Protocol Number: VPED-101

Official Title: A Phase 1, Open-Label, Randomized, Single-Dose, Crossover Study to Determine the Bioavailability of Vonoprazan Sprinkle Capsules on Pudding or on Applesauce Relative to A Vonoprazan Tablet in Healthy Subjects

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Phathom Pharmaceuticals, Inc.

VPED-101

A PHASE 1, OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, CROSSOVER STUDY TO DETERMINE THE BIOAVAILABILITY OF VONOPRAZAN SPRINKLE CAPSULES ON PUDDING OR ON APPLESAUCE RELATIVE TO A VONOPRAZAN TABLET IN HEALTHY SUBJECTS

14/06/2022

Final Statistical Analysis Plan

Version 1.0

Prepared by:

[redacted]

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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$\%AUC_{ext}$	percentage extrapolation of area between AUC_{0-t} to AUC_{0-inf}
AUC_{0-inf}	area under the plasma concentration versus 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
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
COVID-19	coronavirus disease 2019
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
EOS	end of study
ET	end-of-treatment period phase
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GMR	geometric mean ratio
IB	investigator's brochure
ICF	informed consent form
INR	international normalized ratio
H^+, K^+-ATPase	hydrogen, potassium-adenosine triphosphatase
λ_z	terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
PCABs	potassium-competitive acid blockers

PK	pharmacokinetic(s)
PPIs	proton pump inhibitors
PT	preferred term
PTE	pre-treatment event
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
sGERD	symptomatic non-erosive gastroesophageal reflux disease
SOC	system organ class
$t_{1/2}$	terminal elimination phase half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WHODrug	World Health Organization Drug Dictionary

1. Introduction

Vonoprazan belongs to a novel class of acid suppressants known as potassium-competitive acid blockers (PCABs) that suppress gastric acid secretion by competitively inhibiting gastric hydrogen, potassium-adenosine triphosphatase (H+, K+-ATPase). Vonoprazan was discovered and developed by Takeda Pharmaceutical Company, Japan and is being developed by Phathom Pharmaceuticals (Phathom) for the treatment of heartburn in patients with symptomatic non-erosive gastroesophageal reflux disease (sGERD), healing of all grades of erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *Helicobacter pylori* infection.

The current adult formulation and size of vonoprazan tablets are appropriate for administration in pediatric subjects 12 years of age and older, and who are capable of swallowing tablets. However, different strengths and formulations will need to be developed to support the pediatric clinical program for the pediatric age group less than 12 years of age and for pediatric patients incapable of swallowing tablets. Phathom is investigating a sprinkle capsule formulation for these pediatric patients. Therefore, this study will investigate the bioavailability (BA) of vonoprazan in healthy adult subjects when administered as 20 mg sprinkle capsules on pudding or on applesauce relative to 20 mg tablets, in accordance with the Food and Drug Administration (FDA) Guidance for industry: Bioavailability Studies Submitted in NDAs or INDs – General Considerations (DHHS 2022). The use of healthy adult subjects is appropriate for the BA study prior to initiation of studies in pediatric patients.

Relative BA will be based on the maximum observed plasma concentration (C_{max}), area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration (AUC_{0-t}), and area under the plasma concentration versus time curve from time 0 extrapolated to infinity (AUC_{0-inf}) to determine the peak and total drug exposure. Analysis of plasma concentrations will characterize the single-dose PK of vonoprazan 20 mg sprinkle capsule (either sprinkled on pudding or on applesauce).

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 protocol VPED-101 amendment 1, version 2.0, dated 25 April 2022.

2. Objectives and Endpoints

2.1 Objectives

2.1.1 Primary Objective

To assess the BA of a single oral dose of vonoprazan 20 mg sprinkle capsule, either sprinkled on pudding or on applesauce, relative to a vonoprazan 20 mg tablet in healthy subjects

2.1.2 Secondary Objectives

- To assess the PK profile of a single oral dose of vonoprazan when administered to healthy subjects as 20 mg sprinkle capsule, either sprinkled on pudding or on applesauce, relative to a 20 mg tablet
- To assess the safety and tolerability of a single oral dose of vonoprazan when administered to healthy subjects as 20 mg sprinkle capsule, either sprinkled on pudding or on applesauce, or as a 20 mg tablet

2.2 Endpoints

2.2.1 Pharmacokinetic Endpoints

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}, terminal elimination rate constant (λ_z), terminal phase half-life ($t_{1/2}$), apparent total body clearance (CL/F), and apparent volume of distribution (V_z/F). Additional PK parameters may be calculated as appropriate.

