Protocol Number: VPED-103

Official Title: A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥ 6 to < 12 Years Who Have Symptomatic Gastroesophageal Reflux Disease

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Phathom Pharmaceuticals, Inc

VPED-103

A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥6 to <12 Years Who Have Symptomatic Gastroesophageal Reflux Disease

11th Jun 2024

Statistical Analysis Plan

Version 1.0

Prepared by:

[redacted] **Biostatistics and Programming**

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Phathom Pharmaceuticals, Inc**
Protocol Number:	**VPED-103**

Document Description:	Final Statistical Analysis Plan
SAP Title:	A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥6 to <12 Years Who Have Symptomatic Gastroesophageal Reflux Disease
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Approved by:

[redacted]

Summary of Changes

Amendment History and Reasons for Amendment

Version	Date	Reasons for Amendment

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
BLQ	below the limit of quantification
BMI	body mass index
CRF	Case Report Form
CTMS	Clinical Trial Management System
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
GERD	gastroesophageal reflux disease
hCG	human chorionic gonadotropin
ICF	informed consent form
IRT	interactive response technology
LAR	legally authorized representative
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	pharmacokinetic
PPI	proton pump inhibitor
PT	preferred Term
PTE	pretreatment event
QD	once daily
QTcB	QT interval from an ECG corrected for heart rate via Bazett's methodology
QTcF	QT interval from an ECG corrected for heart rate via Fredericia's methodology
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
SoE	schedule of events
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

1. Introduction

Vonoprazan belongs to a new class of acid-inhibitory agents called "potassium-competitive acid blockers". Vonoprazan is being developed in adults for the treatment of heartburn in subjects with symptomatic non-erosive gastroesophageal reflux disease (sGERD), 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.

The purpose of this study is to determine a dose of vonoprazan in children aged ≥6 to <12 years with symptomatic GERD that provides an exposure similar to the exposure in adults after administration of vonoprazan 10 mg or 20 mg once daily (QD). Like proton pump inhibitors (PPIs), vonoprazan is expected to provide benefit in pediatric patients with GERD.

The pediatric doses for this study were selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD.

This document outlines the statistical methods to be implemented in the analysis of data collected within the scope of Phathom Pharmaceuticals, Inc., Protocol VPED-103 (A Phase 1, Randomized, Parallel-group, Open-label, Multicenter Study to Evaluate the Pharmacokinetics, Pharmacodynamics and Safety of Vonoprazan (10 or 20 mg Once Daily) in Children Aged ≥6 to <12 Years Who h7ave Symptomatic Gastroesophageal Reflux Disease).

The purpose of this statistical analysis plan (SAP) is to define the planned statistical methods consistent with the study objectives. This plan should be read in conjunction with the study protocol version 3.0 (30 August 2023) and the case report forms (CRFs) version 1.0 (Date: 26 Sep 2023). All analyses will be conducted using SAS® Version 9.4 or higher.

2. Objectives

2.1. Primary Objective

To evaluate the pharmacokinetic profile of vonoprazan (10 or 20 mg QD) in children ≥6 to <12 years of age who have symptomatic GERD.

2.2. Safety Objective

To evaluate the safety of vonoprazan (10 or 20 mg QD) in children ≥6 to <12 years of age who have symptomatic GERD.

2.3. Exploratory Objective

To evaluate symptom relief and pharmacodynamics of vonoprazan (10 or 20 mg QD) in children ≥6 to <12 years of age who have symptomatic GERD.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 1, randomized, open-label, parallel-group, multiple-dose study in children aged ≥6 to <12 years who have symptomatic GERD. Subjects will be screened for up to 28 days. Successfully screened subjects will be randomized to receive 10 or 20 mg of vonoprazan QD for 14 days. Approximately 18 subjects are expected to be enrolled into the study. Blood samples for pharmacokinetic testing will be collected on Days 7 and 14. If deemed clinically indicated by the principal investigator, gastric pH may be monitored for 24 hours on Day -1 and Day 7. The study will include 3 periods:

Screening Period (⩽4 weeks): Subjects will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will be randomized and enter the Treatment Period.
Treatment Period (Day 1 to Day 14): Subjects will be randomized to receive vonoprazan 10 mg or vonoprazan 20 mg QD for 14 days.
Follow-up Period (2 weeks): A safety follow-up phone call will occur 2 weeks after the last dose of study drug to assess adverse events (AEs).

