Protocol Number: NERD-201

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

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Phathom Pharmaceuticals, Inc.

NERD-201

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

25th Jan 2022

Statistical Analysis Plan

Version 2.0

Prepared by:

Signature Page

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Approved by:

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Senior Director, Biostats & Programming
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DOCUMENT HISTORY – CHANGES COMPARED TO FINAL VERSION 1.0

Version	Date	Changes
Final version 1.0	16-Aug-2021	Final version
Final version 2.0	25-Jan-2022	1. A supplementary analysis of the primary endpoint was added in Section 8.1.2 to account for multiple heartburn episodes within a subject. 2. An additional sensitivity analysis of the primary endpoint was added to Section 8.1.3 to consider heartburn episodes with any use of rescue antacid as not completely relieved. 3. Sensitivity analyses were added for secondary endpoints in Section 8.2.1 for the percentage of evaluable heartburn episodes for each subject that are relieved, among subjects who experienced 4 or more episodes of heartburn and for the percentage of 24-hour heartburn free days for which no rescue medication was taken. 4. A subset of the exploratory endpoints during the On-Demand Treatment Period will also be summarized among subjects who experienced 4 or more episodes of heartburn. 5. An additional exploratory endpoint was added for the Run-In Period, the percentage of subjects that are heartburn free over the last 7 days of the Run-In Period. 6. In Section 4.3.1, clarity added for definition of Run-In treatment end date. 7. In Section 4.3.2, the definition of Day 1 and last day of the On-Demand Treatment Period was clarified. 8. In Section 4.3.3, definitions for the start and end of the Follow-Up Period were added. 9. Added Section 4.5 to clarify that data summarized by visit will be based on the visit as collected on the eCRF. 10. Changed the analysis set for summaries of medical history and concomitant medications from the Safety On-Demand set to the Randomized set. 11. In Section 11.3.3.3, clarified the data handling for diary entries indicating absence of heartburn during the On-Demand Treatment Period. 12. Throughout the document, additional edits were made for clarity and formatting with no change to content.

LIST OF ABBREVIATIONS

AE	adverse event
AESI	Adverse Events of Special Interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
COVID-19	coronavirus disease 2019
CRF	case report form
CTMS	Clinical Trial Management System
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EE	erosive esophagitis
H2RA	Histamine-$_2$ receptor antagonist
GEE	Generalized Estimating Equations
GERD	Gastroesophageal reflux disease
ICF	informed consent form
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NERD	non-erosive gastroesophageal reflux disease
PAGI-QoL	Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life
PAGI-SYM	Patient Assessment of Gastrointestinal Disorders-Symptom Severity Index
PPI	proton pump inhibitor
PT	preferred term
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard Deviation
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO	World Health Organization

1.0 INTRODUCTION

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

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

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 2.0, dated 16Jul2021.

2.0 OBJECTIVES

The primary objectives of this study are as follows:

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

The secondary objective of this study is as follows:

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

3.0 INVESTIGATIONAL PLAN

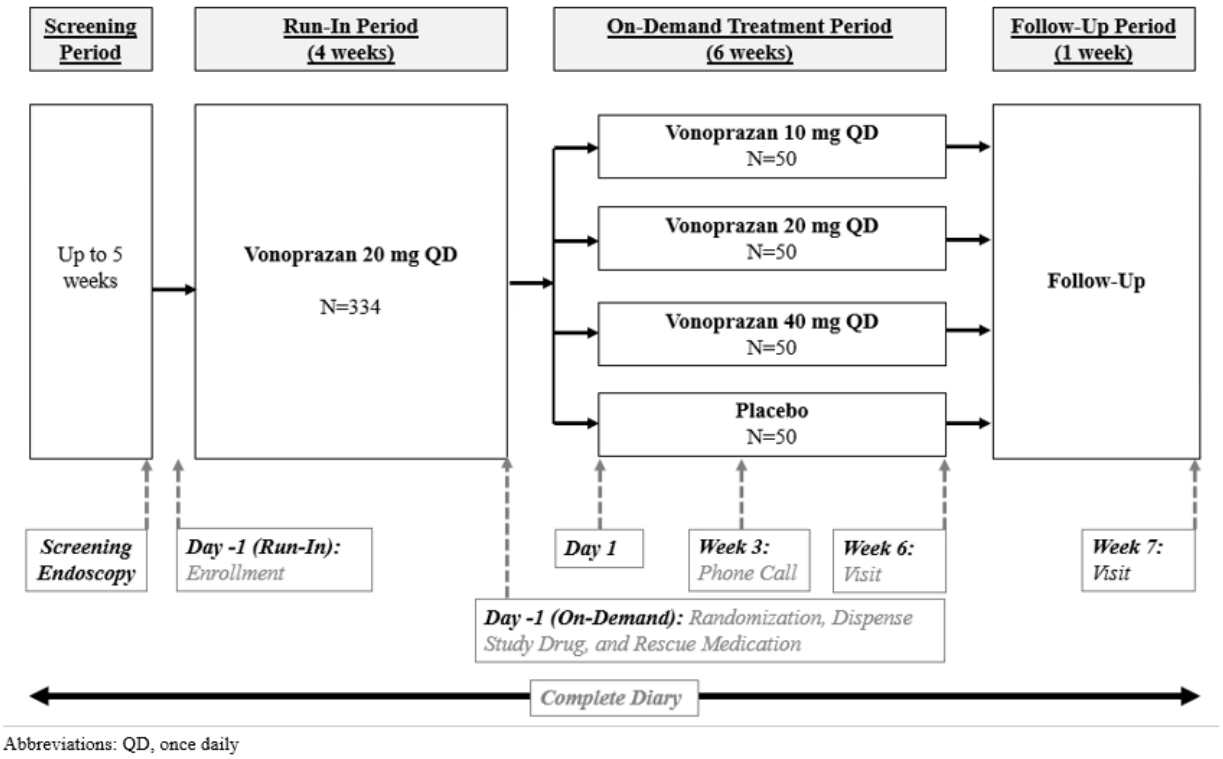
3.1 Overall Study Design and Plan

This is a Phase 2, multicenter, double-blind study of vonoprazan versus placebo assessing the relief of episodic heartburn. Subjects with symptomatic NERD (as confirmed by endoscopy) and heartburn symptoms (as documented in the electronic diary) will receive open-label vonoprazan 20 mg QD for 4 weeks. Subjects with stable disease (ie, no heartburn on the last 7 days of the Run-In Period) who are compliant with the diary and study medication and meet all other eligibility criteria will be randomized to receive either vonoprazan 10 mg, 20 mg, 40 mg or

placebo On-Demand for 6 weeks to treat episodic heartburn. Subjects will complete an electronic diary to assess presence and severity of heartburn symptoms and use of rescue antacid (if needed) in all periods. During the On-Demand Treatment Period, a more detailed diary will also document time of study drug administration and when heartburn relief occurs.

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

Figure 1 Study Scheme



Abbreviations: QD, once daily

3.2 Study Endpoints

The primary efficacy endpoint is as follows:

- The percentage of evaluable[(a)] heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug[(b).]

