Protocol Number: VPED-105

Official Title: A Phase 1, Open-label, Randomized, Single-dose, 5-Period Crossover Study to Determine The Bioavailability Of Two Vonoprazan Orally Disintegrating Tablet Formulations Administered Without Water or Mixed With Water And Administered Via A Syringe Relative To The Vonoprazan Tablet In Healthy Subjects

NCT Number: NCT06831344

Document Date: 10 December 2024

CLINICAL STUDY PROTOCOL
IND NUMBER: [redacted]

A Phase 1, Open-label, Randomized, Single-Dose, 5-Period Crossover Study to Determine the Bioavailability of Two Vonoprazan Orally Disintegrating Tablet Formulations Administered Without Water or Mixed With Water and Administered via a Syringe Relative to the Vonoprazan Tablet in Healthy Subjects

PROTOCOL NO. VPED-105

Sponsor:	Phathom Pharmaceuticals, Inc. 2150 East Lake Cook Road, Suite 800 Buffalo Grove, IL 60089 USA
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Version of Protocol:	Version 1.0
Date of Protocol:	10 December 2024

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R3): Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 1, Open-Label, Randomized, Single-Dose, 5-Period Crossover Study to Determine the Bioavailability of Two Vonoprazan Orally Disintegrating Tablet Formulations Administered Without Water or Mixed With Water and Administered via a Syringe Relative to the Vonoprazan Tablet in Healthy Subjects
Protocol Number	VPED-105
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PROTOCOL ACCEPTED AND APPROVED BY PHATHOM PHARMACEUTICALS:

[redacted]

10-Dec-2024 | 14:29 PST

Date

10-Dec-2024 | 16:32 CST

Date

10-Dec-2024 | 16:31 CST

Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 1, Open-Label, Randomized, Single-Dose, 5-Period Crossover Study to Determine the Bioavailability of Two Vonoprazan Orally Disintegrating Tablet Formulations Administered Without Water or Mixed With Water and Administered via a Syringe Relative to the Vonoprazan Tablet in Healthy Subjects" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 1.0, dated 10 December 2024, the International Council for Harmonisation harmonised tripartite guideline E6(R3): Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Phathom Pharmaceuticals, Inc. or implement protocol changes without Institutional Review Board approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a subinvestigator.

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

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

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number: VPED-105

Title: A Phase 1, Open-Label, Randomized, Single-Dose, 5-Period Crossover Study to Determine the Bioavailability of Two Vonoprazan Orally Disintegrating Tablet Formulations Administered Without Water or Mixed With Water and Administered via a Syringe Relative to the Vonoprazan Tablet in Healthy Subjects

Sponsor: Phathom Pharmaceuticals, Inc.
2150 East Lake Cook Road, Suite 800
Buffalo Grove, IL 60089 USA

Study Phase: 1

Study Sites: 1 site in the United States (US)

Indication: Not applicable

Rationale: Vonoprazan tablets are approved in the US for the healing of all grades of erosive esophagitis (EE) and relief of heartburn associated with EE, to maintain healing of all grades of EE and relief of heartburn associated with EE, for the relief of heartburn associated with non-erosive gastroesophageal reflux disease (GERD), and in combination with amoxicillin or in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* infection in adults.

Phathom is developing an orally disintegrating tablet (ODT) formulation as an alternate formulation for the pediatric population and adults with difficulty swallowing tablets.

The purpose of this study is to determine the bioavailability (BA) of two vonoprazan ODT formulations (ODT-1 and ODT-2) administered without water or mixed with water and administered via a syringe relative to the vonoprazan tablet.

Objectives:

Primary:

- To assess the BA of a single oral dose of the vonoprazan ODT-1 or ODT-2 administered without water or mixed with water and administered via a syringe relative to the vonoprazan tablet in healthy subjects.

Secondary:

- To assess the pharmacokinetic (PK) profile of a single oral dose of vonoprazan when administered to healthy subjects as the ODT-1 or ODT-2 administered without water or mixed with water and administered via a syringe relative to the tablet.

Safety:

- To assess the safety and tolerability of a single oral dose of vonoprazan when administered to healthy subjects as ODT-1, ODT-2, or the tablet.

Study Population: Healthy adult subjects, aged 18 to 55 years, inclusive

Study Design: This is a Phase 1, randomized, open-label, single-dose, 5-period, 5-sequence crossover study designed to assess the BA of the vonoprazan ODT-1 or ODT-2 administered without water or mixed with water and administered via a syringe relative to the vonoprazan tablet in healthy subjects.

The study will include a Screening Period, 5 Treatment Periods and a Follow-up Period:

Screening Period: 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 Periods.

Treatment Periods: Subjects will be randomly assigned to 1 of 5 treatment sequences in a 1:1:1:1:1 ratio to receive the following:

- **Treatment A:** Vonoprazan 10 mg ODT-1 without water
- **Treatment B:** Vonoprazan 10 mg ODT-1 mixed with water and administered via a syringe
- **Treatment C:** Vonoprazan 10 mg ODT-2 without water
- **Treatment D:** Vonoprazan 10 mg ODT-2 mixed with water and administered via a syringe
- **Treatment E (reference):** Vonoprazan 10 mg tablet

The treatment periods will include administration of single doses of vonoprazan 10 mg on Day 1 of each period. There will be a washout interval of a minimum of 5 days between study drug dosing in each period.

PK samples will be collected through 48 hours following dosing, and safety endpoints will be evaluated throughout the study.

Follow-up Period: A safety follow-up phone call will occur on Day 28 (±2 days) to assess adverse events (AEs).

A subject will be considered to have completed the study if the subject completes all Treatment Periods and the safety follow-up phone call.

Estimated Study Duration: The Screening Period is up to 28 days. Subjects will be confined to the clinical unit from Day –1 until discharge on Day 23. A follow-up

	telephone call will occur on Day 28 (±2 days). The duration of the study, excluding Screening will be approximately 28 days.
Pharmacokinetic Assessments:	The primary vonoprazan PK endpoints will include the following PK parameters: • Maximum observed drug concentration (C_{max}) • Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration (AUC_{0-t}) • Area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{0-inf}) The secondary PK endpoints will include t_{max}, t_{lag}, λ_z, $t_{1/2}$, CL/F, and V_z/F.
Safety Assessments:	Safety will be assessed by the following: • AEs • Laboratory test values (hematology, serum chemistry, urinalysis) • Electrocardiograms • Vital signs
Study Drug, Dosage, and Route of Administration:	Open-label vonoprazan ODT-1, ODT-2 or tablets will be administered orally. Vonoprazan ODT-1 and ODT-2 will be administered without water or mixed with 5 mL of room temperature water and administered via a syringe. Vonoprazan tablets will be administered with 240 mL of room temperature water. All study drug doses will be taken after a 10 hour fast.
Sample Size:	This crossover study will enroll 25 subjects. The study will provide at least 95% power to conclude bioequivalence between a test treatment (A, B, C, or D) and the reference treatment (E). This assumes that the vonoprazan PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} are log-normally distributed, there is no more than a 5% difference between the true geometric means of a pair of treatments, and the intrasubject coefficient of variation is no greater than 16%. The sample size allows for up to 5 dropouts in the study. Subjects will be randomly assigned to 1 of 5 treatment sequences in a 1:1:1:1:1 ratio.
Statistical Methods:	<u>Pharmacokinetic Endpoints:</u> Individual PK parameter estimates will be summarized descriptively by vonoprazan treatment. A linear mixed model with fixed effects for treatment, sequence, and period and subject within sequence as a random effect will be performed on the natural log-transformed values of AUC_{0-t}, AUC_{0-inf}, and C_{max}. The ratio of geometric least square means (Treatment A, Treatment B,

Treatment C, and Treatment D versus Treatment E) and corresponding 90% CIs will be computed for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}, by taking the antilog of the difference of the least squares means and associated 90% confidence interval (CI) from the linear mixed effect model analyzing the natural logarithms of the corresponding PK parameters. No adjustment will be made for multiplicity.