A subject will be considered to have completed the study if the subject completes the Treatment Period and the safety follow-up phone call. Following completion of study drug dosing or early discontinuation, the subject will be transitioned to local standard of care in accordance with each site's prespecified process.

The total duration of the study is up to 8 weeks. The Screening Period is up to 4 weeks, Treatment Period is 2 weeks, and safety follow-up phone call is 2 weeks after last study drug administration.

3.2. Study Endpoints

3.2.1. Pharmacokinetic Assessments

The primary vonoprazan pharmacokinetic endpoints will include the following parameters for each subject estimated from a population PK model:

- Maximum observed drug concentration at steady state ($C_{max,ss}$)
- Area under the plasma concentration-time curve during the dosing interval τ (AUC_{τ})
- Apparent oral clearance (CL)
- Apparent volume of distribution (V_c)

3.2.2. Efficacy and Pharmacodynamic Assessments

Efficacy and pharmacodynamic characteristics will be assessed by the following:

- The severity of GERD symptoms at baseline and Days 7 and 14 as assessed by the investigator.

- Mean pH and percentage of time above pH 4, 5, and 6 at baseline (Day -1) and Day 7 in the subset of subjects for whom intragastric pH monitoring is performed when clinically indicated per the investigator.

3.2.3. Safety Assessments

Safety will be assessed by the following:

- AEs
- Laboratory test values (hematology, serum chemistry, urinalysis)
- Electrocardiograms
- Vital signs

3.3. Treatments

The pediatric doses for this study were selected to approximate equivalent adult exposures following administration of vonoprazan 10 or 20 mg QD in pediatric subjects ≥6 to < 12 years of age. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to 1 of the following 2 groups during the Treatment Period:

- Vonoprazan 10 mg QD for 14 days
- Vonoprazan 20 mg QD for 14 days

4. General Statistical Considerations

In general, descriptive statistics will be presented by treatment group and by visit, as applicable. Continuous data will be summarized using descriptive statistics (i.e., n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be summarized using the subject count and percentage in each category. Non-zero percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported up to a maximum of 3 decimal places. Mean and median will be displayed to one level of precision greater than the data collected up to a maximum of 3 decimal places. Standard deviation and standard error (SE) will be displayed to two levels of precision greater than the data collected up to a maximum of 3 decimal places. When count data are presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for missing values. The denominator for all percentages will be the number of subjects in that treatment group within the population of interest, unless otherwise specified. Refer to Appendix 1 for imputation rules for partial and missing AE onset dates as well as partial and missing prior/concomitant medication start and end dates. Data will be displayed in all listings sorted by treatment group.

4.1. Sample Size

Approximately 18 subjects are expected to be enrolled with 9 subjects in each dose group. Attempts will be made to enroll subjects across the ≥6 to < 12 years age range. Because this is a pharmacokinetic and safety trial with no comparator, there is no power determination affecting the sample size. The sample size of approximately 18 subjects is considered sufficient to assess the pharmacokinetics, safety, and tolerability of vonoprazan in this population. Fewer subjects may be enrolled based on preliminary data, if considered sufficient to adequately characterize the PK profile.

4.2. Randomization, Stratification, and Blinding

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in a 1:1 ratio to 1 of the following 2 groups during the Treatment Period:

- Vonoprazan 10 mg QD for 14 days
- Vonoprazan 20 mg QD for 14 days

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

This is an open-label study.

4.3. Study Day and Study Start Date

The screening period for the study will be from Day -28 to Day -1. The treatment period will be from Day 1 to Day 14 where the final Visit will be on Day 14. The Safety Follow Up period will be from Day 15 to Day 28.