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

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

The secondary efficacy endpoints are as follows:

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

The exploratory efficacy endpoints of the On-Demand Treatment Period are as follows:

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

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

The exploratory efficacy endpoints of the Run-In Period are as follows:

- The percentage of 24-hour heartburn-free days over the Run-In Period.
- The percentage of subjects that are heartburn free over the last 7 days of the Run-In Period.
- The percentage of days without daytime heartburn over the Run-In Period.
- The percentage of days without nighttime heartburn over the Run-In Period.

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

3.3 Treatments

3.3.1 Run-In Period

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

3.3.2 On-Demand Treatment Period

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

3.3.3 Rescue Antacid

Subjects may use up to 12 tablets per day (not more than 4 tablets at one time) of study provided rescue antacid (Gelusil®) during the Screening Period, Run-In Period, On-Demand Treatment Period, and Safety Follow-up Period. During the On-Demand Treatment Period, rescue antacid should not be taken until 3 hours after study drug administration.

3.4 Dose Adjustment/Modifications

No dose adjustments or modifications are allowed for this study.

4.0 GENERAL STATISTICAL CONSIDERATIONS

In general, descriptive statistics will be presented by treatment group and by visit, as applicable. For continuous variables, summary statistics for the observed 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.

For the Run-In Period, all analyses will be conducted on the Safety Run-In set. See Section 4.4 for the Safety Run-In set definition.

For the On-Demand Treatment Period, efficacy analyses will be conducted on the Intent-to-Treat On-Demand set using the planned randomized treatment. Safety analyses will be conducted on the Safety On-Demand set using the actual treatment. If a subject receives more than one type of randomized study drug during this period, the planned randomized treatment will be assigned as the actual treatment received for this subject in the safety summary tables for this period. If a subject receives only one type of randomized study drug during this period, but this randomized study drug type is inconsistent with the planned randomized 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 for the ITT On-Demand set and Safety On-Demand set definitions.

All the statistical tests will be 2-sided and will be conducted at the 5% significance level, unless otherwise specified. 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

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

- Subjects will be randomized to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo with a randomization ratio of 1:1:1:1.
- Each subject experiences at least 4 evaluable heartburn episodes.

- Comparison between each dose of vonoprazan to placebo will be performed using the Fisher's Exact test.

- A clinically relevant difference of 15% between each dose of vonoprazan and placebo in the proportion of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug.

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

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

The hypothesis testing is as follows:

Null Hypothesis $H_0: P_{vono} = P_{placebo}$

Alternative Hypothesis $H_a: P_{vono} \neq P_{placebo}$

where P is the proportion of heartburn episodes.

4.2 Randomization and Blinding

Subjects who meet the eligibility criteria for the On-Demand Treatment Period will be randomized using a 1:1:1:1 allocation ratio to receive either vonoprazan 10 mg, 20 mg, or 40 mg or placebo during the 6-week On-Demand Treatment Period.

4.3 Study Day

4.3.1 Run-In Period

The date of the first dosing day of the Run-In Period is defined as Day 1. When study day is used for display or in comparisons the following algorithm will be used:

- study day = date of assessment - Day 1 +1,
  if date of assessment ≥ Day 1.
- study day = date of assessment - Day 1,
  if date of assessment < Day 1.

If the Run-In Treatment Period end date is missing, then the first date of the Run-In Treatment Period + 27 days will be used.

4.3.2 On-Demand Treatment Period

Since subjects will take study drug on-demand during the On-Demand Treatment Period, the first dosing day may differ for each subject. Study day during the On-Demand Treatment Period will be defined relative to the date of randomization.

The date of possible first dosing of the On-Demand Treatment Period is defined as Day 1. It is calculated as:

- date of possible first dosing = date of randomization +1, or date of the actual first dose of study drug, whichever is earlier.

When study day is used for display or in comparisons the following algorithm will be used:

- study day = date of possible first dosing - Day 1 +1,
  if date of assessment ≥ Day 1.
- study day = date of possible first dosing - Day 1,
  if date of assessment < Day 1.

Similarly, the last dosing day during the On-Demand Treatment Period will likely differ for each subject. The end of the On-Demand Treatment Period will be defined as the date of the possible last dose, i.e. the last visit date, the date of the last record in Timed Assessment Diary, or actual last dose of study drug, whichever is later.

4.3.3 Follow-Up Period

The start date of the Follow-Up Period will be defined as the last date of the On-Demand Treatment Period +1.

The end date of the Follow-Up Period will be the last visit date or the date of the last evening, morning, or rescue antacid diary entry, whichever is later.

4.4 Analysis Sets

4.4.1 Screened Set

All subjects who signed the informed consent form (ICF) before entering the Run-In Period. Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered into the Run-In Period of the study.

4.4.2 All Subjects Set

All subjects who enrolled into the Run-In Period. Run-In failures refer to instances when subjects consent to participate in the clinical study, are subsequently entered in the Run-In Period of the study, and do not meet the eligibility criteria for the On-Demand Treatment Period. Run-In failures may also include those subjects who withdraw from the study drug or the study during the Run-In Period.

4.4.3 Randomized Set

All subjects randomly assigned to receive study drug regardless of whether or not they received a dose of study drug during the On-Demand Treatment Period.

4.4.4 Safety Sets

4.4.4.1 Safety Run-In Set

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

4.4.4.2 Safety On-Demand Set

The Safety On-Demand set includes all subjects in the Safety Run-In set who were randomized and treated at least one heartburn episode with randomized treatment during the On-Demand Treatment Period. All analyses using the Safety On-Demand set will group subjects according to the treatment actually received.

4.4.5 Intent-to-Treat (ITT) On-Demand Set

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

4.5 Visit Windows

All data summarized by visit will be based on the visit name collected on the eCRF page. For data from unscheduled visits, these will be listed but not included in any by-visit summaries or analyses.

5.0 SUBJECT DISPOSITION

5.1 Disposition

5.1.1 Screened and Screen Failure Subjects

The number of screened and screen failure subjects will be presented for overall subjects included in the Screened set.

The following will be summarized for the Screened set:

- The total number of screened subjects.
- The number of subjects who enrolled into the Run-In Period.
- The number and percentage of screen failures.
- The number and percentage of each primary reason for screen failures.

Percentages will be based on the Screened set.

Reasons for screen failure will be listed for the Screened set. A list of Inclusion/Exclusion criteria will be listed. Subjects who met eligibility criteria for both run-in period and on-demand period will be listed, associated exclusion criteria will be displayed as well as inclusion criteria that is not met for the Screened set.

5.1.2 Run-In Period All Subjects

The following will be summarized for All Subjects set:

- The total number of subjects who enrolled into the Run-In Period.
- The number and percentage of subjects who are in the Safety Run-In set.
- The number and percentage of Run-In failures.
- The number and percentage of each primary reason for Run-In failures.

Percentages will be based on the All Subjects set.

Subject disposition data for the Run-In period will be listed for the All Subjects set.

