indicates the presence of heartburn.

Diary days will not be included in the denominator if the subject missed both the morning and evening entries for that day or if the subject completed only one diary entry and this diary entry indicates the absence of heartburn.

A diary day will be included in the numerator as a heartburn-free day if the following conditions are satisfied:

- both the morning and evening diary for that day were completed and both entries indicate the absence of heartburn
- no rescue antacid was used on that day
- no H2RAs or PPIs were used on that day.

For subjects who prematurely discontinue treatment during the Placebo-controlled Treatment Period, the percentage of days without daytime or nighttime heartburn after discontinuation up to Day 28 will be imputed using the percentage of heartburn-free days

during the Screening Period. The percentage of heartburn-free days during the Screening Period will be calculated using the same data handling rules for the percentage of heartburn-free days during the Placebo-controlled Treatment Period. For subjects who prematurely discontinue treatment prior to Day 7 of the Placebo-controlled Treatment Period and have less than 4 days of diary entries, the percentage of heartburn-free days will be imputed using the percentage of heartburn-free days during the Screening Period.

If there are more than 2% of ITT subjects who have been on treatment for at least 7 days and have less than 4 days of diary entries, multiple imputation will be used to compute the percentage of days without daytime or nighttime heartburn while on treatment, as the estimated percentage of days without heartburn may be unreliable for subjects with only a few completed diaries. The multiple imputation will be performed under a missing-at-random (MAR) assumption using the Placebo-controlled Treatment Period treatment group and the severity and frequency of heartburn at baseline as variables in the model. The general linear model with treatment group as a factor and severity and frequency of heartburn at baseline as covariates will be run on each of 100 imputed datasets. The difference in the percentage of days without daytime or nighttime heartburn between treatment groups with 95% confidence intervals from each of the 100 imputed datasets will be combined using Rubin's Method. For further details on the derivation of the diary-based endpoints, see Section 12.3.1.

If less than 2% of ITT subjects require multiple imputation, the percentage of days without daytime or nighttime heartburn for all subjects with less than 4 days of diary entries will be imputed using the more conservative percentage of heartburn-free days during the Screening Period.

8.1.3. Assumption Testing

Since linear regression methods are generally robust to departures in normality for large sample sizes, testing of distributional assumption of the endpoint is not planned.

8.1.4. Sensitivity/Supplementary Analyses

To assess how intercurrent events in Section 4.5 affect the robustness of the primary analysis results for Estimand 1 (primary), the following analyses will be performed. See Section 12.5 for the detailed description of the estimand and planned primary and sensitivity/supplementary analyses.

8.1.4.1. Non-parametric test

The percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary for each of the vonoprazan treatment groups will be compared to the placebo treatment group using a Wilcoxon rank-sum test using the ITT Set.

8.1.4.2. Use of acid reducing medications

To explore how the use of acid reducing medications affects the primary analysis, the percentage of days without daytime or nighttime heartburn irrespective of rescue antacid, H2RA, and PPI over the Placebo-controlled Treatment Period will also be summarized.

8.1.4.3. Imputation for missing diary entries

To explore how missing data affects the robustness of the primary analysis on the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period, a sensitivity analysis will be performed in which days with missing diary entries (either no diary entries or only one diary entry) will be imputed as a day with heartburn for all subjects. In addition, for subjects who discontinue the Placebo-controlled Treatment Period prior to Day 28, days after discontinuation date will be imputed as having heartburn. The percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period will be calculated based on the number of planned days in the Placebo-controlled Treatment Period, that is, 28 days.

8.1.5. Subgroup Analysis

The primary efficacy endpoint will be analyzed separately for the following subgroups per subgroup level in the ITT set using a general linear model with treatment group as a factor:

- Age group 1 at Baseline (<45, ≥45 - <65, ≥65)
- Sex (Male, Female)
- BMI category (<25, ≥25 - <30, ≥30)
- Mean severity of baseline daytime or nighttime heartburn (0, >0 - ⩽ 1, > 1 - ⩽ 2, > 2 - ⩽ 3, >3 – 4)
- Frequency (number of days) of baseline daytime or nighttime heartburn (0-3, 4-5, 6-7)

Severity and frequency of heartburn at baseline will be based on symptoms reported in the daily diary from the last 7 days prior to Day -1 of the Placebo-controlled Treatment Period.

In addition, an analysis across each subgroup will be performed using a general linear model with factors for treatment group, subgroup level, and treatment by subgroup interaction.

For the subgroup analyses of the primary efficacy endpoint, given the complexity of implementing multiple imputation within each subgroup, the percentage of days without daytime or nighttime heartburn for all subjects with less than 4 days of diary entries will be imputed using the more conservative imputation of the percentage of heartburn-free days during the Screening Period. Otherwise, the subgroup analyses for the percentage of days without daytime or nighttime heartburn will be summarized following the data handling methods for Estimand 1.

8.1.6. Supportive Analyses

A supportive analysis of the primary endpoint (Estimand 2) will be conducted in the ITT set in which the percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period will be summarized prior to treatment discontinuation and irrespective of rescue antacid, H2RA, and PPI use.

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

A diary day will be included in the denominator for the calculation of the percentage of days without daytime or nighttime heartburn if at least one diary entry (either morning only, evening only, or both) was completed. Diary days will not be included in the denominator if the subject missed both the morning and evening entries for that day. For example, if the subject has at least one entry for 24 out of 28 days and has missed both the morning and evening diary entries for 4 days, then 24 days will be used as the denominator. Subjects with no available diary entries in the Placebo-controlled Treatment Period will not be included in the analysis.

All entries on a day need to be heartburn-free for the day to be counted as a day with neither daytime nor nighttime heartburn. This will also apply if more than two diary entries are assigned to the same study day. If a subject has only one diary entry on a day and that entry does not indicate heartburn, the day will be considered heartburn-free for the analysis.