Relative BA will be reported as the test to reference ratios (A/E), (B/E), (C/E) and (D/E) of the geometric means and their corresponding CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} PK parameters. Bioequivalence will be concluded if the 90% CI for the geometric mean ratio (GMR) between the test treatment (A, B, C, D) and the reference treatment (E) are wholly contained within 0.80 and 1.25 for the vonoprazan PK parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$.

Nonparametric methods will be used to examine median differences in t_{max} for vonoprazan.

Safety:

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

Clinical laboratory tests, electrocardiograms, and vital signs will be summarized with descriptive statistics at each time point by treatment group.

Version and Date of Protocol: Version 1.0
10 December 2024

List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
BA	Bioavailability
BLQ	Below the limit of quantification
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	apparent oral clearance
C_{max}	maximum observed drug concentration
COVID-19	coronavirus disease 2019
CV	Coefficient of variation
CYP	cytochrome P450
ECG	Electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
eGFR	estimated glomerular filtration rate
EOS	End of study
ET	Early termination
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
GMR	geometric mean ratio
H+, K+-ATPase	hydrogen, potassium–adenosine triphosphatase
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
λ_z	terminal elimination rate constant
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
ODT	Orally disintegrating tablet
PCAB	potassium-competitive acid blocker
Phathom	Phathom Pharmaceuticals, Inc.
PK	pharmacokinetic
PPI	Proton pump inhibitor
PTE	pretreatment adverse event
QD	once daily
RBC	Red blood cell
SAE	serious adverse event
SD	standard deviation
SGPT	serum glutamic-pyruvic transaminase
SGOT	serum glutamic-oxaloacetic transaminase
SoE	schedule of events
SARS-Cov-2	severe acute respiratory syndrome coronavirus 2
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal phase half-life
Takeda	Takeda Pharmaceutical Company Limited
TEAE	treatment-emergent adverse event
t_{lag}	time until first measurable concentration in plasma

Abbreviation	Definition
t_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution
WBC	White blood cell

1 Introduction

Vonoprazan belongs to a new class of gastric acid secretion inhibitory agents called potassium-competitive acid blockers (PCABs). In the United States (US), vonoprazan tablets are approved for the healing of all grades of erosive esophagitis (EE) and relief of heartburn associated with EE, to maintain healing of all grades of EE and relief of heartburn associated with EE, for the relief of heartburn associated with non-erosive gastroesophageal reflux disease (GERD), and in combination with amoxicillin or in combination with amoxicillin and clarithromycin for the treatment of *Helicobacter pylori* infection in adults.

In countries other than the US, vonoprazan has been studied in other gastric acid-related diseases such as healing of gastric ulcer and duodenal ulcers, and for the prevention of recurrence of gastric or duodenal ulcer during nonsteroidal anti-inflammatory drug or aspirin administration. Vonoprazan has received regulatory approval in Japan, Russia, and other countries in Asia and Latin America for a variety of indications.

Phathom Pharmaceuticals, Inc. (Phathom) licensed the exclusive rights from Takeda Pharmaceutical Company Limited (Takeda) to develop, manufacture, and commercialize vonoprazan in the US, Europe, and Canada. Phathom is developing an orally disintegrating tablet (ODT) formulation as an alternate formulation for the pediatric population and adults with difficulty swallowing tablets.

1.1 Study Rationale

The purpose of this study is to determine the bioavailability (BA) of two vonoprazan ODT formulations (ODT-1 and ODT-2) administered without water or mixed with water and administered via a syringe relative to the vonoprazan tablet.

The study will be conducted in accordance with the FDA Guidance for Industry (April 2022): "*Bioavailability Studies Submitted in NDAs or INDs – General Considerations"*. The use of healthy adult subjects is appropriate for the BA study.

Relative BA will be based on the maximum observed drug concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), and AUC from time 0 extrapolated to infinity (AUC_{0-inf}). The pharmacokinetic (PK) profile following administration of the vonoprazan ODTs will be characterized relative to that of the vonoprazan tablet.

1.2 Background

1.2.1 Vonoprazan

The gastric hydrogen, potassium–adenosine triphosphatase (H+, K+-ATPase), also known as the proton pump, is responsible for acid secretion from parietal cells in the stomach. It is inactive in the cytosol but relocates from the cytosol to the secretory membrane of the parietal cells when food is present in the stomach, thereby becoming active and pumping H+ ions out of the cells and into the canaliculi in exchange for K+ ions. It represents an attractive pharmacological target since it is the final step of the acid secretion process.

Two classes of pharmaceuticals, with distinct mechanisms of action for inhibiting the gastric proton pump, have been developed for clinical application: Proton pump inhibitors (PPIs) and PCABs. As a PCAB, vonoprazan has a unique mechanism of action and pharmacokinetics relative to PPIs:

- Acid activation and stability: Conventional PPIs are prodrugs, which are activated by acid and covalently bind to the H+, K+-ATPase; however, activated PPIs are not stable in acidic conditions. In contrast, vonoprazan does not require acid activation, is stable in acidic conditions, and has a more durable effect. Further, vonoprazan is rapidly protonated in the parietal cell canaliculi, which concentrates the drug proximal to the H+, K+-ATPase [Scarpignato 2019].

- Activity against proton pumps: Vonoprazan inhibits acid secretion by competitively inhibiting the binding of potassium ions to the H+, K+-ATPase. Vonoprazan may selectively concentrate in the parietal cells in both the resting and stimulated states and binds to the active pumps in a noncovalent and reversible manner. In contrast, PPIs covalently bind H+, K+-ATPase only when the pump is active, as an acidic environment is required for the activation and accumulation of PPIs in the parietal cell [Scott 2015].

- Vonoprazan maintains acid control over 24 hours with once daily (QD) dosing [Engevik 2020]. Vonoprazan can also be dosed in the presence or absence of food, while most PPIs require dosing before a meal to optimize their acid suppressant effect because activated pumps are at their highest level post-prandially due to activation of pumps by the meal [Shin 2013].

- Extended half-life: The mean plasma half-life is typically 7 to 8 hours after single and multiple QD administration of vonoprazan 20 mg (TAK-438_107). This is significantly longer than the half-life of conventional PPIs (<2 hours) [Shin 2013].

- Metabolism: Vonoprazan is metabolized by a combination of cytochrome P450 (CYP) isoforms including CYP3A4/5, which does not have a high degree of genetic polymorphism as compared with CYP2C19, which is the primary enzyme responsible for the metabolism of PPIs [Shin 2013].

These unique aspects of the vonoprazan mechanism of action and pharmacokinetics relative to PPIs translate into greater magnitude and duration of gastric acid suppression, which are reflected in the pharmacodynamic profile [Jenkins 2015; Sakurai 2015; Laine 2022].