5.1.3 Randomized Subjects

The following will be summarized for the Randomized set:

- The total number of randomized subjects.
- The number and percentage of subjects in the Safety On-Demand set and the ITT On-Demand set.
- The number and percentage with each reason for exclusion from the Safety On-Demand set and the ITT On-Demand set.
- The number and percentage of subjects who completed the participation of the entire study.
- The number and percentage of each primary reason for study discontinuation.
- The number and percentage of subjects who discontinued from the follow-up period.

The number of subjects and percentage will be presented by treatment group and overall for all randomized subjects.

Subject disposition data for the On-Demand Treatment Period will be listed for the Randomized set. Disposition data for the On-Demand Treatment Period will be listed separately for subjects who discontinued from study for the Randomized set.

5.2 Protocol Deviations

Protocol deviations will be recorded within the [redacted] 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 significant protocol deviations will be summarized by CTMS activity subtype, treatment group and overall using the Randomized set.

Individual subject protocol deviations, both significant and non-significant, will be presented in a data listing using the All Subjects set.

6.0 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

6.1 Demographics and Baseline Characteristics

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

Demographic variables collected at Screening, such as age (years), sex, race, ethnicity, height (cm), weight (kg), and body mass index (BMI) will be summarized. Continuous variables collected at Screening, including age, BMI, weight, height, and mean severity of daytime and nighttime heartburn will be summarized using descriptive statistics. The following categorical variables will be summarized by reporting the number and percentage of subjects in each category for both periods.

- Age group at Screening (<45, ≥45 - <65, ≥65 - <75, ≥75)
- Age group 2 at Screening (≥18 - ≤64, ≥65 - ≤84, ≥85)
- Sex (Male, Female)

- BMI category (<25, ≥25 - <30, ≥30)
- Serum gastrin (<200, ≥200)
- Pepsinogen I/II level (≤2, >2 - ≤3, >3)
- Smoking status (never smoked, current smoker, ex-smoker)
- Alcohol use (drink every day, drink a couple of days per week, drink a couple of days per month, never drink)

For all three demographic and baseline characteristic summaries, the following variables will be summarized based on symptoms reported during the Screening Period in the Morning Diary and Evening Diary from the last 7 days prior to Day -1 (i.e. Day -8 to Day -2) of the Run-In Period.

- Mean severity of:
  - Daytime/Nighttime Heartburn (mild, moderate, severe and very severe)
  - Heartburn during the day (mild, moderate, severe and very severe)
  - Heartburn at night (mild, moderate, severe and very severe)
- Number of days with:
  - Daytime or nighttime heartburn (≥0 - ≤3, >3 - ≤5, >5 - ≤7)
  - Daytime heartburn (≥0 - ≤3, >3 - ≤5, >5 - ≤7)
  - Nighttime heartburn (≥0 - ≤3, >3 - ≤5, >5 - ≤7)
- Number of days with use of rescue antacid ((≥0 - ≤3, >3 - ≤5, >5 - ≤7)
- Mean number of rescue antacid tablets taken per day

Refer to Section 11.3 for diary data handling. Demographic and baseline characteristics data will be listed using the All Subjects 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 system organ class (SOC) and preferred term (PT) will be summarized. For the Run-In Period, medical history will be summarized by treatment group and overall using the Safety Run-In set. For the On-Demand Treatment Period, medical history will be summarized by treatment group and overall using the Randomized set.

Each subject's medical history will be listed using the All Subjects set.

7.0 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.

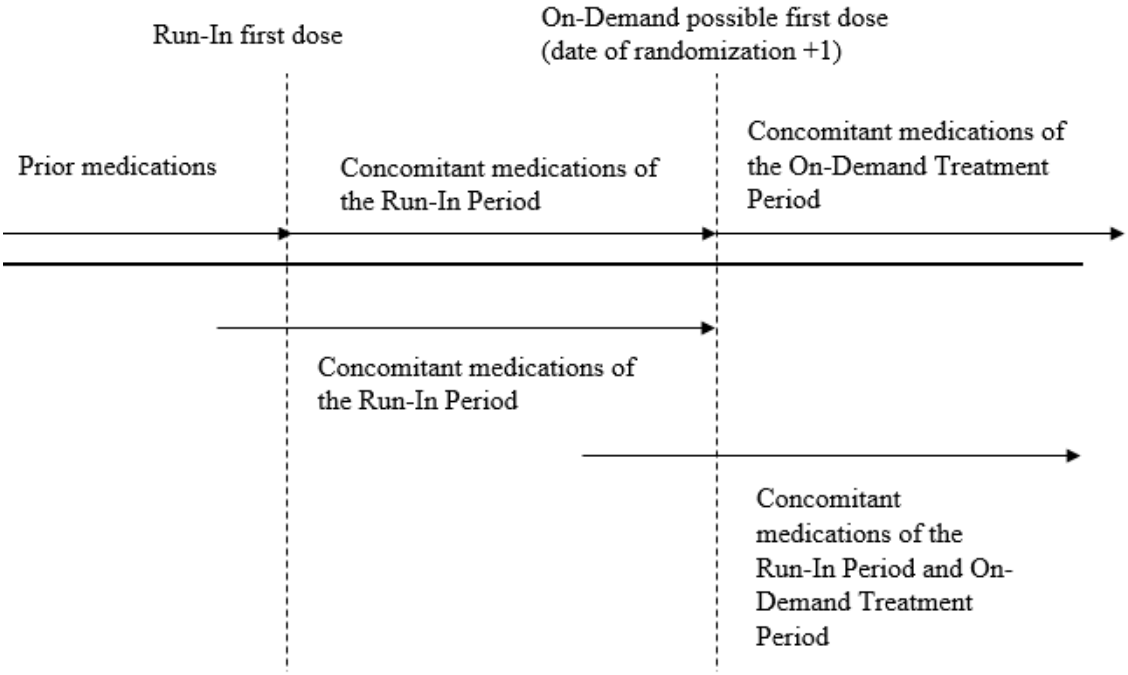
For the Run-In Period, prior medications are those with the start and stop dates prior to the first dose of the Run-In Period study drug. Concomitant medications are those with start dates prior to the first dose of the Run-In Period and continuing after the first dose of the Run-In Period or with start dates between the first dose of the Run-In Period and Day 1 of the On-Demand Treatment Period (see Section 4.3.2 for the definition of Day 1 of the On-Demand Treatment Period).

For the On-Demand Treatment Period, concomitant medications are those with start dates prior to Day 1 of the On-Demand Treatment Period and continuing after Day 1 of the On-Demand Treatment Period or with start dates on or after Day 1 of the On-Demand Treatment Period.

The number and percentage of subjects with prior use of histamine-2 receptor antagonists (H2RAs) or proton pump inhibitors (PPIs) will be summarized by treatment and overall, using the ITT On-Demand Set. The number and percentage of subjects who had relieved symptoms per H2RA or PPI will also be summarized. A supportive listing will be provided.

See Figure 2 for details on the categorization of prior and concomitant medications.

Figure 2 Prior and Concomitant Medications



Prior and concomitant medications will be summarized and listed for both periods. For the Run-In Period, prior and concomitant medications will be summarized separately using the Safety Run-In set. For the On-Demand Treatment Period, concomitant medications will be summarized and listed by treatment group using the Randomized Set.

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 Section 11.2.