8.2. Secondary Efficacy Endpoint

For the secondary endpoint, the percentage of days without rescue antacid use over the Placebo-controlled Treatment Period as assessed by the daily diary, each vonoprazan treatment group will be compared to the placebo treatment group using a general linear model like that used for the primary endpoint. See Section 12.5 for the summary of estimand and associated statistical methods.

The percentage of days without rescue antacid use will be obtained using all days with at least one diary entry (either morning only, evening only, or both) during the respective periods (Placebo-controlled Treatment, Extension, and Follow-up). That is, the study days in which the subject missed both the morning and evening entries will not be counted towards the denominator. For example, if the subject has at least one entry for 24 out of 28 days and has missed the morning and evening diary entries for 4 days, then 24 days will be used as the denominator. In addition, a given day will be counted towards the numerator (days without rescue antacid use) if all entries for that study day indicate that rescue antacid was not used. This will also be applicable on days with more than two diary

entries. Also, if a day only has one diary entry and the entry indicates that rescue antacid was not used, this day will be considered as a day without rescue antacid use.

8.3. Exploratory Endpoints

For all exploratory endpoints in which comparison between each vonoprazan treatment group and placebo is of interest, testing will be performed with no multiplicity adjustment to the alpha level. Each exploratory endpoint will be tested independently at an alpha level of 0.05. All exploratory endpoints will be analyzed using the ITT Set.

8.3.1. Placebo-controlled Treatment Period

The following exploratory endpoints will be compared between each vonoprazan treatment group and placebo using a general linear model like that used for the primary endpoint using the ITT Set except that the nighttime heartburn severity and frequency at baseline will be used as covariates for the percentage of days without nighttime heartburn over the Placebo-controlled Treatment Period and daytime heartburn severity and frequency at baseline will be used as covariates for the percentage of days without daytime heartburn over the Placebo-controlled Treatment Period endpoints respectively.

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

For the above exploratory endpoints, the percentage of days without nighttime heartburn or without daytime heartburn will be summarized two ways, following the data handling and analysis methods for both Estimand 1 and Estimand 2 for the primary endpoint.

The following exploratory endpoints will be compared between each vonoprazan treatment group and placebo using a general linear model like that used for the primary endpoint using the ITT Set.

- The percentage of days without daytime or nighttime heartburn over the last 7 days of the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of daytime and nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of daytime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The mean severity of nighttime heartburn over the Placebo-controlled Treatment Period as assessed by the daily diary
- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the PAGI-SYM questionnaire
- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the PAGI-QoL questionnaire
- The change from baseline to the end of the Placebo-controlled Treatment Period for the EQ-5D-5L

- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the N-GSSIQ
- The change from baseline to the end of the Placebo-controlled Treatment Period for each subscale and the total score of the PSQI

Cumulative incidences of the time to sustained resolution of heartburn during the Placebo-controlled Treatment Period will be estimated using Kaplan-Meier method. For each comparison of vonoprazan treatment groups with placebo, the 95% CI will be presented, along with the p-value from the log-rank test. For details on endpoint derivation and censoring, see Section 12.3.3. Details of obtaining subscale and total scores for PAGI-SYM, PAGI-QoL, EQ-5D-5L, N-GSSIQ, and PSQI are provided in Section 12.4.

8.3.2. Extension Period

The following exploratory endpoints will be summarized by treatment group. The extension period baseline is defined as the last visit during the Placebo-controlled Treatment Period prior to the first dose of study drug in the Extension Period. The first four endpoints related to the percentage of days without heartburn will be summarized two ways, following the data handling methods for both Estimand 1 and Estimand 2; however, for subjects who prematurely discontinue treatment during the Extension Period, there will be no imputation of the percentage of days without daytime or nighttime heartburn after discontinuation.

- The percentage of days without daytime or nighttime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without nighttime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without daytime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without daytime or nighttime heartburn from Week 4 to Week 8 in subjects re-randomized at Week 4 from placebo to either vonoprazan 10 mg or 20 mg
- The mean severity of daytime and nighttime heartburn over the Extension Period as assessed by the daily diary
- The mean severity of daytime heartburn over the Extension Period as assessed by the daily diary
- The mean severity of nighttime heartburn over the Extension Period as assessed by the daily diary
- The percentage of days without rescue antacid use over the Extension Period as assessed by the daily diary
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the PAGI-SYM questionnaire
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the PAGI-QoL questionnaire

- The change from baseline to Week 12 and Week 24 of the Extension Period for the EQ-5D-5L
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the N-GSSIQ
- The change from baseline to Week 12 and Week 24 of the Extension Period for each subscale and the total score of the PSQI

For subjects who received vonoprazan throughout the study, the following exploratory endpoints will be summarized by treatment group across the Placebo-controlled Treatment and Extension Period of the study. The first three endpoints related to the percentage of days without heartburn will be summarized two ways, following the data handling methods for both Estimand 1 and Estimand 2; however, for subjects who prematurely discontinue treatment during the Extension Period, there will be no imputation of the percentage of days without daytime or nighttime heartburn after discontinuation.

- The percentage of days without daytime or nighttime heartburn over both Treatment Periods as assessed by the daily diary
- The percentage of days without nighttime heartburn over both Treatment Periods as assessed by the daily diary
- The percentage of days without daytime heartburn over both Treatment Periods as assessed by the daily diary
- The mean severity of daytime and nighttime heartburn over both Treatment Periods as assessed by the daily diary
- The mean severity of daytime heartburn over both Treatment Periods as assessed by the daily diary
- The mean severity of nighttime heartburn over both Treatment Periods as assessed by the daily diary
- The percentage of days without rescue antacid use over both Treatment Periods as assessed by the daily diary

In addition, the percentage of subjects without daytime or nighttime heartburn by study day across the Placebo-controlled Treatment and Extension Period will be presented by treatment group in a figure.