For this study, Day 1 is defined as the day of the first dose of study drug. For assessments done on or after Day 1, study day is defined as assessment/event date – Day 1 + 1. For assessments done before Day 1, study day is defined as assessment/event date – Day 1.

4.4. Analysis Sets

4.4.1. Screened Set

The Screened Set will include all subjects whose legally authorized representative (LAR) signed the study informed consent form (ICF).

4.4.2. Enrolled Set

The Enrolled Set will include all subjects whose LAR signed the study ICF and have been randomized.

4.4.3. Pharmacokinetic Set

The Pharmacokinetic (PK) Set will include subjects who receive at least 1 dose of study

drug and have sufficient concentration data to support accurate estimation of at least 1 pharmacokinetic parameter. Where subjects experience issues which may affect exposure to study drug (e.g., emesis, dosing errors, etc.), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK population on a case-by-case basis. All subjects excluded from the PK population will be documented in the data listings.

4.4.4. Pharmacodynamic Set

The Pharmacodynamic (PD) Set will include subjects who receive at least 1 dose of study drug and have sufficient pH data to support calculation of pharmacodynamic parameters.

4.4.5. Safety Set

The Safety Set will include all subjects who receive at least 1 dose of study drug.

4.5. Visit Windows

All data summarized by visit will be based on the nominal 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. Subject Disposition

5.1. Disposition

Disposition will be summarized for all enrolled subjects by treatment and overall. The number and percentage of subjects who have been treated (i.e., Safety Set), have completed the study treatment, have completed the study, have discontinued from the study treatment, have discontinued from the study, as well as the primary reason for study treatment discontinuation and study discontinuation (if applicable) will be tabulated.

Screen failures are defined as subjects whose LAR signs the ICF to participate in the clinical study but are not subsequently entered in the Treatment Period of the study. The number and percentage of screened, enrolled, and screen failure subjects, as well as the primary reason for screen failure will be tabulated for all screened subjects. Subjects who fail screening and the reasons for screen failure will be listed for all screen failure subjects. Additionally, a summary of the analysis sets will be provided to include the number and percentage of subjects in each analysis set by treatment group and overall. Subject disposition and analysis sets will also be presented in a listing.

5.2. Protocol Deviations

Protocol deviations will be recorded within the [redacted] Clinical Trial Management System (CTMS) and undergo cross-functional team review prior to database lock. In addition, protocol deviation classification (i.e., significant vs. not significant) as determined by Phathom Pharmaceuticals, Inc. prior to database lock will be documented in CTMS.

The number and percentage of subjects with significant protocol deviations will be summarized by CTMS activity subtype, treatment group and overall using the Safety Set. Individual subject protocol deviations, both significant and non-significant, will be presented in a data listing using the Enrolled Set.

6. Demographics and Baseline Characteristics

6.1. Demographics

Baseline demographics will be summarized by treatment and overall, for all subjects in the Safety Set and Pharmacokinetic Set. Baseline demographic data to be evaluated will include age, sex, race, ethnicity, fertility status, height (cm), weight (kg) and body mass index (BMI) (kg/m^2) . Descriptive statistics will be presented for age, height, weight and body mass index. Sex, race, ethnicity, body mass index category, fertility status and Tanner staging will be summarized categorically. Demographic and baseline characteristics data will be listed for all subjects in the Safety Set.

6.2. Medical History

Medical history will be summarized by treatment and overall, for all subjects in the Safety Set. Medical history data will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The dictionary version used for reporting the study will be described in the relevant table and listing footnotes. Percentages will be calculated based on the number of subjects in the Safety Set. Medical history will be coded using MedDRA Version 23.0 or higher.

Medical history data including specific details will be presented in a listing.

6.3. Inclusion and Exclusion Criteria

The details of Inclusion and Exclusion criteria are listed in Section 4.1.1 and 4.1.2 of the protocol. All inclusion/exclusion criteria related information for enrolled subjects will be presented in a data listing. The listing will include those failed inclusion/exclusion criteria.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All medications will be coded according to the World Health Organization Drug Dictionary (WHODrug Global), Version March 2021 or later.