The efficacy and safety of vonoprazan for the healing of all grades of EE and relief of heartburn associated with EE, to maintain healing of all grades of EE and relief of heartburn associated with EE and for relief of heartburn associated with non-erosive GERD has been established in adults. The most common adverse events were gastritis, diarrhea, abdominal distention, abdominal pain, nausea, dyspepsia, constipation, hypertension, and urinary tract infection [VOQUEZNA 2024].

Vonoprazan has been studied in an extensive nonclinical pharmacology and toxicology program as well as in a large global clinical program in multiple indications. The nonclinical pharmacology data are consistent with the pharmacological effect observed in humans. The nonclinical toxicology studies support repeated doses up to 40 mg in humans without significant toxicology findings. The safety profile of vonoprazan in Phase 3 studies of adults across indications showed no evidence of a dose-related increase in adverse effects with vonoprazan from 5 mg to 40 mg QD. As of 25 December 2023, the global cumulative post-marketing patient exposure to vonoprazan is estimated to be approximately 129 million patients.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.3 Justification for Dose

A single 10 mg dose of vonoprazan was selected because this is the highest currently developed ODT dosage strength. Oral dosing will be used as this is the intended route of

clinical administration for both vonoprazan formulations. Multiple oral doses of vonoprazan 20 mg tablet formulations have been shown to be safe and well tolerated in patients and at a single dose of up to 120 mg in healthy adult subjects.

2 Study Objectives and Endpoints

Study objectives with corresponding endpoints are presented in Table 2-1.

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the BA of a single oral dose of the vonoprazan ODT-1 or ODT-2 administered without water or mixed with water and administered via a syringe relative to the vonoprazan tablet in healthy subjects.	• C_{max}, AUC_{0-t}, AUC_{0-inf}
Secondary	
• To assess the PK profile of a single oral dose of vonoprazan when administered to healthy subjects as the ODT-1 or ODT-2 administered without water or mixed with water and administered via a syringe relative to the tablet.	• t_{max}, t_{lag}, λ_z, $t_{1/2}$, CL/F, V_z/F
Safety	
• To assess the safety and tolerability of a single oral dose of vonoprazan when administered to healthy subjects as ODT-1, ODT-2, and as the tablet	• Adverse events • Laboratory test values (hematology, serum chemistry, urinalysis) • Electrocardiograms (ECG) • Vital signs

AUC_{0-inf}: area under the drug concentration-time curve from time 0 extrapolated to infinity; AUC_{0-t}: area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; BA: bioavailability; CL/F: apparent oral clearance; C_{max}: maximum observed plasma concentration; ECG: electrocardiogram; ODT: orally disintegrating tablet; PK: pharmacokinetic; $t_{1/2}$: terminal phase half-life; t_{lag}: time until first measurable concentration in plasma; t_{max}: time to maximum observed plasma concentration; V_z/F: apparent volume of distribution, λ_z: terminal elimination rate constant.

3 Investigational Plan

3.1 Study Design

This is a Phase 1, randomized, open-label, single-dose, 5-period, 5-sequence crossover study designed to assess the BA of two vonoprazan ODT formulations (ODT-1 and ODT-2) administered without water or mixed with water and administered via a syringe relative to the vonoprazan tablet in healthy subjects.

The study will consist of a screening period, a Check-in, 5 treatment periods, and a follow-up (telephone call). Each treatment period will include administration of a single dose of vonoprazan 10 mg (See treatments and Table 3-1) on Day 1 of each treatment period. There will be a washout interval of a minimum of 5 days between study drug dosing in each period.

Subjects who meet all the inclusion and none of the exclusion criteria will be randomly assigned to 1 of 5 treatment sequences in a 1:1:1:1:1 ratio.

On the first day of each dosing period, subjects will receive 1 of the following study treatments according to the treatment sequence they are randomly assigned to:

- **Treatment A:** Vonoprazan 10 mg ODT-1 without water
- **Treatment B:** Vonoprazan 10 mg ODT-1 mixed with water and administered via a syringe
- **Treatment C:** Vonoprazan 10 mg ODT-2 without water
- **Treatment D:** Vonoprazan 10 mg ODT-2 mixed with water and administered via a syringe
- **Treatment E (reference):** Vonoprazan 10 mg tablet

Table 3-1 Study Treatment Sequence

Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	A	B	C	D	E
2	B	D	E	C	A
3	C	E	B	A	D
4	D	C	A	E	B
5	E	A	D	B	C

Treatment A: vonoprazan 10 mg ODT-1 without water
Treatment B: vonoprazan 10 mg ODT-1 mixed with water and administered via a syringe
Treatment C: vonoprazan 10 mg ODT-2 without water
Treatment D: vonoprazan 10 mg ODT-2 mixed with water and administered via a syringe
Treatment E: vonoprazan 10 mg tablet

Pharmacokinetic samples will be collected through 48 hours following dosing, taste assessments will be conducted for Treatments A, B, C and D, and safety endpoints will be evaluated throughout the study.

Subjects will be confined to the clinical unit from Day -1 until discharge on Day 23.

A safety follow-up phone call will occur on Day 28 (±2 days) to assess adverse events (AEs).

A subject will be considered to have completed the study if the subject completes all Treatment Periods and the safety follow-up phone call.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

In this study, 25 healthy male and female subjects will be enrolled at a single center in the US to achieve at least 20 evaluable subjects.

4.1.1 Inclusion Criteria

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

1. The subject is 18 to 55 years of age, inclusive, at Screening.
2. The subject has a body mass index (BMI) 18 to 32 kg/m^2, inclusive, at Screening.
3. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at Screening.
4. Subjects of reproductive potential must use an acceptable method of birth control (ie, diaphragm with spermicide, intrauterine device, condom with foam or vaginal spermicide, oral contraceptives, or abstinence) from signing the informed consent form (ICF) until 4 weeks after the last dose of study drug or be surgically sterile (ie, hysterectomy or bilateral oophorectomy) or postmenopausal (defined as amenorrhea for 12 consecutive months and documented plasma follicle stimulating hormone [FSH] level >40 IU/mL during Screening). See Section 13.2 for more details.
5. Female subjects must have a negative pregnancy test at Screening and upon Check-in.
6. The subject agrees to comply with all protocol requirements.
7. The subject is able to provide written informed consent.

4.1.2 Exclusion Criteria

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

1. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at Screening.

2. The subject has a positive test result for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at Check-in.

3. The subject has a history of a clinically significant neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality that may impact the ability of the subject to participate.

4. The subject has current or recent (within 6 months) gastrointestinal conditions that would be expected to influence the absorption of drugs (eg, history of malabsorption, esophageal reflux, peptic ulcer disease, EE), frequent (more than once per week) occurrence of heartburn, or any surgical intervention.

5. The subject has any other clinically significant findings on physical examination, clinical laboratory abnormalities, and/or ECG results that preclude his/her participation in the study, as deemed by the investigator.

6. The subject has used any prescription (excluding hormonal birth control) and/or over-the-counter medications (including CYP3A4 inducers) except acetaminophen (up to 2 g per day), including herbal or nutritional supplements, within 14 days before the first dose of study drug, and/or is expected to require any such medication during the course of the study until the end of confinement on Study Day 23.

7. The subject has consumed grapefruit and/or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or other food products that may be CYP3A4 inhibitors (eg, vegetables from the mustard green family [kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard] and charbroiled meats) within 7 days before the first dose of study drug and/or is expected to be unable to abstain through the study.

