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

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Phathom Pharmaceuticals, Inc.

Protocol VPED-105

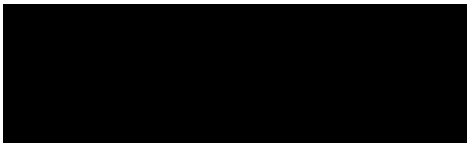
A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, 5-PERIOD CROSSOVER STUDY TO DETERMINE THE BIOAVAILABILITY OF TWO VONOPRAZAN ORALLY DISINTEGRATING TABLET FORMULATIONS ADMINISTERED WITHOUT WATER OR MIXED WITH WATER AND ADMINISTERED VIA A SYRINGE RELATIVE TO THE VONOPRAZAN TABLET IN HEALTHY SUBJECTS

12 March 2025

Final Statistical Analysis Plan

Version 1.0

Prepared by:



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List of Abbreviations

Term	Definition
λ_z	apparent terminal elimination rate constant
$\%AUC_{ext}$	Percentage of area under the plasma concentration versus time curve from time 0 extrapolated to infinity due to extrapolation
AE	Adverse event
AUC	area under the plasma concentration curve
$AUC_{0\text{-}inf}$	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
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximum observed plasma concentration
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
EOS	end of study
FDA	Food and Drug Administration
GERD	gastroesophageal reflux disease
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
NR	not reported
ODT	orally disintegrating tablet
PCABs	potassium-competitive acid blockers
PD	pharmacodynamic
PTE	pretreatment event
PK	pharmacokinetic
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event

Term	Definition
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{lag}	time to the first measurable plasma concentration
TLFs	tables, listings, and figures
T_{max}	time of maximum observed plasma concentration
US	United States
V_z/F	apparent volume of distribution during the terminal phase

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.

The purpose of this study is to determine the bioavailability (BA) of two vonoprazan orally disintegrating tablet (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 US Food and Drug Administration (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.

The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives. This SAP is written based on clarification letters and Protocol VPED-105, version 1.0, dated 10 December 2024.

2. Objectives and Endpoints

2.1. Primary Objective and Endpoints

Primary objective	Primary Endpoints
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.	• Maximum observed plasma concentration (C_{max}), area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), AUC from time 0 extrapolated to infinity (AUC_{0-inf})

2.2. Secondary Objective and Endpoints

Secondary objective	Primary Endpoints

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.	• Time of maximum observed plasma concentration (T_{max}), time to the first measurable plasma concentration. (T_{lag}), apparent terminal elimination rate constant (λ_z), apparent terminal elimination half-life ($t_{1/2}$), apparent total body clearance (CL/F), apparent volume of distribution during the terminal phase (V_z/F).

2.3. Safety Objective and Endpoints

Safety objective	**Safety Endpoints**
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

3. 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 (Table 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 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.

Schedules of events can be found in Section 13.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will include number of subjects, arithmetic mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

All tables and figures will be presented by treatment or overall.

Adverse events and taste assessment will be presented by treatment, meanwhile disposition, demographic, protocol deviations, clinical laboratory evaluations, vital signs and electrocardiograms will be presented by overall.

All data listings will be sorted by subject number.

No algorithm for imputation of missing data will be employed.

Study days are calculated with respect to the first dose date as below:

- If the assessment/observation date is on or after the first dose date, then Study Day = Assessment/Observation Date – First Dose Date + 1;
- Otherwise, Study Day = Assessment/Observation Date – First Dose Date

Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before the first dose of study drug administration, unless otherwise specified.

For summary of safety assessments, if there are repeated measurements at a time point, the first non-missing assessment at that time point will be used in the summary tables.

Unscheduled results will not be included in the summary tables, except for determining Baseline, but will be presented in data listings.

The methodology and data handling specifications for PK data are detailed in Section 8.

4.1. 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%.

4.2. Randomization and Blinding

This is a randomized study and 25 subjects will be randomly assigned to 1 of 5 treatment sequences in a 1:1:1:1:1 ratio on Day 1 of Period 1.

This study is being conducted as an open-label study. Blinding of treatments will not be performed.

4.3. Analysis Populations

The screened population will include all subjects who signed the informed consent form (ICF).

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 (see Section 8.1.1 for additional details on PK profile exclusions).