A prior medication is defined as any medication that is taken prior to the first dose of study drug. A concomitant medication is defined as any medication taken on or after the first dose of study drug.

The total number of both prior/concomitant medications and the number and percentages of subjects with at least one prior/concomitant medication will be summarized. The number

and percentages of all prior/concomitant medications will be summarized and listed by Anatomical Therapeutic Chemical (ATC) level 4 and preferred term. Algorithms for imputing partially missing start or end dates are included in Appendix 1. If the start date of a medication is completely missing and the end date is before dosing of study drug on Day 1, it will be counted as a prior medication. If the start date of a medication is completely missing and the end date is after dosing of study drug on Day 1, it will be counted as both prior and concomitant medication. If the start date of a medication is on or after the dose of study drug on Day 1 and the end date of the medication is completely missing, it will be counted as a concomitant medication.

All summaries will be performed using the Safety Set. All prior and concomitant medications will be presented in a listing for subjects in the Safety Set .

7.2. Study Drug

The study drug details related to study drug administration and accountability will be listed for each subject in the Safety Set.

7.3. Study Treatments

7.3.1. Extent of Exposure

Duration of exposure is defined as the total number of days a subject is exposed to any study drug and will be presented as the total number of days from the first dose date and time (Day 1) to the last dose date and time (date of last known study drug administration minus the date and time of first dose + 1) as recorded on the End of Study page on the eCRF. If the last dose date and time on the End of Study page is missing, then the last dose date and time recorded on the Study Drug Administration page on the eCRF will be used. The number of days of missed doses will be summarized in the same table as well. Duration of exposure and number of days of missed doses will be categorized into time intervals and frequency counts and percentages will be presented for the number (%) of subjects in each interval. Percentages will be computed from the number of subjects in the Safety Set. A listing on Extent of Exposure will also be presented.

7.3.2. Treatment Compliance

Treatment compliance overall and by treatment will be summarized using descriptive statistics. For each subject, the compliance will be calculated as the total number of actual doses divided by the total number of planned doses.

8. Efficacy Analysis

8.1. Pharmacokinetic analyses

A population PK model will be used to analyze the plasma concentration data, estimate pharmacokinetic parameters, and address the primary objective of this study. The planned analyses will be included in a separate document.

Blood samples will be collected at the following time points for PK assessment using a population PK approach:

> Day 7: Pre-dose (prior to morning administration of Vonoprazan) and at 0.5 to 1.5, and 2.5 to 3.5, hours after drug administration.
> Day 14: Pre-dose (prior to morning administration of Vonoprazan) and at 1 to 2 and 3 to 4 hours after drug administration

Individual plasma concentrations will be presented in data listings with their scheduled collection times.

8.2. Exploratory analyses

8.2.1. GERD Symptom Assessment

The GERD Symptom Assessment-Investigator scale evaluates 4 symptoms of GERD: heartburn, vomiting, acid regurgitation, and trouble eating. The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit, Day 7 and Day 14 will be assessed. The severity for each symptom will be recorded as either none, mild, moderate, severe or very severe. The severity of GERD symptoms at baseline, Day 7 and Day 14 as assessed by the investigator will be summarized overall and by treatment group. GERD Symptom Assessment and GERD diagnostic testing will be listed for the Safety Set.

8.2.2. Pharmacodynamic Assessment

Mean pH and percentage of time above pH 4, 5, and 6 at baseline (Day -1) and Day 7 will be summarized for the subset of subjects for whom intragastric pH monitoring is performed when clinically indicated per the investigator.

The investigator reported clinical criteria that supported the need for 24-hour gastric pH monitoring in individual subjects will be presented in a data listing.

The pharmacodynamic assessments will be analyzed for the Pharmacodynamic Set.

9. Safety Analysis

Safety will be assessed based on AEs, vital sign measurements, electrocardiogram (ECG) results, and clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis). All safety analyses will be conducted for the Safety Set.