8. The subject has consumed caffeine- or xanthine-containing products within 48 hours (or 5 half-lives) before the first dose of study drug and/or is unable to abstain through the study.

9. The subject is a smoker and/or has used nicotine or nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, or inhalers) within 6 months before the first dose of study drug.

10. The subject has a history of alcohol abuse and/or drug addiction within the last year or excessive alcohol consumption (regular alcohol intake >21 units per week for male subjects and >14 units of alcohol per week for female subjects; 1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits) or use of alcohol 48 hours before the first dose of study drug.

11. The subject has a positive test result for drugs of abuse, alcohol, or cotinine (indicating active current smoking) at Screening or Check-in.

12. The subject is involved in strenuous activity or contact sports within 24 hours before the first dose of study drug and during the study.

13. The subject has donated blood or blood products >450 mL within 30 days before the first dose of study drug.

14. The subject has a history of relevant drug and/or food allergies (ie, allergy to vonoprazan or excipients (Section 5.3) or any significant food allergy that could preclude a standard diet in the clinical unit).

15. The subject has received a study drug in another investigational study within 5-times the plasma half-life ($t_{1/2}$) of the study drug or 30 days of dosing, whichever is longer.

16. Female subjects who are pregnant or lactating; intend to become pregnant before, during, or within 4 weeks after participating in this study; or intend to donate ova during this time period.

17. The subject is not suitable for entry into the study in the opinion of the investigator.

4.1.3 Screen Failures

Screen failures are defined as subjects who signed the ICF to participate in the clinical study but are not subsequently entered in the Treatment Period of the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, pretreatment adverse events (PTEs), AEs, and any serious adverse events (SAEs).

Subjects may be allowed to be rescreened upon discussion with and approval by the medical monitor.

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

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject meets any of the following criteria:

1. Is noncompliant with the protocol
2. Experiences an SAE or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study
3. Has laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values (if a subject's ALT or AST is 3x upper limit of normal [ULN] or total bilirubin is >2 × ULN at any time during study medication treatment, the study medication should be discontinued immediately with appropriate clinical follow-up, including repeat laboratory tests, until the subject's laboratory profile has returned to normal/baseline status)
4. Develops symptoms or conditions that are listed in the exclusion criteria during the course of the study

5. Requires a medication prohibited by the protocol
6. Requests early discontinuation for any reason
7. Becomes pregnant

The investigator can also withdraw a subject upon the request of the sponsor or if the sponsor terminates the study. If withdrawal is considered because of an SAE or intolerable PTE/AE, the investigator will confer with the sponsor Medical Monitor. If a subject is discontinued because of a PTE/AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant.

4.2.2 Handling of Withdrawals

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, any subject who prematurely withdraws from the study will undergo all Early Termination (ET) assessments. Any subject who fails to return for final assessments will be contacted by the site in a reasonable attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

4.2.3 Replacements

Subjects may be rescreened at the discretion of the investigator and the sponsor, after consultation with the sponsor Medical Monitor.

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws before completing the study may be replaced to retain the target of 20 evaluable subjects. Any replacement subject will be assigned to receive the same treatment sequence as the subject he or she is replacing.

5 Study Drugs

5.1 Method of Assigning Subjects to Treatment Groups

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned to a treatment sequence in a 1:1:1:1:1 ratio as described in Table 3-1.

Randomization numbers (in sequential order) will be assigned before the first dose of study drug is administered on Day 1 of Period 1 (Section 3). There will be no stratification.

5.2 Treatments Administered

In each period, subjects will fast overnight (nothing to eat or drink except water) for at least 10 hours before study drug administration in the morning. Subjects will remain fasted for 4 hours after dosing with study drug and thereafter receive standardized meals scheduled at the same time throughout the study. Water (other than the water consumed with the administration of vonoprazan Treatment B, D and E) is permitted as desired except for 1 hour before and 1 hour after administration of vonoprazan.

- The subject should not chew the vonoprazan ODT or tablet.
- The subject should remain in an upright (seated or standing) position for at least 4 hours following dosing.

Treatment A and C

Administer the vonoprazan ODT on the tongue, allow it to disintegrate and swallow without water.

Treatment B and D

Prepare the dose just prior to administration and administer the vonoprazan ODT as follows:

1. Place one vonoprazan ODT in a 20 mL oral syringe and draw up 5 mL of room temperature water.
2. Swirl the syringe gently to dissolve.
3. After the ODT has dissolved, administer the entire contents of the syringe immediately into the mouth.

Treatment E

Administer the vonoprazan tablet whole with 240 mL of room temperature water and swallow immediately.

5.3 Identity of Investigational Product

Vonoprazan study medication will be supplied as 10 mg ODT-1, 10 mg ODT-2 and 10 mg tablets. [redacted] manufactures the vonoprazan fumarate drug substance. The vonoprazan ODTs are manufactured and packaged by [redacted]. The vonoprazan tablets are manufactured and packaged by [redacted] applies the clinical labels and distributes to the clinical site.

Vonoprazan ODT-1 contains 10 mg vonoprazan free base (MW 345.39) and the following inactive excipients: [redacted]

Vonoprazan ODT-2 contains 10 mg vonoprazan free base (MW 345.39) and the following inactive excipients: [redacted]

Vonoprazan tablets contain 10 mg vonoprazan free base (MW 345.39) and the following inactive excipients: [redacted]

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Phathom will provide the investigator and clinical unit with adequate quantities of vonoprazan ODT-1, ODT-2, and vonoprazan tablets for the conduct of the study plus required retention samples [DHHS 2024]. The vonoprazan ODT-1 will be supplied in 6-count blisters. The vonoprazan ODT-2 will be supplied in 10-count blisters. The vonoprazan tablets will be provided in 30-count high-density polyethylene bottles. The clinical unit pharmacy will prepare the study treatments for each subject according to the SoE (Section 13.1).

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

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

5.5 Overdose Management

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

Cases of overdose without manifested signs or symptoms are not considered AEs. Adverse events associated with an overdose will be documented on the AE eCRF(s) according to Section 6.3.1.3.1. The SAEs associated with overdose should be reported according to the procedure outlined in Section 6.3.1.3.2.

5.6 Blinding

This is an open-label study.

5.7 Study Compliance

5.7.1 Treatment Compliance

All doses of study drug will be administered in the clinical unit under direct observation of clinic personnel and will be recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug by conducting a hand and mouth check for each treatment administered.

The date and time of study drug dosing will be recorded on the appropriate page of the eCRF. If a subject is not administered study drug, the reason for the missed dose will be recorded.

5.8 Prior and Concomitant Medications and Therapies

Restrictions for prior and concomitant medications and therapies are provided in Section 4.1.2.

5.8.1 Prior Medications

Information regarding prior medications taken by the subject within the 30 days before signing the ICF will be recorded in the subject's eCRF.

5.8.2 Concomitant Medications

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

6 Study Assessments and Procedures

Prior to undergoing any protocol-specific procedures or assessments, all potential subjects must sign and date the ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign and date the ICF.

Study procedures and their timing are summarized in the Schedule of Events (SoE) (Section 13.1). Adherence to the study design requirements, including those specified in the SoE, is essential and required for study conduct. All safety concerns should be discussed with the principal investigator and medical monitor immediately to determine if any active intervention is needed, including action taken with study drug. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1 Pharmacokinetic Assessments

The following PK parameters for vonoprazan will be calculated as endpoints using standard noncompartmental methods: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, the time to maximum observed plasma concentration (t_{max}), time until first measurable concentration in plasma (t_{lag}), terminal elimination rate constant (λ_z), terminal phase half-life ($t_{1/2}$), apparent oral clearance (CL/F), and apparent volume of distribution (V_z/F). Additional PK parameters may be calculated as appropriate.