8.3.3. Follow-up Period

The following exploratory endpoints will be summarized by treatment group. The first endpoint of the percentage of days without daytime or nighttime heartburn will be summarized following the data handling methods for both Estimand 1 and Estimand 2.:

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

9. SAFETY ANALYSIS

Safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I/II levels, ECGs and vital signs. For all safety analyses, baseline for the Placebo-controlled Treatment Period will be the last available assessment prior to the first dose of study drug. Baseline for the Extension period will be the last available assessment on the last visit during the Placebo-controlled Treatment Period prior to the first dose of study drug in the Extension Period.

All safety analyses will be conducted for each treatment group and overall using the Safety Set.

9.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0.

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

For subjects who did not enter the Extension Period, any AE that starts after more than 30 days of the last dose of study drug in the Placebo-controlled Treatment Period will not be counted as TEAE in the Placebo-controlled Treatment Period. For subjects who did enter the Extension Period, any AE that starts after more than 30 days of the last dose of study drug in the Extension Period will not be counted as TEAE in the Extension Period.

A subject with multiple adverse events within a primary SOC or preferred term is only counted once towards the total for that SOC and/or preferred term. For the AE severity and relationship summaries, if a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity or relationship will be presented. If a subject reported more than one adverse event within the same primary system organ class, then the subject will be counted only once with the greatest severity or relationship at the system organ class level. For table summaries, if severity is missing then ‘severe’ is assumed. If relationship is missing, relationship to study drug is assumed to be ‘related’.

The following AE summaries will be presented separately, using the Safety Set, for the Placebo-controlled Treatment Period and Extension Period using the treatment groups indicated in Section 4. Summaries will also be presented for subjects who received vonoprazan throughout the study across both treatment periods.

- An overall summary of the number of events and the number of subjects with TEAEs in each treatment group will be presented, including TEAEs, serious TEAEs, study drug related TEAEs, study drug related serious TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death.
- The number and percentage of subjects with TEAEs will be summarized in the following ways:

  - by primary system organ class, preferred term, and treatment group
  - by primary system organ class, preferred term, maximum severity, and treatment group
  - by primary system organ class, preferred term, relationship to study drug, and treatment group
- The number and percentage of subjects with TEAEs related to study drug will be summarized in the following ways:
  - by primary system organ class, preferred term, and treatment group
  - by primary system organ class, preferred term, maximum severity, and treatment group
- The most common TEAEs (≥5% of subjects in any treatment group) and TEAEs related to study drug (≥2% of subjects in any treatment group) will be presented by preferred term in descending frequency starting from the most common event. The criteria for most common TEAEs may be adjusted as appropriate based on the number of TEAEs reported.
- The most common non-serious AEs (>5% of subjects in any treatment group) will be presented by primary system organ class, preferred term and treatment group.
- The number and proportion of subjects as well as the number of events (except for deaths) with the following types of events will be summarized by primary system organ class, preferred term and treatment group:
  - Adverse events leading to treatment discontinuation
  - Serious Adverse Events (SAEs)
  - Deaths
  - Adverse events of special interest (AESI)
  - Adverse Events leading to study discontinuation

All adverse events data will be listed using the Safety Set for the Placebo-controlled Treatment Period and for the Extension Period. All adverse events over the Follow-up Period will also be listed using the Safety Set.

For each period, separate listings will also be provided for the following using the Safety Set:

- Deaths
- SAEs (including serious pretreatment events)
- Adverse events leading to treatment discontinuation
- Adverse events of special interest
- Adverse Events leading to study discontinuation

9.1.1. Adverse Events of Special Interest (AESI)

The number and percentage of subjects with TEAEs and SAEs that are in one of the AESI categories presented in Table 7 will be summarized by AESI category, primary system

organ class and preferred term for each treatment group and overall. The search criteria that will be used to identify AESIs are specified in the table.

Table 7. Adverse Events of Special Interest – Search Criteria

Adverse Event of Special Interest	Search Criteria
Hepatotoxicity	• Drug related hepatic disorders - comprehensive search (SMQ) (Narrow) • Cholestasis and jaundice of hepatic origin (SMQ) (Broad) • Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (Broad) • Hepatitis, non-infectious (SMQ) (Broad) • Liver related investigations, signs and symptoms (SMQ) (Narrow)
Severe cutaneous adverse reactions	• Severe cutaneous adverse reactions SMQ (Narrow)
Clostridium difficile infections	• Pseudomembranous colitis SMQ (Narrow)
Gastric Cancer	Gastric Neoplasms Malignant MedDRA High Level Term
Bone fracture	Bone Fracture Custom Query (PTs defined below) Acetabulum fracture Ankle fracture Atypical femur fracture Atypical fracture Avulsion fracture Bone fissure Bone fragmentation Chance fracture Clavicle fracture Comminuted fracture Complicated fracture Compression fracture Craniofacial fracture Epiphyseal fracture Facial bones fracture Femoral neck fracture Femur fracture Fibula fracture Foot fracture Forearm fracture Fracture Fracture blisters Fracture displacement Fracture malunion Fracture nonunion Fracture of clavicle due to birth trauma Fractured coccyx Fractured ischium Fractured sacrum Fractured skull depressed Greenstick fracture Hand fracture Hip fracture Humerus fracture Ilium fracture Impacted fracture Jaw fracture Limb fracture Lower limb fracture Lumbar vertebral fracture Metaphyseal corner fracture Multiple fractures Open fracture Osteoporotic fracture Patella fracture Pathological fracture Pelvic fracture Pubis fracture Radius fracture Rib fracture Sacroiliac fracture Scapula fracture Skull fracture Skull fractured base Spinal compression fracture Spinal fracture Spinal fusion fracture Sternal fracture Stress fracture Subchondral insufficiency fracture Thoracic vertebral fracture Tibia fracture Torus fracture Traumatic fracture Ulna fracture Upper limb fracture Wrist fracture

MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SMQ: Standardized MedDRA Queries.