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

5. Subject Disposition

5.1. Disposition

The following will be summarized for the screened population, by overall:

- The number of subjects who failed screening
    - Reason for screen failure
- The number of subjects randomized
- The number of subjects who completed all study treatment
- The number of subjects who completed the study
- The number of subjects who did not complete all study treatment (both overall and according to reasons for discontinuation from the study treatment)
- The number of subjects who did not complete the study (both overall and according to reasons for discontinuation from the study)
- The number of subjects in each analysis population

Subject disposition data will be presented in a data listing.

5.2. Protocol Deviations

Significant protocol deviations will be summarized by overall, and all protocol deviations will be presented in a data listing.

5.3. Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic information collected at screening will be presented in a data listing.

The following summaries will be presented by overall for the safety population.

Descriptive statistics will be calculated for the following continuous demographic characteristics:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2)

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Race
- Ethnicity

6.2. Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version to be delineated in the clinical study report [CSR]) and presented in a data listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Medications that stop prior to the first dose of study drug will be classified as prior medication.

Medications that start on or after the first dose of study drug will be classified as concomitant. 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 interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the electronic case report form (eCRF).

If a medication starts before the first dose of study drug and stops on or after the first dose of study drug, the medication will be classified as both prior and concomitant. All prior and concomitant medications will be coded according to the World Health Organization Drug Dictionary (version to be delineated in the CSR) and presented in a data listing.

7.2. Study Treatment

The study drug administration as collected on eCRF will be presented in a data listing.

8. Pharmacokinetics

The concentration data listing will be presented using the safety population, and subjects not included in the PK population will be flagged. Individual PK concentration-time profiles will be presented graphically using the safety population. PK tables, mean figures and all statistical analyses will be presented using the PK population.

8.1. Data Handling

8.1.1. Pharmacokinetic Profile Exclusions

Subjects who experience vomiting within 4 hours [2 × expected median T_{max}] after study drug dosing will be excluded from the PK analysis for that treatment. Where subjects experience any additional issues pertaining to a specific dose of study drug which may affect exposure to study drug during the affected treatment period (eg, dosing errors, etc), individual PK profiles will be reviewed and evaluated by the study pharmacokineticist on a case-by-case basis for exclusion from treatment summaries and/or the PK analysis for that treatment. All exclusions will be documented throughout the concentration data listing and the affected PK tables.

8.1.2. Data Rounding

Data rounding specifications for PK data are documented in the PK tables, listings, and figures (TLFs) shells.

8.1.3. Below the Limit of Quantification

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for calculation of concentration descriptive statistics.

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. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

8.1.4. Missing Data

All missing concentration data will be presented as missing in concentration data listing and excluded from the estimation of concentration summary statistics. However, for the estimation of PK parameters the following imputations will be made:

- Missing predose concentrations observed before administration of the first dose will be imputed as zero. This imputation is performed automatically by the analysis software.
- Missing actual sampling times will be imputed as the corresponding nominal times.

Otherwise, missing results will be treated as missing and not imputed.

8.1.5. Predose Samples Collected Postdose

Predose samples collected in error after dosing will be excluded from the calculation of concentration summary statistics and included in the estimation of PK parameters using the actual time relative to dosing.

8.1.6. Summary Statistics

Summary statistics to be presented for each output are as follows:

- Plasma concentrations: number of subjects receiving the treatment (N), number of non-missing observations (n), arithmetic mean, SD, coefficient of variation (CV), median, minimum, and maximum.
- Plasma PK parameters: N, n, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum. T_{max} and t_{lag} will be summarized using number of observations, median, minimum, and maximum only.

Where only one observation is observed (ie, n=1), only the number of observations, arithmetic mean, median, minimum, and maximum will be presented.

8.1.7. Carry-over

If carry-over occurs between study periods (ie, if predose plasma concentrations of vonoprazan after Period 1 are above the lower limit of quantification), the subject's data (without any adjustments) will be included in all PK TLFs and statistical evaluations where the pre-dose concentration is ≤ 5% of the C_{max} for the affected subject profile. If the pre-dose value is > 5% of C_{max}, the affected profile will be excluded from all PK summaries and statistical evaluations. The subject will be flagged and the exclusion will be documented in all PK TLFs.

8.2. Plasma Concentrations

Serial blood samples will be collected at the following time points for vonoprazan PK assessment in plasma:

- Pre-dose (within 15 mins 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 after drug administration 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. PK collections that have an actual sampling time that deviates from these predefined collection time windows will be flagged in the concentration data listing. The associated concentrations will be presented as NR (not reported) in the PK concentration table and will be excluded from the summary statistics.

Individual plasma concentrations will be presented in the concentration data listing and will also be summarized by treatment and time point in the PK concentration table.