7.2 Study Treatments

7.2.1 Extent of Exposure

Treatment exposure for the Run-In Period will be summarized using the Safety Run-In set. Treatment exposure for the On-Demand Treatment Period will be summarized by treatment using the Safety On-Demand set.

7.2.1.1 Run-In Period

Appropriate statistical summaries will be applied to present the following statistics for the Run-In Period:

- Duration of dosing (days): date of last dose of the Run-In period – date of first dose of the Run-In period + 1

7.2.1.2 On-Demand Treatment Period

Appropriate statistical summaries will be applied to present the following statistics for the On-Demand Treatment Period:

- Duration of dosing (days): number of days on which subjects have recorded taking on-demand study drug in the on-demand heartburn episode diary
- Cumulative duration of dosing (days): total days of dosing since first dose of the On-Demand treatment period
- Duration of participation (days): date of Week 6/End Of Study visit – date of possible first dose + 1
- Total dose (mg): total number of capsules taken × dose level

Duration of dosing and duration of participation will be categorized and summarized as follows: ≥1 to ≤7 days, >7 to ≤14 days, >14 to ≤21 days, >21 to ≤28 days, >28 to ≤35 days, >35 to ≤42 days and >42 days.

Treatment exposure will be listed for the On-Demand Treatment Period using the Safety On-Demand Set. Drug accountability will be listed for the Run-In Period and On-Demand Treatment Period using the Safety Run-In Set and Safety On-Demand Set, respectively.

7.2.2 Treatment Compliance of the Run-In Period

Treatment compliance will be calculated only for the Run-In Period using the Safety Run-In set as:

> Compliance (%) = (total actual capsules taken / total expected capsules) × 100, where
> total expected capsules = (date of last dose of this period – date of first dose of this period + 1) and
> Total actual capsules taken = total number of capsules dispensed for this period – total number of capsules returned for this period

If a kit is not returned, the compliance of the lost kit will be imputed as 100%. Overall compliance information will be used to categorize subjects as being either compliant or not. A subject is considered compliant if the overall study drug compliance is greater than or equal to 80% and less than or equal to 120%.

Summary statistics for treatment compliance percentages and compliance categories (<80, ≥80 - ≤100, >100 - ≤120, >120) will be summarized. Individual drug accountability for the Run-In Period will be listed using the Safety Run-In set.

8.0 EFFICACY ANALYSIS

For efficacy analyses, On-Demand Treatment Period is defined as any diary with analysis day on or after Day 1 and on or before Week 6/End Of Study visit (see Section 4.3.2 for the definition of Day 1 of the On-Demand Treatment Period; see Section 11.3 for the definition of analysis day for diary data). Run-In Period is defined as any diary with analysis day on or after the date of first dose, and on or before the date of last dose during the Run-In Period.

For the On-Demand Treatment Period, each treatment comparison of vonoprazan 10 mg, 20 mg, and 40 mg to placebo will be tested at the 0.05 significance level using the ITT On-Demand set. For the Run-In Period, the exploratory endpoints will be summarized for the Run-In treatment, i.e. vonoprazan 20 mg, using the Safety Run-In set.

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

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug. An evaluable heartburn episode is an episode for which study drug was taken and for which the subject completed at least one entry in the heartburn episode diary. For a heartburn episode to be considered completely relieved, a subject must not have taken rescue antacid within 3 hours of taking study drug. See Section 11.3 for details on diary data handling.

8.1.1 Primary Analysis

The primary endpoint of the percentage of evaluable heartburn episodes completely relieved within 3 hours and with no further heartburn reported for 24 hours after taking study drug will be compared between each dose of vonoprazan and placebo using Fisher's Exact test for the ITT On-Demand set. The percentage will be based on the total number of evaluable heartburn episodes within each treatment group. Difference in percentages, 95% CI and p-value will be provided for the comparisons between each dose of vonoprazan and placebo.

Data collected in the Heartburn Diary and Timed Assessments Diary will be listed using the ITT On-Demand set. Data collected in the Rescue Antacid Diary will be listed separately for rescue antacid use during the Run-In period and On-Demand Treatment periods, using the Safety Run-In and Safety On-Demand sets, respectively.

8.1.2 Supplementary Analyses

A supplementary analysis on the primary analysis will be performed to account for the possibly multiple evaluable heartburn episodes within a subject. During the On-Demand period, a subject

could experience more than one episode followed by intake of the study drug. Therefore, a generalized linear model with the Generalized Estimating Equation (GEE) method will be used to analyze this correlated binary data. The probability each episode will be completely relieved will be modeled using GEE within SAS Proc GENMOD. Treatment will be fit as a categorical factor. A compound symmetric (exchangeable) correlation structure within subjects will be assumed. The GEE for binary data will be based on a binomial distribution with the logit link function.

Results will be presented for the odds ratio [back transformed log-odds] for the comparisons between each dose of vonoprazan and placebo along with the associated 95% CI and 2-sided p-value.

8.1.3 Sensitivity Analyses

A sensitivity analysis will be performed by including heartburn episodes with rescue antacid use within 3 hours after taking study drug as completely relieved, using the same method as the primary analysis. In this analysis, heartburn episodes indicated by the subject in the diary as completely relieved within 3 hours after taking study drug will be included, regardless of rescue antacid use.

A sensitivity analysis will also be performed by considering heartburn episodes with any use of rescue medication as not completely relieved, using the same method as the primary analysis.

8.1.4 Subgroup Analysis

The primary efficacy endpoint will be analyzed separately for the following subgroups using the same method as the primary analysis:

- Age group at Screening (<45, ≥45 - <65, ≥65 - <75, ≥75)
- Sex (Male, Female)
- Baseline BMI category (<25, ≥25 - <30, ≥30)
- Mean heartburn severity during the Screening Period (mild, moderate, severe, very severe)

If the number of subjects within a subgroup in a treatment group is not sufficient to run a Fisher's Exact test, subgroups might be combined to perform the test. Alternatively, only summary statistics might be reported for such subgroups.

8.2 Secondary Efficacy Endpoint

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

The following secondary endpoints will be compared using Fisher's Exact test using the same method as the primary analysis.

- The percentage of evaluable heartburn episodes completely relieved within 3 hours after taking study drug.

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

The following secondary endpoints will be compared using a Wilcoxon rank-sum test.

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

- The percentage of days study drug was taken over the On-Demand Treatment Period.

- The mean number of tablets of rescue antacid taken per day over the On-Demand Treatment Period.

- The percentage of 24-hour heartburn-free days over the On-Demand Treatment Period.

8.2.1 Sensitivity Analyses

The following sensitivity analyses will be made for the secondary endpoints using a Wilcoxon Rank Sum test:

- The percentage of evaluable heartburn episodes for each subject (who experienced 4 or more episodes) that are completely relieved within 3 hours and with no further evaluable heartburn episodes reported for 24 hours after taking study drug.

- The percentage of 24-hour heartburn-free days with no rescue antacid taken over the On-Demand Treatment Period

8.3 Exploratory Endpoints

8.3.1 On-Demand Treatment Period

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

The following exploratory endpoints will be compared using Fisher's Exact test using the same method as the primary analysis.