9.2. Clinical Laboratory Evaluations

Descriptive statistics for clinical laboratory values (hematology, chemistry and urinalysis laboratory tests; in SI units and in US conventional units) and serum gastrin and pepsinogen I, pepsinogen II, and pepsinogen I/II ratio will be presented by treatment group

and overall for each period. Changes from baseline will also be presented for quantitative variables by treatment group and overall for each period. For categorical variables (ie, normal or abnormal findings, or qualitative clinical laboratory tests), shift tables for the change from baseline to each post-baseline time point will be presented by treatment group and overall for each treatment period.

For each period, the number and percentage of subjects with at least one post-baseline serum gastrin value >500 ng/L and >1000 ng/L and with the test value higher than the baseline value, if available, will be presented. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

Abnormal liver function tests are defined as liver test values that meet at least one of the criteria listed below. For each period, the number and percentage of subjects with at least one post-baseline abnormal liver function test and with the test value higher than baseline, if available, will be presented by treatment group and overall. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

- ALT > 3xULN
- ALT > 5xULN
- ALT > 10xULN
- ALT > 3xULN and Total Bilirubin > 2xULN
- AST > 3xULN
- AST > 5xULN
- AST > 10xULN
- AST > 3xULN and Total Bilirubin > 2xULN
- Total Bilirubin > 2xULN
- AST > 3xULN or ALT > 3xULN
- AST > 5xULN or ALT > 5xULN
- AST > 10xULN or ALT > 10xULN
- (AST > 3xULN or ALT > 3xULN) and Total Bilirubin > 2xULN
- AST > 3xULN and ALT > 3xULN
- AST > 5xULN and ALT > 5xULN
- AST > 10xULN and ALT > 10xULN
- AST > 3xULN and ALT > 3xULN and Total Bilirubin > 2xULN
- Alkaline phosphatase > 1.5xULN
- ALT > 3xULN and Alkaline phosphatase > 1.5xULN
- AST > 3xULN and Alkaline phosphatase > 1.5xULN
- Alkaline phosphatase > 3xULN
- ALT > 3xULN and Alkaline phosphatase > 3xULN
- AST > 3xULN and Alkaline phosphatase > 3xULN

All other laboratory parameters that correspond to FSH, serum HCG pregnancy test, serology (HIV antibody, HBsAg, and HCV antibody, hepatitis C viral load RNA [qualitative]), and urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone, and phencyclidine will be listed for the Safety Set.

9.3. Vital Sign Measurements

For each period, descriptive statistics for vital signs, including body temperature, systolic blood pressure, diastolic blood pressure and pulse rate, will be presented by treatment group and overall. Changes from baseline will also be presented by treatment group and overall.

Abnormal vital sign values are defined as vital sign values that meet one of the criteria listed below. For each period, the number and percentage of subjects with at least one post-baseline abnormal vital sign value and with the value worse than the baseline value, if available, will be presented by treatment group and overall. A supportive listing of subjects with such abnormal values will be provided including the subject ID, baseline, and post-baseline values.

- Systolic blood pressure (mmHg):
  - <50
  - >180
- Diastolic blood pressure (mmHg):
  - <50
  - >100
- Heart rate (bpm):
  - <50
  - >120

9.4. Physical Examination

All data collected from the physical examinations assessments must be available in the source documents but will not be added to the analysis database.

9.5. Electrocardiogram

Descriptive statistics for ECG parameters, including heart rate, RR interval, PR interval, QT interval, QTc Fridericia (QTcF), and QRS interval, will be presented by treatment group and overall for each period. All ECG assessment values and interpretations will be listed for all subjects in the Safety Set. Changes from baseline will also be presented for quantitative variables by treatment group and overall for each period.

For ECG interpretations (within normal limits, abnormal but not clinically significant, or abnormal and clinically significant), shift tables for the change from baseline to each post-baseline time point will be presented by treatment group and overall.

Abnormal QTcF values are defined as ECG values that meet at least one of the criteria listed below. The number and percentage of subjects with at least one of the post-baseline abnormal values and with post-baseline value higher than baseline value, if available, will be presented by treatment group and overall for each period. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

- Absolute QTcF interval prolongation:
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500
- Change from baseline in QTcF interval:
  - QTc interval increases from baseline >30
  - QTc interval increases from baseline >60
  - QTc interval > 450 with increase from baseline >30

10. INTERIM ANALYSIS/OTHER ANALYSES

10.1. Interim Analysis

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

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

10.2. Coronavirus Pandemic

In accordance with guidance issued by regulatory agencies, study data collection will document missed/delayed visits due to COVID-19-related reasons and assessments completed via alternative method due to COVID-19-related reasons.

The COVID-19 impact on individual subjects collected on the COVID-19 eCRF pages will be listed for the Randomized Set. Protocol deviations related to COVID-19 will be marked in the protocol deviation listing for the Randomized Set. COVID-19 infection history and vaccine information will also be listed for the Randomized Set.

The anticipated impact of COVID-19 is widely regarded as unknown. If the impact of COVID-19 on the conduct of this study is observed to be significant, further summaries and listings of the impact will be explored.

11. REFERENCES

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2. Spiegel BM, Roberts L, Mody R, Harding G, Kothari-Talwar S, Kahrilas PJ, Camilleri ML, Dabbous O, Revicki DA. The development and validation of a Nocturnal Gastro-oesophageal Reflux Disease Symptom Severity and Impact Questionnaire for adults. Alimentary Pharmacology and Therapeutics, 2010; 32(4): 591-602.