Individual plasma concentrations will be plotted by actual time on both linear and semi-logarithmic scales. Arithmetic mean plasma concentrations will be plotted by nominal time on both linear and semi-logarithmic scales with all treatments overlaid on the same plots.

8.3. Plasma Pharmacokinetic Parameters

Plasma concentration-time data will be analyzed by non-compartmental analysis using Phoenix® WinNonlin® Version 8.3 or higher (Certara USA, Inc., Princeton, NJ). The following PK parameters will be calculated for vonoprazan, where data permit:

C_{max}	Maximum observed plasma concentration.
T_{max}	Time of maximum observed plasma concentration.
T_{lag}	Time to the first measurable plasma concentration.
AUC_{0-t}	Area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration (C_{last}), calculated using the linear trapezoidal rule.
AUC_{0-inf}	Area under the plasma concentration versus time curve from time 0 extrapolated to infinity, calculated as $[AUC_{0-t} + (C_{last} / \lambda_z)]$ where C_{last} is the last quantifiable concentration.
$t_{1/2}$	Apparent terminal elimination half-life, calculated as: $\ln(2) / \lambda_z$.

CL/F	Apparent total body clearance, calculated for parent drug only as: Dose / $AUC_{0\text{-}inf}$.
V_z/F	Apparent volume of distribution during the terminal phase, calculated for parent drug only as: Dose / [λ_z * $AUC_{0\text{-}inf}$].

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed and summarized (separately) to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.
Number points	Number of data points used to estimate λ_z; a minimum of 3 data points must be used, and C_{max} must not be included.
λ_z lower	Lower bound used for the estimation of λ_z.
λ_z upper	Upper bound used for the estimation of λ_z.
Rsq	r^2, the coefficient of determination (goodness of fit statistic); $t_{1/2}$, $AUC_{0\text{-}inf}$, CL/F and V_z/F will be flagged and excluded from summary statistics where $r^2 < 0.80$.
$\%AUC_{ext}$	Percentage of $AUC_{0\text{-}inf}$ due to extrapolation; $AUC_{0\text{-}inf}$, CL/F and V_z/F values will be flagged and excluded from summary statistics where $\%AUC_{ext} >$ 20%.

Actual sampling times will be used for the estimation of all plasma PK parameters, and all concentrations associated with scheduled sampling times will be included in the analysis (including concentrations collected outside predefined collection windows). Unscheduled and/or early termination PK samples may be included in the estimation of PK parameters if deemed appropriate by the sponsor.

Individual plasma PK parameters will be presented and summarized by treatment in the PK parameters table.

8.4. Pharmacokinetic Statistical Analyses

8.4.1. Bioequivalence/Relative Bioavailability

A linear mixed-effect 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 C_{max}, AUC_{0-t}, and AUC_{0-inf} for vonoprazan. No adjustment will be made for multiplicity. The ratio of geometric least square means for a pair of formulations and corresponding 90% confidence intervals (CIs) will be computed for AUC_{0-t}, AUC_{0-inf}, and C_{max} by taking the antilog of the difference of least square means and associated 90% CIs from the linear mixed effect model analyzing the natural logarithms of the corresponding PK parameters. The formulations compared (ratios of geometric least squares means and corresponding 90% CIs described above) will be computed for each parameter for the following treatment comparisons:

- Treatment A / Treatment E
- Treatment B / Treatment E
- Treatment C / Treatment E
- Treatment D / Treatment E
- Treatment B / Treatment A
- Treatment D / Treatment C

Bioequivalence will be concluded if the 90% CI for the geometric mean ratio between the test treatment (A, B, C or D) and the reference treatment (E) and between each ODT mixed with water (B or D) to the ODT without water (A or C) are wholly contained within 80.00% and 125.00% for the vonoprazan PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}.

Relative BA will be reported as the test to reference ratios (A/E), (B/E), (C/E), (D/E), (B/A), and (D/C) of the geometric means and their corresponding CIs for C_{max}, AUC_{0-t}, and AUC_{0-inf}.

Forest plots will also be presented for C_{max}, AUC_{0-t}, and AUC_{0-inf} to visualize the relative bioavailability.

Nonparametric methods (Wilcoxon signed-rank test) will be used to examine the differences in T_{max} and T_{lag} for vonoprazan between treatments. The Hodges-Lehmann estimate and its 90% CI will be calculated for the median difference between treatments, and a p-value will be generated by the Wilcoxon signed-rank test.

9. Safety Assessment

All safety summaries and analyses will be based upon the safety population.