9.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality or relationship to the drug. A treatment-emergent adverse event (TEAE) is defined as any event that occurs after the first dose of study drug or any event at baseline that worsens in either intensity or frequency after the first dose of study drug in that period. A pretreatment adverse event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject whose informed consent to participate in a study has been signed, which has occurred prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

Overall TEAEs 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 Events of Special Interest
- 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 will only be 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 SOC, then the subject will be counted only once with the greatest severity or relationship at the SOC 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 by treatment in the following ways:

- by primary SOC and preferred term
- by primary SOC, preferred term and maximum severity
- by primary SOC, preferred term and relationship to study drug

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

- by primary SOC, preferred term and maximum severity

The number and percentage of subjects as well as the number of events (except deaths) with the following types of events will be summarized by primary SOC, preferred term and treatment group:

- Adverse events leading to treatment discontinuation.
- Adverse events leading to study discontinuation.
- Serious Adverse Events (SAEs)
- Deaths

All adverse events will be included in a listing using the Safety Set. Pre-treatment AEs will be listed using the Screened Set. TEAEs and serious AEs will be listed using the Safety Set. In addition, the following select adverse events will be displayed in separate listings:

- 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 that are in one of the AESI categories presented in Table 1 will be summarized by AESI category, primary SOC and preferred term. 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
Clostroides 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, including hypersensitivity	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)
Acute interstitial nephritis/tubulointerstitial nephritis	Tubulointerstitial nephritis (PT)

Hematologic abnormalities	Haematopoietic cytopenias SMQ Haematopoietic cytopenias affecting more than one type of blood cell SMQ (Broad) Haematopoietic erythropenia SMQ (Broad) Haematopoietic leukopenia SMQ (Broad) Haematopoietic thrombocytopenia SMQ (Broad) In addition, 10 PTs not encompassed by these SMQs but associated with possible thrombocytopenia, leukopenia, cytopenia, and agranulocytosis will be included. Disseminated intravascular coagulation Henoch-Schonlein purpura Immune thrombocytopenic purpura Neutropenic colitis Neutropenic infection Neutropenic sepsis Platelet function test abnormal Thrombocytopenic purpura Thrombophlebitis septic Thrombotic thrombocytopenic purpura
Hypersensitivity reactions (anaphylaxis)	Hypersensitivity SMQ (narrow)

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

9.2. Clinical Laboratory Evaluations

Safety lab parameters, including clinical chemistry, hematology and urinalysis will be presented at Screening, Day 7 and 14.

Descriptive statistics for clinical laboratory values (hematology, chemistry and urinalysis laboratory tests) will be presented. 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 study will be presented. Results of clinical laboratory values will be categorized as low, normal, or high according to laboratory range specifications. Shifts from baseline to each scheduled post-baseline time point will be presented to show the number and percentage of subjects in each category by parameter.

9.2.1. Clinical Chemistry

Abnormal liver function tests are defined as liver test values that meet at least one of the criteria listed below. 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

- ALT or AST >3xULN and a 2-fold increase above baseline for subjects with normal baseline ALT or AST levels
- ALT or AST > 8xULN for subjects with normal baseline ALT or AST levels

9.2.2. Urinalysis

Microscopic urinalysis results will be listed only. All laboratory data test results will be included in data listings.

9.3. Vital Sign Measurements

Summary tables will be presented by treatment for vital sign data, including height (cm), weight (kg), heart rate (beats/min), sitting systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg), respiratory rate (breaths/min), and temperature (C) in the Safety Set. Observed results and change from baseline to each scheduled post-baseline time point will be presented. Change from baseline will only be calculated for subjects having non-

missing baseline and post-baseline measurements. All vital signs data will be presented in a listing.

Abnormal vital sign values are defined as vital sign values that meet one of the criteria listed below. 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):
  - <85
  - >130
- Diastolic blood pressure (mmHg):
  - <55
  - >85
- Heart rate (bpm):
  - <60
  - >120

9.4. Physical examination

All data collected from physical examinations assessment must be available in the source documents but will not be added to the analysis database. Documentation of the completion of physical examinations will be presented in a listing.