12. APPENDICIES

12.1. Schedule of Events

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Study Subject Informational Questionnaire	X	X										
Demographic and medical history	X											
Smoking status and alcohol use	X											
Medication history	X											
Physical examination [d]	X	X			X		X			X	X	X
Vital signs	X	X			X		X			X	X	X
Height	X											
Weight	X									X		
Concomitant medications	X	X		X	X	X	X	X	X	X	X	X
Concurrent medical conditions	X											
FSH [e]	X											
Hepatitis B and C; HIV	X											

	Screening Period [a]	Placebo-controlled Treatment Period				Extension Period					Follow-up Visit	Unscheduled Visit [b]
Timing	**Up To 5 Weeks**	**Day-1 [c]**	**Day 1 [c]**	**Week 2 Phone Day 15**	**Week 4 Day 28**	**Week 8 Phone Day 56**	**Week 12 Day 85**	**Week 16 Phone Day 113**	**Week 20 Phone Day 141**	**Week 24 Day 169 Final Visit/ET**	**Week 28 Day 197**	
Visit windows (days)	**Day -35 to -2**			**12 to 18**	**25 to 31**	**53 to 59**	**82 to 92**	**110 to 120**	**138 to 148**	**166 to 176**	**194 to 200**	
Visit number:	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Telephone call to subject				**X**		**X**		**X**	**X**			
Test for active H *pylori* infection[f]	X											
Urine drug screen	X											
Clinical laboratory test including hematology, serum chemistry, and urinalysis [g]	X				X		X			X	X	X
Fasting serum gastrin and pepsinogen I and II levels [h]		X			X		X			X	X	
Pregnancy test (serum hCG) [i]	X											
Pregnancy test (urine hCG) [i]		X			X		X			X	X	
Guidance on avoidance of pregnancy	X	X		X	X	X	X	X	X	X	X	
Electrocardiogram	X				X					X		
Distribute subject diary [j]	X											
Review subject diary		X		X	X	X	X	X	X	X	X	
PAGI-SYM		X			X		X			X		
PAGI-QoL		X			X		X			X		
EQ-5D-5L		X			X		X			X		
PSQI		X			X		X			X		
N-GSSIQ		X			X		X			X		
Endoscopy	X [k]											

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

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

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

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

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

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

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

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

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

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

i Only female subjects with childbearing potential.

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

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

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

12.2. Imputation Rules for Missing Date Information

12.2.1. Rules for Concomitant Medication Start Date Imputation

The following rules will be applied to impute the missing (numerical) start dates. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

If the start date is completely missing or the year of the start date is missing, then the start date will be imputed as the date of the first dose of study drug.

Missing day and month

- If the year of the partial start date is the same year as the date of the first dose of study drug, then the day and month of the date of the first dose of study drug will be used to impute the missing day and month.
- If the year of the partial start date is before the year of the date of the first dose of study drug, then the missing month and day will be imputed as December 31.
- If the year of the partial start date is after the year of the date of the first dose of study drug, then the missing month and day will be imputed as January 01.

Missing month only

If only the month of the partial date is provided, then the day will also be treated as missing, and the rules above will be applied.

Missing day only

- If the month and year of the partial date are the same as the month and year of the date of the first dose of study drug, then the day of the date of the first dose of study drug will be used to impute the missing day.
- If the year of the partial date is same as the year of the date of the first dose of study drug but the month of the partial date is before the month of the date of the first dose of study drug or if the year of the partial date is before the year of the date of the first dose of study drug, then the missing day will be imputed as the last day of the month.
- If the year of the partial date is same as the year of the date of the first dose of study drug but the month of the partial date is after the month of the date of the first dose of study drug or if the year of the partial date is after the year of the date of the first dose of study drug, then the missing day will be imputed as the first day of the month.

12.2.2. Rules for Concomitant Medication End Date Imputation

The following rules will be applied to impute the missing (numerical) end dates. If the date of the last dose of study drug is missing, then the last visit date will be used instead. If the

imputed stop date is before the start date (either imputed or non-imputed), then the stop date will be set to be the same as the start date.

Missing day and month

- If the year of the partial stop date is the same year as the date of the last dose of study drug, then the day and month of the date of the last dose of study drug will be used to impute the missing day and month.
- If the year of the partial stop date is before the year of the date of the last dose of study drug, then the missing month and day will be imputed as December 31.
- If the year of the partial start date is after the year of the date of the last dose of study drug, then the missing month and day will be imputed as January 01.

Missing month only

If only the month of the partial date is provided, then the day will also be treated as missing, and the rules above will be applied.

Missing day only

- If the month and year of the partial date are the same as the month and year of the date of the last dose of study drug, then the day of the date of the last dose of study drug will be used to impute the missing day.
- If the year of the partial date is the same as the year of the date of the last dose of study drug but the month of the partial date is before the month of the date of the last dose of study drug or if the year of the partial date is before the year of the date of the last dose of study drug, then the missing day will be imputed as the last day of the month.
- If the year of the partial date is the same as the year of the date of the last dose of study drug but the month of the partial date is after the month of the date of the last dose of study drug or if the year of the partial date is after the year of the date of the last dose of study drug, then the missing day will be imputed as the first day of the month.

12.2.3. Rules for AE Start Date Imputation

For AEs, incomplete (ie., partially missing) start dates will be imputed in the same manner as described in Section 12.2.1. Partial stop dates will not be imputed.

12.3. Morning and Evening Diary

12.3.1. Diary Data Handling

Subjects will document the presence (yes/no) and maximum severity (1=Mild, 2=Moderate, 3=Severe, or 4=Very Severe; definitions provided in table below) of daytime and nighttime heartburn symptoms and use of rescue antacid (yes/no) twice daily in their diary.

Table 8. Definitions of Heartburn Severity (Daytime/Nighttime)

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

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

The electronic diary is completed every morning upon waking to record the previous evening's maximum heartburn severity rating, and every evening before bedtime to record that day's maximum heartburn severity rating. Thus, for analysis purposes, the diary entries will be assigned to a study day based on the start of the collection interval in which the collection interval consists of an evening entry for the daytime and a morning entry for the nighttime. For example, the diary entries for Day 1 would include the evening diary completed on Day 1 and the morning diary completed on Day 2, the diary entries for Day 2 would include the evening diary completed on Day 2 and the morning diary completed on Day 3, and so on. If the presence of heartburn is answered as “no” in a diary, the question of maximum severity will not be answered, and the maximum severity will be considered as 0 (0=None) in the analysis. Only evening diaries will be used for assessing daytime heartburn, and only morning diaries will be used for assessing nighttime heartburn.