The primary endpoints will be $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of vonoprazan. The secondary endpoints will be t_{max}, t_{lag}, λ_z, $t_{1/2}$, CL/F, and V_z/F of vonoprazan.

The timing and frequency of PK sample collection is listed in the SOE (Section 13.1).

Blood samples will be collected into sodium heparin vacutainer collection tubes and processed into plasma. Details of collection, processing, storage and shipping will be contained in the Clinical Laboratory Manual.

Bioanalytical Methods

Plasma concentrations of vonoprazan will be measured at [redacted] using a validated liquid chromatography/mass spectrometry

method with an analytical range of 0.1 to 100 ng/mL and will be used for the calculation of the plasma vonoprazan PK parameters.

6.2 Other Assessments

6.2.1 Taste Assessment

After receiving each of Treatments A, B, C, and D, subjects will complete a taste assessment (Section 13.4).

6.3 Safety Assessments

6.3.1 Pretreatment Events and Adverse Events

6.3.1.1 Definitions

6.3.1.1.1 Definitions of Pretreatment Adverse Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject 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.

6.3.1.1.2 Definitions of Adverse Events

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

A treatment-emergent adverse event (TEAE) is defined as any event that occurs after the first dose of study drug or any event at baseline that worsens in either intensity or frequency after the first dose of study drug until 30 days after the last dose of study drug.

6.3.1.1.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence at any dose for which the following occurs:

1. Results in DEATH.
2. Is LIFE-THREATENING. The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above
    - May include any event or symptoms described in the medically significant AE list (Table 6-1)
    - Exposes the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization

Table 6-1 Medically Significant Adverse Event List

Term
Acute respiratory failure / acute respiratory distress syndrome
Torsade de pointes / ventricular fibrillation / ventricular tachycardia
Malignant hypertension
Convulsive seizure
Agranulocytosis
Aplastic anemia
Toxic epidermal necrolysis/Stevens-Johnson syndrome
Hepatic necrosis
Acute liver failure
Anaphylactic shock
Acute renal failure
Pulmonary hypertension
Pulmonary fibrosis
Confirmed or suspected endotoxin shock
Confirmed or suspected transmission of infectious agent by a medicinal product
Neuroleptic malignant syndrome / malignant hyperthermia
Spontaneous abortion / stillbirth and fetal death

The PTEs that fulfill one or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Section 6.3.1.3.2 and Section 6.3.1.3.3).

If a subject is noted to have an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value >3 × the upper limit of normal (ULN) and a total bilirubin value >2 × ULN, for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 6.3.1.3.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history or concurrent medical conditions. Follow-up laboratory tests, as described in Section 6.3.3, must also be performed. In addition, if the LFT increases are SAEs, a Liver Function Test Increase Form must be completed and transmitted (see Section 13.3).

6.3.1.1.4 Adverse Events of Special Interest

An AE of special interest is a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or nonserious (eg, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

Adverse events of special interest include any event listed in Table 6-2.

Table 6-2 Adverse Events of Special Interest List

Term
Hepatotoxicity
Severe cutaneous adverse reactions, including hypersensitivity
Clostridium difficile infections and pseudomembranous colitis
Hypersensitivity reactions (anaphylaxis)
Acute interstitial nephritis/tubulointerstitial nephritis
Bone fracture
Hematologic abnormalities
Gastric cancer
Vitamin B-12 deficiency
Hypomagnesemia
Lupus erythematosus

For additional details on liver function monitoring, see Section 13.3.

6.3.1.1.5 Additional Points to Consider for PTEs and AEs

An untoward finding generally may involve the following:

- Indicates a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitates therapeutic intervention.
- Requires an invasive diagnostic procedure.

- Requires discontinuation or a change in dose of study drug or a concomitant medication.

- Is considered unfavorable by the investigator for any reason.

- Is caused by a study procedure (eg, a bruise after blood collection); these events should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

- Each event is required to be recorded to represent a single diagnosis or disorder using standard medical terminology rather than individual symptoms. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (eg, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory retest and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation, or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of a pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Abnormal findings identified at baseline evaluations and screening assessments (eg, laboratory tests, ECG, endoscopy, or X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or

complication of a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy), any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg "worsening of…").

- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study drug, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

- At each required study visit, all AEs that have occurred since the previous visit or AEs that have changed in severity since the previous visit must be recorded in the AE record of the eCRF.

Changes in severity of AEs/serious PTEs:

- If the subject experiences change in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned procedures:

- Preplanned procedures that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned procedure should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

6.3.1.2 Documenting Adverse Events

6.3.1.2.1 Assessment of Severity

The severity or intensity of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated as mild, moderate, or severe using the following criteria:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.3.1.2.2 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of study drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the study drug, such as underlying diseases, complications, concomitant drugs, and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

6.3.1.2.3 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as not related.

6.3.1.2.4 Start Date and Time

The start date and time of the AE/PTE is the date and time that the first signs/symptoms were noted by the subject and/or physician.

6.3.1.2.5 Stop Date and Time

The stop date and time of the AE/PTE is the date and time at which the subject recovered, the event resolved but with sequelae, or the subject died.

6.3.1.2.6 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are considered intermittent. All other events are considered continuous.

6.3.1.2.7 Action Concerning Study Drug

- Drug withdrawn: A study drug is stopped due to the particular AE.
- Dose not changed: The particular AE did not require stopping a study drug.
- Unknown: Only to be used if it has not been possible to determine what action has been taken.
- Not applicable: A study drug was stopped for a reason other than the particular AE, eg, the study has been terminated, the subject died, or dosing with the study drug was already stopped before the onset of the AE.
- Dose interrupted: The dose was interrupted/held due to the particular AE.

6.3.1.2.8 Outcome

- Recovered/resolved: Subject returned to baseline status with respect to the AE/PTE.
- Recovering/resolving: The intensity is lowered by one or more stages: the diagnosis or signs/symptoms have lessened/improved; the abnormal laboratory value improved but has not returned to the normal range or to baseline; or the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving."
- Not recovered/not resolved: There is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period has worsened from when it started; is an irreversible

congenital anomaly; or the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved."

- Resolved with sequelae: Subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).

- Fatal: The AEs/PTEs are considered the cause of death.

- Unknown: The course of the AE/PTE cannot be followed up due to a hospital change or residence change at the end of the subject's participation in the study.

6.3.1.3 Time Period and Frequency for Collecting AE and SAE Information

6.3.1.3.1 Collection and Reporting of Adverse Events

Collection of PTEs will commence from the time the informed consent to participate in the study has been signed and will continue until the subject is first administered study drug or until screen failure. For subjects who discontinue the study prior to study drug administration, PTEs are collected until the subject discontinues study participation. Collection of AEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection will continue until the follow-up phone call or withdrawal from the study.

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Nonserious PTEs, related or unrelated to the study procedure, need not be followed up for the purposes of the protocol. All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed.

All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term
- Start and stop date and time
- Severity
- Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs)
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
- Action concerning study drug (not applicable for PTEs)
- Outcome of event
- Seriousness

6.3.1.3.2 Collection and Reporting of Serious Adverse Events

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

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

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug(s)

- Causality assessment

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

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

[redacted] 24-Hour Safety Contact Information

SAE Hotline: [redacted]

SAE Fax: [redacted]

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Investigators are not obligated to actively seek information regarding new AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor. Reporting of serious PTEs will follow the procedure described for SAEs.