- The percentage of evaluable heartburn episodes completely relieved within 30 minutes or 1, 1.5, or 2 hours and with no further heartburn reported for 24 hours after taking study drug.

- The percentage of evaluable heartburn episodes that are completely relieved within 30 minutes or 1, 1.5, or 2 hours after taking study drug.

- The percentage of evaluable heartburn episodes that improved (including complete relief) at 30 minutes or 1, 1.5, 2, or 3 hours after taking study drug.

- The percentage of episodes for which subjects continue to be heartburn-free after 24 or 48 hours of taking study drug.

- The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours with no further heartburn reported for 24 hours after taking study drug.

- The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours after taking study drug.

- The percentage of subjects with complete relief of the first episode of heartburn within 3 hours after taking study drug.

In addition, the following subset of the above exploratory endpoints will be compared using the same method as the primary analysis, but only including subjects with 4 or more evaluable episodes.

- The percentage of evaluable heartburn episodes that are completely relieved within 30 minutes or 1, 1.5, or 2 hours and with no further heartburn reported for 24 hours after taking study drug.

- The percentage of evaluable heartburn episodes that are completely relieved within 30 minutes or 1, 1.5, or 2 hours after taking study drug.

- The percentage of evaluable heartburn episodes that improved (including complete relief) at 30 minutes or 1, 1.5, 2, or 3 hours after taking study drug.

- The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours with no further heartburn reported for 24 hours after taking study drug.

- The percentage of subjects with at least 50%, at least 75%, and 100% of their evaluable heartburn episodes completely relieved within 3 hours after taking study drug.

The following exploratory endpoints will be compared using a Wilcoxon rank-sum test.

- The mean number of days between heartburn episodes.
- The percentage of days without daytime heartburn over the On-Demand Treatment Period.
- The percentage of days without nighttime heartburn over the On-Demand Treatment Period.
- The mean severity of daytime and nighttime heartburn over the On-Demand Treatment Period.
- The mean severity of nighttime heartburn over On-Demand Treatment Period.
- The mean severity of daytime heartburn over the On-Demand Treatment Period.
- The percentage of days without rescue antacid use over the On-Demand Treatment Period.
- The change from baseline (i.e. last assessment on or before first dose on Run-In period) to the end of the Run-In, and to the end of the On-Demand Treatment Period for each subscale and the total score of the PAGI-SYM questionnaire.
- The change from baseline (i.e. last assessment on or before first dose on Run-In period) to the end of the Run-In, and to the end of the On-Demand Treatment Period for each subscale and the total score of the PAGI-QoL questionnaire.

The following exploratory endpoints will be summarized using descriptive statistics.

- The patient global impression of change in GERD symptoms at the end of the On-Demand Treatment Period.
- The patient global impression of severity in GERD symptoms over the last 7 days of the On-Demand Treatment Period.

The following exploratory endpoint will be collected on the Patient Preference Questionnaire eCRF and will be summarized using descriptive statistics.

- The percentage of subjects with each dosing preference.

Data collected from each questionnaire will be listed separately using the ITT On-Demand set.

8.3.2 Run-In Period

The following exploratory endpoints will be summarized using descriptive statistics based on the Safety Run-In set.

- The percentage of 24-hour heartburn-free days over the Run-In Period.
- The percentage of subjects that are heartburn free over the last 7 days of the Run-In Period.
- The percentage of days without daytime heartburn over the Run-In Period.
- The percentage of days without nighttime heartburn over the Run-In Period.
- The mean severity of daytime and nighttime heartburn over the Run-In Period.
- The mean severity of nighttime heartburn over the Run-In Period.
- The mean severity of daytime heartburn over the Run-In Period.
- The percentage of days without rescue antacid use over the Run-In Period.
- The mean number of tablets of rescue antacid taken per day over the Run-In Period.
- The change from baseline to the end of the Run-In Period for each subscale and the total score of the PAGI-SYM questionnaire.
- The change from baseline to the end of the Run-In Period for each subscale and the total score of the PAGI-QoL questionnaire.
- The patient global impression of change in GERD symptoms at the end of the Run-In Period.
- The patient global impression of severity in GERD symptoms over the last 7 days of the Run-In Period.

Data collected in the Morning Diary and Evening Diary will be listed using the Safety Run-In set.

8.3.3 Follow-Up Period

The following exploratory endpoints will be summarized using descriptive statistics based on the ITT On-Demand set.

- The percentage of 24-hour heartburn-free days over the Follow-Up Period.
- The percentage of days without daytime heartburn over the Follow-Up Period.
- The percentage of days without nighttime heartburn over the Follow-Up Period.
- The mean severity of daytime and nighttime heartburn over the Follow-Up Period.
- The mean severity of nighttime heartburn over the Follow-Up Period.
- The mean severity of daytime heartburn over the Follow-Up Period.
- The percentage of days without rescue antacid use over the Follow-Up Period.
- The mean number of tablets of rescue antacid taken per day over the Follow-Up Period.

9.0 SAFETY ANALYSIS

Safety will be summarized separately for the Run-In Period and the On-Demand Treatment Period. Safety data collected during the Follow-Up Period will be summarized with the On-Demand Treatment Period. For each period, safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, gastrin and pepsinogen I/II levels, ECGs and vital signs. The first baseline will be the last assessment on or before the date of first dose of study drug in the Run-In Period. For the On-Demand Treatment Period, a second baseline will be derived as the last assessment on or before the date of randomization. Changes from both baselines will be summarized.

For the Run-In Period, all safety analyses will be summarized using the Safety Run-In set. For the On-Demand Treatment Period, all safety analyses will be conducted for each treatment group using the Safety On-Demand set.

9.1 Adverse Events

Adverse events will be coded using Version 23.0 of the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent AE (TEAE) is defined as any event that occurs after the first dose of study drug or any event at baseline that worsens in either intensity or frequency after the first dose of study drug in that period. For Run-In failure subjects, all AEs collected will be summarized in the Run-In Period. For subjects who entered the On-Demand Treatment

Period, all AEs that start before the date of possible first dose (Day 1 of the On-Demand Treatment Period) will be summarized in the Run-In Period. All AEs that start on or after the date of possible first dose (Day 1 of the On-Demand Treatment Period) will be counted as a TEAE of the On-Demand Treatment Period. Adverse events collected during the Safety Follow-Up Period will be included with the On-Demand Treatment Period summaries.

Overall AEs for the Run-In Period and On-Demand Treatment Period will be summarized separately, for the following adverse events.

- Treatment-Emergent Adverse Event
- Serious Treatment-Emergent Adverse Event
- Study Drug-Related Treatment-Emergent Adverse Event
- Study Drug-Related Treatment-Emergent Serious Adverse Event
- Treatment-Emergent Adverse Event Leading to Treatment Discontinuation
- Treatment-Emergent Adverse Event Leading to Study Discontinuation
- Adverse Event Leading to Death

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 number and percentage of subjects with TEAEs will be summarized in the following ways:

- by primary system organ class and preferred term
- by primary system organ class, preferred term and maximum severity
- by primary system organ class, preferred term and relationship to study drug

The number and percentage of subjects with TEAEs related to study drug will be summarized in the following ways:

- by primary system organ class and preferred term
- by primary system organ class, preferred term and maximum severity

For the On-Demand Treatment Period, a separate summary will be provided including AEs that are Treatment-Emergent with the AE onset day within 3 days of a subject taking any on-demand treatment.