12.3.2. Derivation of Severity of Heartburn Exploratory Endpoints

For each period, the mean severity of daytime and nighttime heartburn will be obtained by taking the mean of the daily average maximum severity across all days that have at least one morning or evening diary entry. The daily average maximum severity will be obtained by first identifying separately the highest recorded severity across morning entries and across evening entries within the day, then taking the average of the morning maximum severity and evening maximum severity.

For each period, the mean severity of daytime heartburn will be obtained by first identifying the highest recorded severity across evening diary entries within a day for all the days within a period. Then the average of the severity across all days with at least one evening diary entry within a period will be obtained. Similarly, the mean severity of nighttime heartburn will be obtained by first identifying the highest recorded severity across morning diary entries within a day for all the days within a period. Then the average of the severity across all days with at least one morning diary entry within a period will be obtained.

12.3.3. Sustained Resolution of Heartburn

Sustained resolution of heartburn will be defined as at least seven consecutive days with no daytime or nighttime heartburn during a particular period. The seven consecutive days should have at least one diary entry (either morning only, evening only, or both). Thus, seven consecutive days of missing diary data will not count as sustained resolution of heartburn.

The time to sustained resolution of heartburn is defined as the time to the first occurrence of sustained resolution, specifically the time from the first dose of study drug to the first day of the first onset of seven consecutive days with no daytime or nighttime heartburn within a period. Subjects who do not achieve sustained resolution of heartburn will be censored on the first day of the last sequence of seven days during the period. To illustrate, for a subject who does not have sustained resolution of heartburn and has the last diary entry on Day 28, the last sequence of seven days would be Day 22 to Day 28 and thus, the censoring time would be Day 22. Subjects who prematurely discontinue the study before they have completed at least 7 days of the diary will be censored at Day 1.

12.4. Questionnaire Scoring

12.4.1. PAGI-SYM Questionnaire

The PAGI-SYM questionnaire includes questions that ask about the severity of symptoms the subject may have related to his/her gastrointestinal problem. The questionnaire consists of 20 items, each with response options based on a 6-point Likert scale (0=None, 1=Very Mild, 2=Mild, 3=Moderate, 4=Severe, 5=Very Severe) and with a recall period of the previous 2 weeks. The items are grouped into 6 subscales and a total score, which are described below.

PAGI-SYM Subscale	Items on PAGI-SYM eCRF
Nausea/Vomiting	Question 1: Nausea Question 2: Retching Question 3: Vomiting
Fullness/Early Satiety	Question 4: Stomach fullness Question 5: Not able to finish a normal-sized meal Question 6: Feeling excessively full after meal Question 7: Loss of appetite
Bloating	Question 8: Bloating Question 9: Stomach or belly visibly larger
Upper Abdominal Pain	Question 10: Upper abdominal pain Question 11: Upper abdominal discomfort
Lower Abdominal Pain	Question 12: Lower abdominal pain Question 13: Lower abdominal discomfort
Heartburn/Regurgitation	Question 14: Heartburn during the day Question 15: Heartburn when lying down Question 16: Feeling of discomfort inside chest during the day Question 17: Feeling of discomfort inside chest at night Question 18: Regurgitation or reflux during the day Question 19: Regurgitation or reflux during when lying down Question 20: Bitter, acid or sour taste in mouth
PAGI-SYM Total Score	Mean of PAGI-SYM Subscale Scores

The subscale scores are obtained by taking the average of the responses on the corresponding non-missing items for each subscale. If there are missing responses for items within a subscale, the half-scale rule will be implemented, that is, the subscale score will only be calculated if the rate of missing items is at most 50%. Otherwise, the subscale score will be set to missing. The PAGI-SYM total score is calculated by taking the mean of the subscale scores. If at least one subscale score is missing, the total score will be set to missing. Higher scores indicate worse symptoms. Thus, a negative change from baseline for a score indicates improvement.

12.4.2. PAGI-QoL Questionnaire

The PAGI-QoL questionnaire includes questions that ask about how some of the gastrointestinal problems the subject may have experienced may have affected his/her quality of life. The questionnaire consists of 30 items, each with response options based on a 6-point Likert scale (0=None of the time, 1=A little of the time, 2=Some of the time, 3=A good bit of the time, 4=Most of the time, 5=All of the time) and with a recall period of the previous 2 weeks. The items are grouped into 5 subscales and a total score which are described below.

PAGI-QoL Subscale	Items on PAGI-QoL eCRF
Daily Activities	Question 1: depending on others to do daily activities Question 2: avoided performing daily activities Question 3: difficulty concentrating Question 4: longer than usual to perform daily activities Question 5: felt tired Question 6: lost desire to participate in social activities Question 7: worried about having stomach symptoms in public Question 8: avoided performing physical activities or sports Question 9: avoided traveling Question 10: felt frustrated about not being able to do what one wanted to do
Clothing	Question 11: felt constricted in the clothes one is wearing Question 12: felt frustrated about not being able to dress as wanted to
Diet and Food Habits	Question 13: felt concerned about what can and cannot eat Question 14: avoided certain types of foods Question 15: restricted eating at restaurant or at someone's home Question 16: felt less enjoyment in food than usual Question 17: felt concerned that change of food habits could trigger symptoms Question 18: felt frustrated about not being able to choose the wanted food Question 19: felt frustrated about not being able to choose wanted type of beverage
Relationship	Question 20: relationship with spouse or partner been disturbed Question 21: relationship with children or relatives been disturbed Question 22: relationship with friends been disturbed
Psychological Well-being and Distress	Question 23: been in bad mood Question 24: felt depressed Question 25: felt anxious Question 26: felt angry Question 27: felt irritable Question 28: felt discouraged Question 29: been stressed Question 30: felt helpless
PAGI-QoL Total Score	Mean of PAGI-QoL Subscale Scores

The subscale scores are obtained by taking the average of the responses on the corresponding non-missing items for each subscale after reversing the item scores. If there are missing responses for items within a subscale, the half-scale rule will be implemented, that is, the subscale score will only be calculated if the rate of missing items is at most 50%. Otherwise, the subscale score will be set to missing. The PAGI-QoL total score is calculated by taking the mean of the subscale scores. If at least one subscale score is missing, the total score will be set to missing. A positive change from baseline score indicates improved quality of life.