9.1. Adverse Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject whose informed consent to participate in a study has been signed, which has occurred prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

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

A treatment-emergent AE (TEAE) is defined as any event that occurs after the first dose of study drug 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.

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on eCRF: related and not related.

The severity of AEs will be classified by the investigator as mild, moderate, or severe.

An overall AE summary will be generated presenting the frequency and percentage of subjects and the number of AEs for the following:

- Any TEAE
- Any treatment-related TEAE
- Any mild TEAE
- Any treatment-related mild TEAE
- Any moderate TEAE
- Any treatment-related moderate TEAE
- Any severe TEAE
- Any treatment-related severe TEAE
- Any serious adverse event (SAE)
- Any treatment-related SAE
- Any TEAE leading to discontinuation of study drug

- Any TEAE leading to early discontinuation
- Any death

All AEs will be coded using MedDRA (version to be delineated in the CSR). The TEAEs will also be summarized by system organ class (SOC), preferred term (PT), by severity and relationship to study treatment. Serious AEs, and AEs leading to discontinuation of study drug will also be summarized.

In summaries of TEAEs by treatment, TEAEs will be summarized according to the most recent treatment received prior to the TEAE onset.

The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A subject with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of subjects in the safety population.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment-related AEs, SAEs, AEs leading to study discontinuation and AEs leading to discontinuation of study drug.

9.2. Clinical Laboratory Evaluations

The following laboratory tests will be performed:

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 (in protocol) for the appropriate guidance on reporting of abnormal liver function tests. For liver function test monitoring, see Section 13.3.1 (in protocol). For temporary and permanent discontinuation of study drugs due to abnormal liver function tests, see Section 13.3.2 (in protocol) and Section 13.3.3 (in protocol), 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.

The hematology, clinical chemistry, routine urinalysis and other screening tests will be performed at the timepoints indicated in the schedule of events (Section 13).

All clinical laboratory test results will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

Hematology, clinical chemistry and routine urinalysis will be summarized in summary tables. Actual results and change from baseline for hematology, clinical chemistry, and routine urinalysis at each time point will be summarized for the safety population by overall using descriptive statistics.

Shift tables in terms of low/normal/high for hematology and clinical chemistry, and in terms of normal/abnormal for urinalysis tests, will be generated for clinical laboratory test results by overall.

9.3. Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature, and will be measured at the timepoints indicated in the schedule of events (Section 13).

All vital signs, body weight, height and BMI will be presented in a data listing. The actual values and change from baseline values at Day 23/Early Termination will be summarized for vital signs and weight by overall for the safety population.

9.4. Physical Examination

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.

Physical examination will be measured at the timepoints indicated in the schedule of events (Section 13).

A data listing will indicate the performance of the physical exams.

9.5. Electrocardiograms

Single 12-lead ECGs will be obtained 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: heart rate, RR interval, PR interval, QRS width, QT interval, QTcF, and interpretation. 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.

Single 12-lead ECG will be performed at the timepoints indicated in the schedule of events (Section 13).

Actual values for numeric ECG data and change from baseline values will be summarized by visit and overall for subjects in the safety population.

All ECG data will be presented in a data listing.

10. Exploratory Analyses

Taste assessment will be performed at the timepoints indicated in the schedule of events (Section 13).

Individual responses to the taste assessment (Section 13.4 in the protocol) will be presented in a data listing.

Responses will be tabulated and summarized with histograms for each question and formulation assessed. Ordinal 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.

11. Interim Analysis

No formal interim analyses will be performed in this study

12. Changes in the Planned Analysis

Any changes from this statistical analysis plan will be documented in the CSR for this study.

13. Schedule of Events

Phase	Screening	Check-in	Treatment Periods 1 to 5[b]															Follow-up (Phone Call)/EOS
Procedure[a] / Day	–28 to –2	–1	Day 1													Day 2		Day 3 (Final Visit/ET)	Day 28 (±2)
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	
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 of the protocol. 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 of the protocol. 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 of the protocol.

(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.

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Phathom Pharmaceuticals, Inc.**
Protocol Number:	**VPED-105**

Document Description:	Final Statistical Analysis Plan
SAP 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
SAP Version Number:	Final v1.0
Effective Date:	12Mar2025

Author(s):

[redacted]

[redacted]

Approved by:

[redacted]

14-Mar-2025

Date *(DD-MMM-YYYY)*

[redacted]

14-Mar-2025

Date *(DD-MMM-YYYY)*