The most common TEAEs (≥10% of subjects in any treatment group) and TEAEs related to study drug (≥5% of subjects in any treatment group) will be presented by preferred term in descending frequency starting from the most common event.

The most common non-serious TEAEs (>5% of subjects in any treatment group) will be presented by primary system organ class, preferred term and treatment group along with the number and proportion of subjects reporting at least one of these most frequent non-serious TEAEs.

The number and proportion of subjects as well as the number of events (except 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
- Adverse events leading to study discontinuation
- Serious Adverse Events (SAEs)
- Deaths
- Adverse events of special interest (AESI)

All adverse events in the On-Demand Treatment Period will be included in a listing using the Randomized set. The adverse events that happen on or after On-Demand Treatment Period Day 1 and before the date of actual first dose will be marked in this listing, but they will not be summarized separately. All adverse events in the Run-In Period will be included in a listing using the Safety Run-In set. Pre-treatment AEs and Serious AEs will be listed using the Screened set.

In addition, the following select adverse events will be displayed in separate listings for each period:

- Deaths
- Serious adverse events
- Adverse events leading to treatment discontinuation
- Adverse events leading to study discontinuation

- Adverse events of special interest

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 1 will be summarized by AESI category, primary system organ class and preferred term for the Run-In Period and the On-Demand Treatment Period. The search criteria that will be used to identify AESIs are specified in the table.

Table 1 Adverse Events Special Interest – Search Criteria

Adverse Event of Special Interest	Search Criteria
Clostridium difficile enteric infection	Pseudomembranous colitis SMQ (Narrow)
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 Greenstick fracture Hand fracture Hip fracture Humerus fracture Ilium fracture Impacted fracture Jaw fracture Limb fracture Lower limb fracture Fractured skull depressed 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
Severe cutaneous adverse reactions	Severe cutaneous adverse reactions SMQ (Narrow)
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)
Gastric cancer	Gastric Neoplasms Malignant MedDRA High Level Term

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 US conventional units) and serum gastrin and pepsinogen I/II levels will be presented for the Run-In Period and the On-Demand Treatment Period. Laboratory assessments collected in the Follow-Up Period will be included in the On-Demand Treatment Period summaries.

Day -1 baseline gastrin levels will not be blinded. Gastrin at the Week 4 Run-In, Week 6 On-Demand treatment, and Safety Follow-up visits and all pepsinogen I and II results will be blinded and will not be reported to investigative sites or other blinded personnel until after the study blind is broken.

Changes from baseline will also be presented for quantitative variables. For categorical variables (i.e., normal or abnormal findings, or qualitative clinical laboratory tests), shift tables for the change from baseline to the end of each period will be presented.

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 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.

- 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

Serum gastrin for all timepoints will be displayed using box plots for the Safety Run-In set and the Safety On-Demand set.

For each period, the number and percentage of subjects with at least one post-baseline serum gastrin value >500 pg/mL and >1000 pg/mL and with the test value higher than 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.

9.3 Vital Sign

Descriptive statistics for vital signs, including body temperature, systolic blood pressure, diastolic blood pressure and pulse rate, will be presented for the Run-In Period and the On-Demand Treatment Period. Changes from baseline will also be presented. Vital signs assessments collected in the Follow-Up Period will be included in the On-Demand Treatment Period summaries.

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. A supportive listing of subjects with such post-baseline elevations 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

ECG parameters, including heart rate, PR interval, RR interval, QRS interval, QT interval, QTc Fridericia (QTcF) will be collected on the eCRF, and a listing will be provided. Descriptive statistics for these ECG parameters will be presented for the On-Demand Treatment Period using the Safety On-Demand set only. For ECG interpretations (within normal limits, abnormal but not clinically significant, or abnormal and clinically significant), shift tables for the change from baseline to the end of the On-Demand Treatment Period will be presented using the Safety On-Demand set.

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 for the On-Demand Treatment Period using the Safety On-Demand set. 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 msec
  - QTc interval > 480 msec
  - QTc interval > 500 msec
- Change from Run-in baseline in QTcF interval:
  - QTc interval increases from baseline >30 msec
  - QTc interval increases from baseline >60 msec
  - QTc interval > 450 msec with increase from baseline >30 msec

10.0 INTERIM ANALYSIS/OTHER ANALYSES

10.1 Interim Analysis

No interim analysis is planned.

10.2 Coronavirus Pandemic

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

The COVID-19 impacts on individual subjects collected on the COVID-19 CRF pages will be listed for the All Subjects set. Protocol deviations related to COVID-19 will be marked in the protocol deviation listing for the All Subjects 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.

11.0 APPENDICES

11.1 Schedule of Events

Table 2 Schedule of Events

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

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

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

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

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

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

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

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

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

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

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

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

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

(k) Subjects should be instructed to complete the electronic diary every morning upon waking (for nighttime symptoms) and every evening before bedtime (for daytime symptoms) on each day of the Screening, Run-In and Follow-up Period. During the On-Demand Treatment Period, subjects will be instructed to complete the electronic diary to document heartburn episodes and study drug administration. Rescue antacid use should be reported during all periods.

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

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

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

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

(p) Run-In failure procedures.

11.2 Imputation Rules for Missing Date Imputation

11.2.1 Rules for Concomitant Medication Start Date Imputation

The following rules will be applied to impute the missing numerical fields for the Run-In Period and the On-Demand Treatment Period. 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.

For the Run-In Period, the date of first dose of study drug is the actual date that the subject took the first dose of Run-In treatment. For the On-Demand Treatment Period, the date of first dose of study drug refers to the date of possible first dose, i.e. date of randomization + 1.

Missing day and month

- If the year of the incomplete start date is the same as the year of 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 assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of study drug, then 31 December will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start 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 assigned to the missing day.
- If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

11.2.2 Rules for Concomitant Medication End Date Imputation

The following rules will be applied to impute the missing numerical fields for the Run-In Period and the On-Demand Treatment Period. For the Run-In Period, if the date of the last dose of study drug is missing, then replace it with the last visit date. For the On-Demand Treatment Period, the date of the last dose is referring to the date of possible last dose, i.e. the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date. If the non-imputed stop date is more complete than the non-imputed start date (eg. stop date has a missing day and start date has missing month or stop date has full date but the start date has missing day or month) then the stop date will be imputed (as per rules below) and the start date will be imputed with the end date.

Missing day and month

- If the year of the incomplete stop date is the same as the year of 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 assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of study drug, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop 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 assigned to the missing day.
- If either the year is before the year of the date of the last dose of study drug or if both years are the same but the month is before the month of the date of the last dose of study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of study drug or if both years are the same but the month is after the month of the date of the last dose of study drug, then the first day of the month will be assigned to the missing day.