9.5. Electrocardiogram results

An overall 12-lead ECG interpretation (Normal, Abnormal – Not Clinically Significant, Abnormal –Clinically Significant) will be available based on central reading of ECG data. Shifts from baseline to each scheduled post-baseline time point will be presented to show the number and percentage of subjects in each category by treatment for subjects in the Safety 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 using the Safety 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 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

Results for ECG parameters heart rate, R-R interval, P-R interval, QRS interval, QT interval, QTcB interval, QTcF interval and interpretation will be listed using the Safety Set.

9.6. Pregnancy test

Pregnancy test results will be presented in a listing for the Safety Set.

10. Interim Analysis/Other Analysis

10.1. Interim Analysis

No formal interim analyses will be performed in this study.

11. Changes in the Planned Analysis

Not Applicable

12. Appendices

12.1. Appendix 1: Imputation Algorithm for Partial and Missing Dates

12.1.1. Rules for Concomitant Medication Start Date Imputation

The following rules will be applied to impute the missing numerical fields. 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.

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.

12.1.2. Rules for Concomitant Medication End Date Imputation

The following rules will be applied to impute the missing numerical fields. 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 (e.g., 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.

12.1.3. 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 12.1.1.

12.1.4. 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 12.1.1. Incomplete stop dates will not be imputed.

12.2. Appendix 2: Schedule of Events

	Screening Period		Treatment Period					Final Visit	Safety FU	
Timing	**Day -28 to Day -2**	**Day-1 [a]**	**Day 1**	**Phone Call Day 6**	**Day 7**	**Day 8 [a]**	**Phone Call Day 13**	**ET Day 14**	**Phone Call Day 28**	**Unscheduled Visit [b]**
Visit Number:	1	2	3	4	5	6	7	8	9	
Informed consent [c]	X									
Inclusion/exclusion criteria	X	X	X							
Demographic and medical history	X									
Physical examination [d]	X				X			X		X
Vital signs [e]	X		X		X			X		X
Weight and height [f]	X				X			X		
Prior/Concomitant medications	X	X	X		X	X		X	X	X
Concurrent medical conditions	X									
Hepatitis B and C; HIV [g]	X									
Clinical laboratory tests [h]	X				X			X		X
Pregnancy test [i]	X		X		X			X		
Guidance on avoidance of pregnancy [i]	X		X		X			X		
12-lead electrocardiogram [j]	X							X		
GERD Symptom Assessment-Investigator	X				X			X		
Randomization [k]			X							
Dispense study drug [l]			X		X					
Study drug administration [l]			X		X			X		
Gastric pH monitoring [a]		X	X		X	X				
PK blood sample collection					X			X		

Day 7: pre-dose, 0.5 to 1.5 hour and 2.5 to 3.5 hours post dose. Day 14: pre-dose, 1 to 2 hours, and 3 to 4 hours post dose. [m]										
Drug return/accountability					X			X		
Telephone call to subject				X			X		X	
AE/pretreatment event assessment [n]	X	X	X		X			X	X	X

AE: adverse event; ET: early termination; FU: follow-up; GERD: gastroesophageal reflux disease; HIV: human immunodeficiency virus; PK: pharmacokinetic; PTE: pretreatment event