12.4.3. EQ-5D-5L Questionnaire

The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life. The EQ-5D-5L consists of a descriptive system and a visual analogue scale. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The visual analogue scale records the subject's self-rated health on a vertical scale (0 to 100).

The EQ-5D-5L will be converted into a single index value. The summary index can be derived from the EQ-5D-5L descriptive system and using the crosswalk link function of the US value sets. Documents containing information on the crosswalk project, tables for values for all 3125 health states and the EQ-5D-5L Crosswalk Index Value Calculator can be downloaded from the EuroQol website. The EQ-5D-5L index score is on a scale from 0 (worst imaginable health state) to 1 (best imaginable health state).

12.4.4. PSQI Questionnaire

The PSQI[1] is a self-reported questionnaire which assesses sleep quality and disturbances over a 1-month recall period. The PSQI has 19 self-rated items organized into 7 subscales, each of which has a range of 0 to 3 points. The subscale measures consist of subjective sleep quality, sleep latency (how long it takes to fall asleep), sleep duration, habitual sleep efficiency (the percentage of time in bed that one is asleep), sleep disturbances, use of sleeping medication, and daytime dysfunction. The 7 subscale scores are then added to produce a global score. Overall scores range from 0 to 21 with a lower score indicating better sleep quality. The subscales and global scores are described below:

PSQI Subscale	Items on PSQI eCRF	Rule	Subscale score
Sleep quality	Question 6: sleep quality overall	Assign score as: "very good" = 0 "fairly good" = 1 "fairly bad" = 2 "very bad" = 3	Score of Question 6
Sleep latency	Question 2: how long (in minutes) usually taken to fall asleep each night	Assign score as: ≤15 minutes = 0 16-30 minutes = 1 31-60 minutes = 2 >60 minutes =3	Assign subscale score based on sum of Questions 2 and 5a as: Sum is 0 = 0 Sum is 1-2 = 1 Sum is 3-4 = 2 Sum is 5-6 = 3
	Question 5a: cannot get to sleep within 30 minutes	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three of more times a week" = 3	
Sleep duration	Question 4: hours of actual sleep get at night	Assign score as follows: ≥7 hours = 0 ≥6-<7 hours = 1 ≥5-<6 hours = 2 <5 hours = 3	Score of Question 4
Habitual sleep efficiency	Question 4: hours of actual sleep get at night Question 3: time usually gotten up in the morning Question 1: time usually gone to bed at night	- Calculate "number of hours spent in bed" from Question 3 and Question 1 - Calculate "habitual sleep efficiency (%)" = (no. of hours slept / no. of hours spent in bed) × 100	Assign subscale score based on "habitual sleep efficiency (%)" as: >85% = 0 75-84% = 1 65-74% = 2 <65% = 3
Sleep disturbances	Question 5b: wake up in the middle of night or early morning	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	Assign subscale score based on sum of Questions 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j as: Sum is 0 = 0 Sum is 1-9 = 1 Sum is 10-18 = 2 Sum is 19-27 = 3
	Question 5c: have to get up to use the bathroom	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	
	Question 5d: cannot breathe comfortably	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	
	Question 5e: cough or snore loudly	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	

	Question 5f: feel too cold	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	
	Question 5g: feel too hot	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	
	Question 5h: had bad dreams	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	
	Question 5i: have pain	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	
	Question 5j: other reason(s)	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3 If comment is null or Question 5j is null, assign a score of 0	
Use of sleeping medication	Question 7: how often have taken medicine to help sleep	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	Score of Question 7
Daytime dysfunction	Question 8: how often have trouble staying awake while driving, eating meals, or engaging in social activity	Assign score as: "not during the past month" = 0 "less than once a week" = 1 "once or twice a week" = 2 "three or more times a week" = 3	Assign subscale score based on sum of Questions 8 and 9 as: Sum is 0 = 0 Sum is 1-2 = 1 Sum is 3-4 = 2 Sum is 5-6 = 3
	Question 9: how much problems has it been to keep enough enthusiasm to get things done	Assign score as: "no problem at all" = 0 "only a very slight problem" = 1 "somewhat of a problem" = 2 "a very big problem" = 3	
PSQI Total Score		Sum of PSQI Subscale Scores	

If response is missing to any of the questions 1 through 9 (except for 5j), then the corresponding subscale score that is calculated using the missing response will be set to missing. Moreover, the PSQI total score will also be set to missing.

12.4.5. N-GSSIQ Questionnaire

The N-GSSIQ[2] is a validated instrument to assess the severity and impact of nocturnal GERD symptoms over the past 2 weeks. The questionnaire is comprised of 20 items covering 3 subscales: Nocturnal GERD Symptom Severity (13 items; score range of 0 to 65), Morning Impact of Nocturnal GERD (2 items; score range of 0 to 10), and Concern about Nocturnal GERD (5 items; score range of 0 to 20). The subscale scores are calculated as the sum of the corresponding items for the subscale. If there are missing responses for items within a subscale, the half-scale rule will be implemented, that is, the subscale score will only be calculated if the rate of missing items is at most 50% in which the missing item's score will be set to the average of the non-missing item scores. The total N-GSSIQ score is calculated as the mean of the subscale scores for the Nocturnal GERD Symptom Severity and Morning Impact of Nocturnal GERD only with higher scores representing greater severity of symptoms, greater symptom impact, and greater concern. If either the subscale score for the Nocturnal GERD Symptom Severity or subscale score for Morning Impact of Nocturnal GERD is missing, the total N-GSSIQ score will be set to missing. Details of the subscale and total score are provided below:

N-GSSIQ Subscale	Items on N-GSSIQ eCRF
Nocturnal GERD Symptom Severity	Question 1: Heartburn after going to bed at night Question 2: Regurgitation or reflux after going to bed at night Question 3: Nausea after going to bed at night Question 4: Burping or belching after going to bed at night Question 5: Feeling of discomfort inside chest after going to bed at night Question 6: Difficulty swallowing back liquid after going to bed at night Question 7: Bubbling or gurgling in the throat after going to bed at night Question 8: Gagging or choking feeling in the throat after going to bed at night Question 9: Waking up with food or liquid in the mouth during the night Question 10: Pain or burning in the stomach, chest or throat upon awakening in the morning Question 11: Trouble falling asleep because of your heartburn/reflux Question 12: Wake up at night because of heartburn/reflux Question 13: Go to bed later than would have liked because of heartburn/reflux
Morning Impact of Nocturnal GERD	Question 14: Wake up in the morning feeling tired Question 15: Wake up in the morning feeling irritable
Concern about Nocturnal GERD	Question 16: Something serious may be wrong because of heartburn/reflux after going to bed at night Question 17: Heartburn/reflux after going to bed at night may result in serious damage to the throat or stomach Question 18: Heartburn/reflux could get worse at night Question 19: Must carefully watch what to eat before bedtime because of heartburn/reflux Question 20: Heartburn/reflux after going to bed at night impacts everyday life
N-GSSIQ Total Score	Mean of Nocturnal GERD Symptom Severity and Morning Impact of Nocturnal GERD Subscale Scores

12.5. Estimands and Sensitivity/Supplementary Analysis

Table 9. Summary of Statistical Methods and Sensitivity Analyses

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/Censoring Rules**	**Analysis Model/Method**	**Sensitivity/Supplementary Analysis**
Estimand 1 (Primary)	Difference in the *mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period* between each dose of vonoprazan and placebo (10mg QD – placebo and 20mg QD - placebo) in subjects with NERD, where a heartburn-free day is a day for which all entries are heartburn-free with no use of rescue antacid, H2RAs, and PPIs and assuming the percentage of heartburn-free days after treatment discontinuation is the percentage of heartburn-free days during the screening period, irrespective of rescue antacid, H2RAs, and PPIs used after treatment discontinuation.	ITT [1]	See Section 8.1.2.	The point estimate and 2-sided 95% CI of the difference in mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period between each dose of vonoprazan and placebo (10 mg QD – placebo and 20 mg QD - placebo) will be obtained through a linear contrast of the least square (LS) means comparing the mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period for each vonoprazan dose with placebo using the general linear model with treatment group as factor, and severity and frequency of heartburn at baseline as covariates.	1. Nonparametric test (i.e., Wilcoxon rank-sum test) 2. Same as the primary analysis but the percentage of days without daytime or nighttime heartburn *irrespective of use of rescue antacid, H2RAs, or PPIs* over the Placebo-controlled Treatment Period will be calculated. 3. Imputation of missing data due to any reason. The days after treatment discontinuation will be imputed as having heartburn on those days. Also, days with missing diary entries prior to treatment discontinuation (either no entries on the day, or with only one diary entry on the day) will be imputed as having heartburn on those days.

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/Censoring Rules**	**Analysis Model/Method**	**Sensitivity/Supplementary Analysis**
Estimand 2 (Primary Supportive)	Difference in the *mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period* as assessed by the daily diary between each dose of vonoprazan and placebo (10mg QD – placebo and 20mg QD - placebo) in subjects with NERD whose response to treatment is of interest only while on study drug, i.e., prior to study drug discontinuation due to any reason and irrespective of excluded/rescue medications and treatments.	ITT [1]	See Section 8.1.6.	The point estimate and 2-sided 95% CI of the difference in mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period between each dose of vonoprazan and placebo (10mg QD – placebo and 20mg QD - placebo) will be obtained through a linear contrast of the least square (LS) means comparing the mean percentage of days without daytime or nighttime heartburn over the Placebo-controlled Treatment Period for each vonoprazan dose with placebo using the general linear model with treatment group as factor, and severity and frequency of heartburn at baseline as covariates.	

		Main Estimation			
Estimand Label	**Estimand Description**	**Analysis Set**	**Imputation/Data/ Censoring Rules**	**Analysis Model/Method**	**Sensitivity/Supplementary Analysis**
Estimand 3 (Secondary)	Difference in the *percentage of days without rescue antacid use over the Placebo-controlled Treatment Period* as assessed by the daily diary between each dose of vonoprazan and placebo (10mg QD – placebo and 20mg QD - placebo) in subjects with NERD whose response to treatment is of interest only while on study drug, i.e., prior to study drug discontinuation due to any reasons and irrespective of excluded (non-rescue) medications and treatments.	ITT [1]	See Section 8.2.	The point estimate and 2-sided 95% CI of the difference in mean percentage of days without rescue antacid use over the Placebo-controlled Treatment Period between each dose of vonoprazan and placebo (10mg QD – placebo and 20mg QD - placebo) will be obtained through a linear contrast of the least square (LS) means comparing the mean percentage of days without rescue antacid use over the Placebo-controlled Treatment Period for each vonoprazan dose with placebo using the general linear model with treatment group as factor, and severity and frequency of heartburn at baseline as covariates.	

Abbreviation: ITT = Intent-to-treat; NERD = Non-Erosive Gastroesophageal Reflux Disease.
Refer to Table 4 for specific intercurrent event definitions.
[1] ITT set for the Placebo-controlled Treatment Period will be defined as all subjects randomized into the Placebo-controlled Treatment Period who receive at least one dose of study drug during the Placebo-controlled Treatment Period.