11.2.3 Rules for Prior Medication Start Date Imputation

For prior medications, incomplete (i.e., partially missing) start dates will be imputed and will follow the same rules as in Section 11.2.1.

11.2.4 Rules for AE Start Date Imputation

For AEs, incomplete (i.e., partially missing) start dates will be imputed and will follow the same rules as in Section 11.2.1. Incomplete stop dates will not be imputed.

11.3 Electronic Diary

Subjects will be given an electronic diary on the first day of the Screening Period. During the Screening, Run-In, and Safety Follow-up Periods subjects will complete the Morning Heartburn Diary, Evening Heartburn Diary, and Rescue Antacid Diary. During the On-Demand Treatment Period, subjects will complete the heartburn episode diaries, including the Heartburn Diary, Timed Assessment Diary, and Rescue Antacid Diary.

11.3.1 Screening, Run-In and Follow-up Period

11.3.1.1 Data Handling for Morning and Evening Heartburn Diaries

During the Screening Period, Run-In Period, and Safety Follow-up Period, subjects will document the presence and severity of daytime and nighttime heartburn symptoms twice daily in their diary.

For analysis purposes, diary entries will be assigned to an analysis day and time based on the day the collection interval started for that entry.

For the Morning Heartburn Diary and the Evening Heartburn Diary, the form open date will be used to determine analysis day. The Day x diary entries will include the evening diary completed on Day x (the collection interval started when the subject awoke on Day x) and the morning entry completed on Day x+1 (the collection interval started when the subject went to bed on Day x).

Subjects will document the presence (yes/no) and severity (1=Mild, 2=Moderate, 3=Severe, or 4=Very Severe) of daytime and nighttime heartburn symptoms in their diary two times per day, once in the Morning Heartburn Diary for nighttime heartburn and once in the Evening Heartburn Diary for daytime heartburn. If the presence of heartburn is answered as “no” in a diary, the heartburn severity will be considered as 0 (0=None) in the analysis.

See Table 3 for details on definitions of heartburn severity.

Table 3 Definitions of Heartburn Severity (Daytime/Nighttime) for the Screening, Run-In, and Follow-Up Periods

Definitions of Daytime Heartburn Severity (Daytime=Awake Time)
None - No heartburn
Mild - Occasional heartburn, can be ignored, does not influence daily routine
Moderate - Heartburn cannot be ignored and/or occasionally influences daily routine
Severe - Heartburn present most of day and/or regularly influences daily routine
Very Severe - Constant heartburn and/or markedly influences daily routine
Definitions of Nighttime Heartburn Severity (Nighttime=Sleep Time)
None - No heartburn
Mild - Occasional heartburn, can be ignored, does not influence sleep
Moderate - Heartburn cannot be ignored and/or occasionally influences sleep
Severe - Heartburn present most of night and/or regularly influences sleep
Very Severe - Constant heartburn and/or markedly influences sleep

For the Run-In Period and the Follow-Up Period, the percentage of days with neither daytime nor nighttime heartburn (i.e. 24-hour heartburn free days) will be calculated using all days with at least 1 Morning Heartburn Diary or Evening Heartburn Diary entry during an observation period. For example, if a subject completed at least 1 diary entry on 22 of 28 days, but missed both entries on 6 days, 22 days will be used as the denominator in the efficacy analysis. All entries on that day will need to be heartburn-free for the day to be counted as a day with neither daytime nor nighttime heartburn. This will also apply when more than 2 diary entries are assigned to the same analysis 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.

Only evening diary entries will be used for assessing daytime heartburn and only morning diary entries will be used for assessing nighttime heartburn. The mean severity of daytime and nighttime heartburn during each period for each subject will be calculated by taking the mean of the average severity on all days with at least 1 morning or evening diary entry. For each day during the Run-In Period and the Follow-Up Period, the highest recorded heartburn severity will be determined separately for all morning diary entries and all evening diary entries. The average severity for the day will be determined by taking the mean of the highest recorded morning and evening diary entries on that day. These daily averages will then be averaged for all days with at least 1 morning or evening diary entry to obtain the endpoint value for each subject.

The mean severity of daytime heartburn for each subject will be calculated by determining the highest recorded severity for all evening diary entries per day, then taking the mean of all days with at least 1 evening diary entry during that phase.

The mean severity of nighttime heartburn for each subject will be calculated by determining the highest recorded severity for all morning diary entries per day, then taking the mean of all days with at least 1 morning diary entry during that phase.

11.3.1.2 Baseline Summary of Subject Diary

Baseline diary assessments will be summarized using diaries from the last 7 days prior to Day -1, i.e, Days -8 to -2, inclusive, of the Screening Period. Only days with at least 1 morning or evening diary entry during the specified days will be included in these summaries.

Summary statistics (n, mean, SD, minimum, 25th percentile, median, 75th percentile, and maximum) will be generated for the mean severity of daytime and nighttime heartburn, mean severity of daytime heartburn, and mean severity of nighttime heartburn. The number of days with daytime or nighttime heartburn, number of days with daytime heartburn, and number of days with nighttime heartburn will be summarized by treatment group in categories of (≥0 - ≤3, >3 - ≤5, >5 - ≤7).

11.3.2 Rescue Antacid Diary

For Rescue Antacid Diary, if the rescue antacid start date is selected as 0 (Yesterday), the analysis day will be Day x-1 (the collection interval started when the subject opened the diary on Day x). If the rescue antacid start date is selected as 1 (Today), the analysis day will be Day x (the collection interval started when the subject opened the diary on Day x). The rescue antacid start time will be used as the analysis time.

During all periods of the study, subjects will record the use of rescue antacid, including the time and number of antacid tablets taken. Rescue antacid endpoints will be calculated using all days during each period.

11.3.3 On-Demand Treatment Period

During the On-Demand Treatment Period, subjects will document episodes of heartburn experienced and the use of on-demand study medication as they occur. Subjects will also receive reminders every morning and every evening to record any unrecorded heartburn episodes (no longer than the prior day) or to document if they have not had any heartburn episodes.

11.3.3.1 Data Handling for On-Demand Heartburn Diary

When subjects experience an episode of Heartburn during the On-Demand Treatment Period, the subject will complete the Heartburn Diary and document the severity of heartburn (Mild, Moderate, Severe, or Very Severe) of the episode (See Table 4 for details on definitions of heartburn severity). If a subject has not reported an episode on a given day, the subject will be prompted to complete the Heartburn Diary each morning and evening during the On-Demand Treatment Period. The subject will either confirm that the subject has not experienced heartburn or will complete the diary to document episodes of heartburn.

Table 4 Definitions of Heartburn Severity for the On-Demand Treatment Period

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

11.3.3.2 On-Demand Timed Assessments

Once a heartburn episode is reported and the subject is eligible to take study drug (ie, 24 hours since the last administration), the subject will be prompted to complete the Timed Assessments Diary. The Timed Assessments Diary will collect heartburn episode assessments for 3 hours to assess when heartburn relief occurs. The diary will prompt responses 30 minutes after study drug administration is reported and then 1, 1.5, 2, and 3 hours after study drug treatment. The response will indicate presence of heartburn (yes/no) and severity (1=Mild, 2=Moderate, 3=Severe, or 4=Very Severe). If the presence of heartburn is answered as “no” in the diary, the episode of heartburn will be considered to have resolved. Subjects will be allowed to opt out of the timed assessments.