6.3.1.3.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should update the SAE eCRF and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be provided, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

6.3.1.3.4 Safety Reporting to Investigators, IRB/IECs, and Regulatory Authorities

The sponsor is responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), as applicable in accordance with the national regulations in the countries the study is conducted. The SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, unless otherwise required by national regulations. The sponsor also will prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the study. The study site also will forward a copy of all expedited reports to their IRB or IEC in accordance with local regulations.

6.3.2 Pregnancy

During the course of the study, human chorionic gonadotropin pregnancy tests will be performed for women, and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Section 13.2).

If any subject is found to be pregnant during the study, she should be withdrawn, and any study drug should be immediately discontinued. If the pregnancy occurs during administration of active study drug or within 4 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 6.3.1.3.2. If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of the treatment the subject received. All pregnancies in subjects receiving study drug will be reported using the pregnancy form and will be followed up to final outcome. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

6.3.3 Laboratory Analyses

See Table 6-3 for the list of clinical laboratory tests to be performed and the SoE (Section 13.1) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Abnormal laboratory findings that are expected with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.

- All laboratory tests with abnormal values considered clinically significant during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

    - All protocol-required laboratory assessments, as defined in Table 6-3, must be conducted in accordance with the laboratory manual and the SoE.

        - If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE, AE, or dose modification), then the results must be recorded in the unscheduled laboratory eCRF.

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be provided in the laboratory manual.

All study-required laboratory assessments will be performed by a central laboratory.

Table 6-3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices: MCV, MCH • WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils
Clinical chemistry [a]	• Blood urea nitrogen • Creatinine • Total and direct bilirubin • ALT/SGPT • AST/SGOT • Alkaline phosphatase • Magnesium • Total protein • Potassium • Sodium • Calcium • Glucose • GGT • eGFR
Routine urinalysis	• Specific gravity, appearance, color, turbidity • pH, glucose, protein, occult blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)
Other screening tests	• COVID-19 • FSH if menopause is suspected [b] • Serology (HIV antibody type 1 and 2, HBsAg, and HCV antibody) • Urine alcohol, cotinine and drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cocaine, opiates, methadone, and phencyclidine • Serum hCG pregnancy test at Screening and Check-in • Urine hCG pregnancy test at Check-out/Early Termination

ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; FSH: follicle stimulating hormone; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HIV: human immunodeficiency virus; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; RBC: red blood cell; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; WBC: white blood cell

a See Section 13.3 for the appropriate guidance on reporting of abnormal liver function tests. For liver function test monitoring, see Section 13.3.1. For temporary and permanent discontinuation of study drugs due to abnormal liver function tests, see Section 13.3.2 and Section 13.3.3, respectively.

b Required only for confirmation of postmenopausal females. Female subjects 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.

Investigators must document their review of each laboratory safety report.

6.3.4 Physical Examinations

Refer to the SoE (Section 13.1) for the timing and frequency for full and brief physical examinations, as well as height and body weight. BMI equals a subject's weight in kilograms divided by the height in meters squared.

A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and body weight will also be measured and recorded. The subject should be dressed in light clothing and without shoes when the body weight is being measured.

A brief physical examination will include, at a minimum, assessments of the skin, cardiovascular, respiratory, and gastrointestinal systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.3.5 Vital Signs

Refer to the SoE (Section 13.1) for the timing and frequency of vital sign assessments.

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and temperature.

6.3.6 Electrocardiograms

Refer to the SoE (Section 13.1) for the timing and frequency of ECG assessments.

A single, standard 12-lead ECG recording will be made after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted during the screening period for eligibility determination. Assessments will include whether the tracings are normal or abnormal (if abnormal, whether clinically significant or not clinically significant).

7 Statistical and Analytical Plan

This section describes the statistical and analytical methods to be used for the study.

7.1 Sample Size Calculations

This crossover study will enroll 25 subjects to ensure 20 evaluable subjects, assuming an approximate dropout rate of 20%. With 20 evaluable subjects, the study will provide at least 95% power to conclude bioequivalence between the test treatments (A, B, C, and D) and the reference treatment (E). This assumes that the vonoprazan PK parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ are log-normally distributed, there is no more than a 5% difference between the true geometric means, and the intrasubject coefficient of variation is no greater than 16%. Subjects will be randomly assigned to 1 of 5 treatment sequences in a 1:1:1:1:1 ratio.

7.2 Analysis Sets

The PK population 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 PK parameter. Subjects who experience vomiting within 4 hours after study drug dosing will be excluded from the PK analysis for that treatment.

The safety population will include all subjects who receive at least 1 dose of study drug.

7.3 Statistical Analysis Methodology

7.3.1 Pharmacokinetic Analyses

Individual plasma concentration and time deviation data will be presented in a data listing. Plasma concentration data will be summarized by time point for each treatment using the following descriptive statistics: number of subjects, arithmetic mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum. Individual and mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales.

Vonoprazan PK parameters will be calculated using actual sampling times. All parameters will be calculated using the latest version of Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) or SAS® (SAS Institute Inc., Cary, North Carolina). The individual PK parameters will be presented in data listings and summarized by treatment using the

following descriptive statistics: number of subjects, mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. For t_{max} and t_{lag} only median, minimum, and maximum will be reported.

A linear mixed model with fixed effects for treatment, sequence, and period and subject within sequence as a random effect will be performed on the natural log-transformed values of AUC_{0t}, $AUC_{0\text{-}inf}$, and C_{max}. The ratio of geometric least square means (Treatment A, Treatment B, Treatment C, and Treatment D versus Treatment E) and corresponding 90% CIs will be computed for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} by taking the antilog of the difference of least square means and associated 90% confidence intervals (CI) from the linear mixed effect model analyzing the natural logarithms of the corresponding PK parameters. No adjustment will be made for multiplicity.

Relative BA will be reported as the test to reference ratios (A/E), (B/E), (C/E) and (D/E) of the geometric means and their corresponding CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. Relative BA will also be reported for the comparison of each ODT mixed with water to the ODT without water (B/A and D/C). Bioequivalence will be concluded if the 90% CI for the geometric mean ratio (GMR) between the test treatment (A, B, C or D) and the reference treatment (E) are wholly contained within 0.80 and 1.25 for the vonoprazan PK parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$.

Nonparametric methods will be used to examine median differences in t_{max} for vonoprazan.

7.3.2 Exploratory Analyses

Individual responses to the taste assessment (Section 13.4) will be presented in a data listing. Responses will be tabulated and summarized with histograms for each question and formulation assessed. Responses for each question will also be summarized by treatment using the following descriptive statistics: number of subjects, arithmetic mean, SD, CV, median, minimum, and maximum. Additional summaries or analyses may be performed if appropriate.

7.3.3 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to

study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in the data listings and summarized by treatment and overall.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized at each time point using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results.

7.4 Handling of Missing Data

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Missing concentrations will be excluded from the calculations.

For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

7.5 Interim Analyses

No formal interim analyses will be performed in this study.

8 Data Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6(R3) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management [DHHS 2023]. The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports and ECG strips.