a. For subjects participating in the pharmacodynamic substudy, Visit 2 (Day -1) and Visit 6 (Day 8) are only required for subjects undergoing gastric pH monitoring if clinically indicated at select sites. pH monitoring will be conducted on Day -1 for 24 hours and on Day 7 for 24 hours. pH probes would be placed on Days -1 and 7 and removed on Days 1 and 8.
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. Informed consent will be signed by the subject's legally authorized representative prior to any activity in the study. Subject assent (if applicable) may be obtained as required per site guidelines.
d. A complete physical examination will be performed at screening (at minimum, assessment of skin, cardiovascular, respiratory, gastrointestinal, neurological systems and Tanner staging). A brief physical examination will be performed at other visits (at minimum, assessment of skin, cardiovascular, respiratory, and gastrointestinal systems). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.
e. Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.
f. Height collected only at screening.
g. Hepatitis B surface antigen, hepatitis C virus antibody, and HIV type 1 and 2 antibodies.
h. Clinical laboratory testing will include hematology, serum chemistry, and urinalysis. Glucose will be obtained after an 8-hour fast at all visits. Blood draws should follow vital signs or electrocardiograms.
i. Only female subjects who have reached menarche, will require guidance on avoidance of pregnancy and urine or serum hCG; if urine hCG is positive, confirm with serum hCG.
j. Single 12-lead electrocardiogram recordings will be made after the subject has been in the supine position for at least 5 minutes at screening. A pediatric cardiologist will interpret the ECG for eligibility and any abnormality. A single repeat measurement is permitted at screening for eligibility determination after the read by a pediatric cardiologist. Assessments should include comments on whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant. An ECG will be collected at the final visit and interpreted by a pediatric cardiologist.
k. Subject will be randomized to study treatment after all eligibility criteria have been met.
l. Study drug will be dispensed and administered in the clinic on Days 1, 7, and 14. Study drug should be taken every day between 7 and 10 am preferably prior to eating any breakfast or food. Study drug for at home administration will be dispensed on Day 1 (to be taken on Days 2 to 6) and Day 7 (to be taken on Days 8 to 13). At home, parents/caregivers will administer study drug to subjects. Clinic staff will review instructions with parents/LARs for administering study drug at home and completing the Study Drug Reminder Card. Phone call reminders may be conducted as required.
m. Blood samples for PK analysis of vonoprazan in plasma will be collected on Days 7 and 14. On Day 7 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 0.5 to 1.5 hours post-dose and one between 2.5 to 3.5 hours post-dose. On Day 14 days, one pre-dose sample will be collected prior to the morning administration of vonoprazan along with two additional samples collected after drug administration: one between 1 to 2 hours post-dose and one 3 to 4 hours post-dose. The exact time of each pharmacokinetic sample should be recorded in the source and eCRF. If a subject terminates early, an attempt should be made to collect one blood sample if it can be collected within 24 hours following the last dose of study drug. The exact date and time of the early termination sample must be recorded.
n. Collection of pretreatment events will start after the informed consent form has been signed. Adverse events will be assessed from time of informed consent signing until the follow-up visit and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

12.3. Appendix 3: GERD Symptom Assessment-Investigator

The following 4 symptoms of GERD will be evaluated.

Symptom	Definition
Heartburn	Hurting or burning in the stomach, chest or throat
Vomiting	Something coming out of your mouth (throw-up)
Acid regurgitation	Food come up from your stomach to your mouth
Trouble eating	Ate less than usual, did not want to eat, did not want to eat certain foods because of hurting or burning

The following 4 symptoms of GERD will be evaluated, as defined below when asked of parents of children 6 to 8 years of age if the child reported or they observed any of the following behaviors.

Symptom	Definition
Heartburn	Hurting or burning in the stomach, chest or throat such as holding his/her stomach/chest/throat, lying in curled up position, crying, acting fussy, or other behaviors
Vomiting	Something coming out of the mouth
Acid regurgitation	Partially digested food or stomach contents coming up in their mouth
Trouble eating	Refused to eat anything, ate less than usual, refused to eat certain foods because of hurting or burning or stomach contents coming up in their mouth

The maximum severity of each GERD symptom occurring during the 7 days prior to the study visit will be assessed as detailed below.

Severity	Definition
None	No symptom
Mild	Symptom did not last long and was easily tolerated
Moderate	Symptom caused discomfort and/or interrupted usual activities (including sleep)
Severe	Symptom caused great interference with usual activities and may have been incapacitating (including sleep)
Very severe	Symptom caused intense and constant discomfort and/or marked interference with usual activities (including sleep)