Table 5 Definitions of Heartburn Severity for Time Assessment Diary

None – No heartburn
Mild – Heartburn is present but can be ignored, does not influence daily routine or sleep
Moderate - Heartburn cannot be ignored and/or occasionally daily routine or sleep
Severe - Heartburn regularly influences daily routine or sleep
Very Severe – Heartburn markedly influences daily routine or sleep

11.3.3.3 Data Handling for Evaluable Heartburn for On-Demand Treatment Period

For analysis purposes, diary entries will be assigned to an analysis day and time based on the day the collection interval started for that entry.

For the Heartburn Diary, if heartburn experience is selected as 0 (I am experiencing heartburn right now), the analysis day will be Day x (the collection interval started when the subject opened the diary on Day x). If the heartburn experience is selected as 1 (I need to record an episode of heartburn that occurred within the past day), the analysis day will be Day x-1 (the collection interval started when the subject opened the diary on Day x). The heartburn start time and the study drug intake time collected in the Heartburn Diary entries will be used as the analysis time.

To meet the criteria for the primary endpoint of evaluable heartburn episodes with complete relief within 3 hours and with no further heartburn reported for 24 hours after study drug is taken, the following requirements must be met:

- A completed entry in the Heartburn Diary indicates presence of heartburn and that study drug was taken
- The last timed assessment for the episode indicates no heartburn within 3 hours of the study drug taken time
- No use of rescue antacid is recorded in the Rescue Antacid Diary, within 3 hours of the study drug taken time
- No heartburn episode is recorded in the Heartburn Diary within 24 hours of the study drug taken time

If a subject does not complete all of the timed assessments for an episode (30 minutes and then 1, 1.5, 2, and 3 hours after study drug treatment), the episode will be considered completely

relieved if the last available assessment indicates that the subject no longer has heartburn and the other requirements are met.

For Heartburn Diary, an episode of heartburn reported with a heartburn start time from 06:00 to 21:59 will be used for assessing daytime heartburn and with a heartburn start time from 22:00 to 05:59 will be used for assessing nighttime heartburn.

For heartburn episodes reported during the On-Demand Treatment Period in the Heartburn Diary, the percentage of days with neither daytime nor nighttime heartburn (i.e. 24-hour heartburn free) will be calculated using all days during the On-Demand Treatment Period with at least one Heartburn Diary entry. In order for a day to be considered heartburn free, no episodes of heartburn can be reported for that day and the subject must have completed a Heartburn Diary for that day confirming that the subject has not experienced heartburn.

The percentage of days without daytime heartburn will be calculated using the same method as above using diary entries that reflect daytime symptoms only. The percentage of days without nighttime heartburn during each period will be calculated using the same method as above using diary entries that reflect nighttime symptoms only. For Heartburn diary entries indicating that the subject has not experienced heartburn, records reported between 18:00 to 05:59 will be considered to reflect daytime symptoms and between 06:00 to 17:59 will be considered to reflect nighttime symptoms.

For heartburn symptoms reported during the On-Demand Treatment Period in the Heartburn Diary, the mean severity of daytime and nighttime heartburn for each subject will be calculated by taking the mean of the severity of each heartburn episode divided by the total number of episodes for that subject during the On-Demand Treatment Period.

11.4 PAGI-QOL and PAGI-SYM Scoring

11.4.1 PAGI-QOL

The PAGI-QOL questionnaire includes questions that ask about how some of the gastrointestinal problems the subject may be experiencing may have affected his quality of life. The final version of the questionnaire consists of 30 items, each with response options based on a 6-point Likert scale and with a recall period of the previous 2 weeks. The items are grouped into 5 subscales and a total score, as described in the following table.

PAGI-QOL Subscale	Description	Location on PAGI-QOL eCRF
Daily Activities	10 items related to avoiding or having difficulties with daily activities	Questions 1-10
Clothing	2 items, 1 related to feeling constricted and 1 related to frustration felt about not being able to dress as wanted	Questions 11-12
Diet and Food Habits	7 items related to restrictions made and induced frustrations	Questions 13-19
Relationship	3 items describing the impact of the disease on relationships with their partner, relatives, and friends	Questions 20-22
Psychological Well-being and Distress	8 items describing disease impact on feelings or emotional state	Questions 23-30
PAGI-QOL Total Score	Mean of PAGI-QOL Subscales	Not applicable
Each item is scored by the subject 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, and 5=All of the time.		

The subscales scores will be calculated by taking the mean of the non-missing items in each subscale after reversing the item scores. The subscale scores will range from 0 (lowest QOL) to 5 (highest QOL). Missing data for the subscales will be handled using the half-scale rule, ie, a subscale score will be calculated when ≤50% of the items within a subscale are missing; if >50% of the items within a subscale are missing, the score will be set to missing. The PAGI-QOL total score will be calculated by taking the mean of the corresponding subscales. If any subscale scores are missing, the total score will be set to missing.

Positive changes indicate improved quality of life.

11.4.2 PAGI-SYM

The PAGI-SYM questionnaire includes questions that ask about the severity of symptoms the subject may have related to his gastrointestinal problem. The final version of the questionnaire consists of 20 items, each with response options based on a 6-point Likert scale and with a recall period of the previous 2 weeks. The items are grouped into 6 subscales and a total score, as described in the following table.

PAGI-SYM Subscale	Description	Location on PAGI-SYM eCRF
Nausea/Vomiting	3 items related to severity of nausea, retching, and vomiting	Questions 1-3
Fullness/Early Satiety	4 items related to severity of stomach fullness, ability to finish a meal, feeling full after meals, and loss of appetite	Questions 4-7
Bloating	2 items related to severity of bloating and stomach size	Questions 8-9
Upper Abdominal Pain	2 items related to severity of upper abdominal pain and discomfort	Questions 10-11
Lower Abdominal Pain	2 items related to severity of lower abdominal pain and discomfort	Questions 12-13
Heartburn/Regurgitation	7 items related to severity of heartburn during the day and when lying down, discomfort inside chest during the day and at night, regurgitation during the day and when lying down, and bitter taste in mouth	Questions 14-20
PAGI-SYM Total Score	Mean of PAGI-SYM Subscales	Not applicable
Each item is scored by the subject on a 6-point Likert scale: 0=None, 1=Very Mild, 2=Mild, 3=Moderate, 4=Severe, and 5=Very Severe.		

The subscales scores will be calculated by taking the mean of the non-missing items in each subscale. The items will not be reversed scored prior to calculating the subscale score. The subscale scores will range from 0 (None) to 5 (Very Severe). Missing data for the subscales will be handled using the half-scale rule, i.e., a subscale score will be calculated when ≤50% of the items within a subscale are missing; if >50% of the items within a subscale are missing, the score will be set to missing. The PAGI-SYM total score will be calculated by taking the mean of the corresponding subscales. If any subscale scores are missing, the total score will be set to missing. Negative changes indicate improvement (decreased severity).