Investigative site personnel will enter subject data into electronic data capture. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures to ensure the integrity of the data, eg, correcting errors and inconsistencies in the data. Adverse event terms will be coded using the MedDRA, and concomitant medications will be coded using the World Health Organization Drug Dictionary.

After the database lock, each study site will receive a file containing all of their site-specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a file of all of the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate file for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Institutional Review Board

Federal regulations, national regulations, and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH GCP will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairperson or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

All potential serious breaches must be reported to the sponsor or designee immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol which is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

9.3 Subject Information and Consent

A written informed consent in compliance with regulatory authority regulations shall be obtained from each subject before the entering the subject in the study or performing any unusual or nonroutine procedure that involves risk to the subject. Participating subjects will provide assent as applicable. An informed consent template may be provided by the sponsor

to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent and assent materials should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent and assent materials will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF or assent form is revised during the course of the study, the active participating subject must sign the revised form as applicable.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF and assent form (if applicable). Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF. If applicable, the subject will be asked to give assent by signing the assent form.

The investigator shall retain the signed original form(s) and give a copy of the signed original form(s) to the subject.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

The Investigator will also be responsible for providing oversight of the conduct of the study or site, including oversight of all personnel involved in the study, and adherence to all applicable laws and regulations as set forth in the Clinical Trial Agreement.

Personnel involved in conducting this study will be qualified by education, training and experience prior to performing their respective tasks.

10.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject, except as necessary for monitoring and auditing by the sponsor, its designee, the US Food and Drug Administration (FDA) or any regulatory authority(ies), or the IRB/IEC.

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

10.2 Financial Disclosure and Obligations

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

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

10.3 Investigator Documentation

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

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

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6. The investigator will conduct all aspects of this study in accordance with all

national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

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

10.6 Adverse Events and Study Report Requirements

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

10.7 Investigator's Final Report

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

10.8 Records Retention

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

10.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it

will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

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

11 Study Management

11.1 Monitoring

The clinical monitor, acting as the main line of communication between the sponsor (or designee) and the investigator and as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

11.1.1 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the subject, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator’s IRB/IEC for approval before subjects can be enrolled into an amended protocol.

11.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and may lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the investigative site staff, the clinical monitor, and/or the contract research organization throughout the course of the study. Principal investigators will be notified in writing by the monitor of any deviations discovered during a monitoring visit. The IRB/IEC should be notified of all protocol deviations they consider reportable in a timely manner.

11.3 Study Termination

Although the sponsor has every intention of completing the study, the sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the follow-up phone call.

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study

reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

The sponsor will submit to clinical trial registries a summary of the results of the clinical trial and where applicable a summary that is understandable to a layperson, and the clinical study report health authorities, within 6 months after the end of the study. The investigator is encouraged to share the summary results with study subjects, as appropriate.

12 Reference List

Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Draft Guidance for industry: E6(R3) Good Clinical Practice (GCP) June 2023. [cited 2024 Jul 08] Available from: https://www.fda.gov/media/169090/download

Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Health and Human Services (HHS), Handling and Retention of BA and BE Testing Samples; Draft Guidance for Industry; March 2024. [cited 2024 Oct 21] Available from: https://www.fda.gov/media/71393/download.

Engevik AC, Kaji I, Goldenring JR. The physiology of the gastric parietal cell. Physiol Rev 2020;100(2):573-602.

Jenkins H, Sakurai Y, Nishimura A, et al. Randomised clinical trial: safety, tolerability, pharmacokinetics and pharmacodynamics of repeated doses of TAK-438 (vonoprazan), a novel potassium-competitive acid blocker, in healthy male subjects. Aliment Pharmacol Ther 2015;41(7):636-648.

Laine L, Sharma P, Mulford D, et al. Pharmacodynamics and pharmacokinetics of the potassium-competitive acid blocker vonoprazan ad the proton pump inhibitor lansoprazole in US subjects. Am J Gastroentrol. 2022; 117(7): 1158-1161.

Sakurai Y, Mori Y, Okamoto H, et al. Acid-inhibitory effects of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male subjects-a randomised open-label cross-over study. Aliment Pharmacol Ther 2015;42(6):719-730.

Scarpignato C, Hunt RH. The potential role of potassium-competitive acid blockers in the treatment of gastroesophageal reflux disease. Curr Opin Gastroenterol 2019;35(4):344–355.

Scott DR, Munson KB, Marcus EA, Lambrecht NW, Sachs G. The binding selectivity of vonoprazan (TAK-438) to the gastric H+, K+ -ATPase. Aliment Pharmacol Ther 2015;42(11-12):1315-1326.

Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. J Neurogastroenterol Motil 2013;19(1):25-35.

VOQUEZNA® (vonoprazan) Tablets [package insert] Buffalo Grove, Illinois. Phathom Pharmaceuticals, Inc.; July 2024.

13 Appendices

13.1 Appendix 1: Schedule of Events

Phase	Screening	Check-in	Treatment Periods 1 to 5[b]																Follow-up (Phone Call)/EOS
Day	–28 to –2	–1	Day 1														Day 2		Day 3 (Final Visit/ET)	Day 28 (±2)
Procedure[a] Hours	—	—	Predose	0	0.25	0.5	1	1.5	2	4	6	8	10	12	16	24	36	48	
Admission to clinic		X																	
Check-out (Day 23)/Discharge from clinic[c]																		X	
Telephone call																			X
Informed consent	X																		
Demographics	X																		
Serology[d]	X																		
COVID-19 screening		X																	
Serum FSH[e]	X																		
Inclusion/exclusion criteria	X	X																	
Medical history	X	X																	
Urine drug/alcohol/cotinine screen[f]	X	X																	
Height, weight, and BMI[g]	X	X																X	
Physical examination[h]	X	X																X	
Vital sign measurements[i]	X	X	X															X	
12-lead ECG[j]	X	X																X	
Clinical laboratory testing[k]	X	X																X	
Pregnancy test[l]	X	X																X	
Guidance on avoidance of pregnancy [m]	X	X																X	
Randomization[n]			X																
Study drug administration[o]				X															
PK sample collection[p]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting (all treatments)[q]		X	X	X	X	X	X	X	X	X									
Taste Assessment (Treatments A, B, C, D only) [r]					X														
PTEs monitoring[s]	X	X	X																
AEs[t]				←										X				→	
Prior/concomitant medications	←													X				→	

Abbreviations: AE: adverse event; BMI: body mass index; COVID-19: coronavirus disease 2019; ECG: electrocardiogram; EOS: end of study; ET: Early Termination; FSH: follicle stimulating hormone; ICF: informed consent form; PK: pharmacokinetic; PTE: pre-treatment event; QTcF: QT interval corrected for heart rate using Fridericia's formula.

Notes:

(a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.

(b) There will be a washout interval of a minimum of 5 days between study drug dosing in each period.

(c) Discharge will occur following the last study assessment on Day 23 (ie, Day 3 of Period 5).

(d) Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus types 1 and 2 antibodies. The testing will be conducted at Screening.

(e) Female subjects with at least 12 months of amenorrhea should have a serum FSH test performed at Screening, if required, to confirm postmenopausal status per Inclusion Criterion #4 (FSH level >40 IU/mL).

(f) A urine drug/alcohol/cotinine screen will occur at Screening and Check-in.

(g) Height and weight will be measured, and BMI (kg/m^2) will be calculated at Screening only. Only weight will be measured at Check-in and Check-out (Day 23/Early Termination.

(h) A full physical examination will be performed at Screening (at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination will be performed at Check-in and Check-out (Day 23)/Early Termination (at minimum, assessment of skin, lungs, cardiovascular system, and abdomen [liver and spleen]). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

(i) Vital signs will be measured at Screening and Check-in, within 15 minutes prior to vonoprazan dosing in each period, and at Check-out (Day 23)/Early Termination. Vital signs will be measured after the subject has been in the seated position for at least 5 minutes and will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

(j) Single 12-lead ECG recordings will be made at Screening, Check-in, and Check-out (Day 23)/Early Termination after the subject has been in the supine position for at least 5 minutes. A single repeat measurement is permitted at Screening for eligibility determination. Measurements of the following intervals will be reported: RR interval, PR interval, QRS width, QT interval, and QTcF. Assessments should include comments on whether the tracings are normal or abnormal; rhythm; presence of arrhythmia or conduction defects; any evidence of myocardial infarction; or ST-segment, T-wave, and U-wave abnormalities.

(k) Clinical laboratory testing will occur at Screening, Check-in, and Check-out (Day 23)/Early Termination. A complete list of assessments is provided in Section 6.3.2. Blood and urine samples will be collected and prepared per the clinic's standard procedures; blood samples will be collected under fasted conditions.

(l) All female subjects will have a serum pregnancy test performed at Screening and Check-in. At Check-out (Day 23)/Early Termination, a urine pregnancy test will be performed, and if the test result is positive, a serum pregnancy test will be performed for confirmation.

(m) Guidance on pregnancy avoidance at Screening, Check-in and Check-out (Day 23)/Early Termination

(n) Subjects will be randomized only on Day 1 of Period 1.

(o) The time of vonoprazan dosing will be called "0" hour in each period and is denoted with gray shading. Study drug will be administered as outlined in Section 3.1. Subjects will maintain an upright (ie, seated or standing) position for at least 4 hours after dosing.

(p) Blood samples for PK analysis of vonoprazan in plasma will be collected within 15 minutes prior to vonoprazan dosing in each period and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 36, and 48 hours following vonoprazan dosing in each period. The window for PK sample collection up to 4 hours following vonoprazan dosing will be ±5 minutes; from 6 hours up to 12 hours post dose will be ±10 minutes; and from 16 hours up to 48 hours post dose will be ±30 minutes.

(q) Subjects assigned to each treatment will undergo fasting period. Further details are provided in Section 5.2.

(r) Taste assessment should be completed between the 15-minute and the 30-minute PK sample collections. Completion of the taste assessment should not interfere with the timing of the PK sample collections.

(s) Collection of PTEs will start after the subject has signed the ICF.

(t) Adverse events will be assessed from the time of the first vonoprazan dosing until the follow-up telephone call or withdrawal from the study and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

13.2 Appendix 2: Contraceptive Guidance

Contraception Guidance:

From signing of informed consent, throughout the duration of the study, and for 4 weeks after the last dose of study drug, female subjects of childbearing potential who are sexually active must use adequate contraception.

Birth Control: Birth control methods considered acceptable for this study include:

Barrier methods (each time that you have intercourse):

- Male condom PLUS spermicide
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide

Intrauterine Devices

- Copper T PLUS condom or spermicide
- Progesterone T PLUS condom or spermicide

Hormonal Contraceptives

- Implants
- Hormone shot/injection
- Combined pill
- Minipill
- Patch
- Vaginal ring PLUS male condom and spermicide

During the course of the study, serum human chorionic gonadotropin (hCG) will be performed at Screening and regular urine hCG pregnancy tests will be performed for all female subjects. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Section 13.1). Female subjects must have a negative serum hCG pregnancy test on Day -1 prior to study drug dispensation.

13.3 Appendix 3: Liver Function Tests

13.3.1 Liver Function Test Monitoring

Liver function will be carefully monitored throughout the study. Additional monitoring may be necessary and is recommended for subjects with abnormal LFTs.

If subjects with normal baseline ALT or AST levels experience ALT or AST >3 × ULN and a 2-fold increase above baseline, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase (GGT), and international normalized ratio [INR]) should be repeated within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

If subjects with normal ALT or AST levels experience ALT or AST >8 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be repeated within a maximum of 48 hours after the abnormality was found.

13.3.2 Considerations for Temporary Discontinuation of Study Drug

If the ALT or AST levels remain elevated >3 × ULN in subjects with normal baseline ALT or AST levels and a 2-fold increase above baseline **OR** if the ALT or AST levels remain elevated >5 × ULN in subjects with elevated baseline ALT or AST levels on 2 consecutive occasions, the investigator must contact the medical monitor to discuss additional testing, recommended monitoring, possible temporary discontinuation of study drug, and possible alternative etiologies.

13.3.3 Permanent Discontinuation of Study Drug

If any of the circumstances occur as mentioned in Table 13-1 at any time during treatment, the study drug should be permanently discontinued:

Table 13-1 Abnormal Liver Function Criteria for Permanent Discontinuation of Study Drug

Criteria for Discontinuation of Study Drug
• ALT or AST >8 × ULN • ALT or AST >5 × ULN and persists for more than 2 weeks • ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value in conjunction with elevated total bilirubin >2 × ULN **or** INR >1.5 • ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; ULN: upper limit of normal

In each of these instances, appropriate clinical follow-up should be instituted (including repeat laboratory tests) until a satisfactory conclusion (ie, until the AE resolves, the laboratory value returns to baseline, or the condition becomes stable).

If a subject meets the liver safety criteria and must be discontinued from study drug, the subject will continue to be followed per the protocol schedule until the study is completed. If the subject refuses to return for the study visits, telephone visits may be conducted; however, this is not preferred or recommended. The reason for discontinuation of study drug should be listed as an LFT abnormality.

If any of the above circumstances occur at any time during the study, the abnormality should be documented as an SAE, and a Liver Function Test Increase Form completed and sent to:

Pharmacovigilance
[redacted]

24-Hour Safety Contact Information
SAE Hotline: [redacted]
SAE Fax: [redacted]

13.3.4 Re-initiation of Study Drug

If the study drug is discontinued due to any of the scenarios provided above, study drug must not be re-initiated without consultation with the medical monitor.

13.4 Appendix 4: Taste Assessment Questionnaire

Taste Assessment Questionnaire

Fill this out with respect to your opinion of today's dose of study medication. Mark only one response for each question.

Subject Number: _____

Date (DD/MMM/YYYY): _____

Time (HH:MM): _____ __ AM __ PM

Please rate the TASTE of the study medication:

____5 = totally acceptable
____4 = quite acceptable
____3 = somewhat acceptable
____2 = slightly acceptable
____1 = not at all acceptable

Please rate the BITTERNESS of the study medication:

____5 = not at all bitter
____4 = slightly bitter
____3 = moderately bitter
____2 = very bitter
____1 = extremely bitter

Please rate the SWEETNESS of the study medication:

____5 = extremely sweet
____4 = very sweet
____3 = moderately sweet
____2 = slightly sweet
____1 = not at all sweet

Please rate the AFTERTASTE of the study medication:

____5 = no aftertaste
____4 = slight aftertaste
____3 = moderate aftertaste
____2 = strong aftertaste
____1 = extreme aftertaste

Based on taste and acceptability, please rate your WILLINGNESS to take the study medication daily:

____5 = I would take this medication daily
____4 = I would likely take this medication daily
____3 = I would possibly take this medication daily
____2 = I would not likely take this medication daily
____1 = I would not take this medication daily