2.2.2 Safety Endpoints

Safety and tolerability endpoints will include monitoring and recording of adverse events (AEs), clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

3. Study Design

This is a Phase 1, single-dose, open-label, randomized, 3-period, 3-sequence crossover study designed to assess the BA of vonoprazan 20 mg sprinkle capsule, either sprinkled on pudding or on applesauce, relative to a vonoprazan 20 mg tablet under fasted conditions in healthy subjects.

The study will consist of a screening period, a Check-in, 3 treatment periods, and a follow-up (telephone call). The treatment periods will include administration of single doses of vonoprazan 20 mg (tablet/sprinkle capsule) on Day 1 of each period. There will be a washout interval of a minimum of 7 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 3 treatment sequences in a 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 20 mg sprinkle capsule on 1 tablespoon of pudding administered orally under fasted conditions.

- Treatment B: Vonoprazan 20 mg sprinkle capsule on 1 tablespoon of applesauce administered orally under fasted conditions.

- Treatment C: Vonoprazan 20 mg tablet administered orally under fasted conditions.

- **Table 3-1 Study Treatment Sequence**

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	C	A	B
3	B	C	A

Subjects will be confined to the clinical unit from Day –1 until discharge on Day 17. A follow-up telephone call will occur on Day 31 (±2 days). The duration of the study, excluding Screening will be approximately 33 days.

Schedules of assessments 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, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

Unless otherwise indicated, all tables, listings, and figures will be presented by treatment sequence.

All data listings will be sorted by treatment sequence and subject number.

Study days will be 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

The sample size for this study is based on a statistical power calculation.

This crossover study will enroll 27 subjects to ensure 24 subjects complete the study, assuming an approximate dropout rate of 15%. With 24 completed subjects, the study will provide at least 97% power to conclude bioequivalence between the test treatments and the reference treatment, assuming that the vonoprazan PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} are log-normally distributed, the true geometric mean ratio (GMR) is 1, and the intrasubject coefficient of variation is no greater than 20%. Subjects will be randomly assigned to 1 of 3 treatment sequences in a 1:1:1 ratio. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

4.2. Randomization and Blinding

[redacted] will generate the randomization schedule. Subjects who meet all the inclusion and none of the exclusion criteria will be randomly assigned to a treatment sequence in a 1:1:1 ratio (Section 3). 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 and treatment sequence will not be blinded.

4.3. Analysis Population

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

The safety population will include all subjects who received at least 1 dose of vonoprazan.

The pharmacokinetic (PK) population will include all subjects who received at least 1 dose of vonoprazan and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. Subjects who experience vomiting within 2 times the median T_{max} after study drug dosing will be excluded from the summary statistics and statistical analysis from the impacted period(s).

In addition, where subjects experience any other issues which may affect exposure to study drug (eg, dosing errors, etc), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the summary statistics and statistical analysis from the impacted period(s) on a case-by-case basis. All subjects excluded from the PK analysis will be documented in the data listings.

5. Subject Disposition

5.1 Disposition

The following will be summarized for the enrolled population, by treatment sequence (if applicable) and overall:

- The number of subjects screened
- The number of subjects who screen failed (both overall and according to reason for screen failure)
- The number of subjects who were randomized
- The number of subjects who completed the treatment
- The number of subjects who did not complete the treatment (both overall and according to reasons for discontinuation from the treatment)
- The number of subjects who completed the study
- 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

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data.

Important protocol deviations will be summarized by treatment sequence in the table and all 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 will be presented in a data listing.

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

The summaries will be presented by treatment sequence and overall for the safety population.

6.2 Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 25.0) 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. If a medication starts before the first dose of study drug and stops on or after the first dose of study drug, then 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 (WHODrug, version 2022-March 1st (Global B3)) and presented in a data listing.

7.2 Medical or Surgical Treatment Procedures

Medical or surgical treatment procedures will be presented in a data listing.

7.3 Study Treatment

The study drug administration and fasting condition data as collected on electronic case report form (eCRF) will be presented in the data listings.

7.4 Meal Status

The meal status information will be presented in the data listing.

8. Pharmacokinetics

All PK listings and individual concentration-time profiles will be presented using the safety population. PK tables, mean figures, and all statistical analyses will be presented using the PK population.

8.1 Data Handling

Data rounding specifications for PK data will be documented in the PK TLF shells.

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for summary statistics and PK profiles representation. Mean BLQ concentrations will be presented as BLQ, and the SD and coefficient of variation (CV) will be reported as not applicable. 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.

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

8.2 Plasma Concentrations

Serial 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 permitted windows for PK sample collection are as follows:

Pharmacokinetic time points	**Window**
Pre-dose	within 15 minutes prior to dosing
0.25 to 4 hours	± 5 minutes
6 to 12 hours	± 10 minutes
16 to 48 hours	± 30 minutes

PK collections that have an actual sampling time that deviates from the predefined collection time windows will be flagged in the data listings and excluded from the calculation of concentration summary statistics.

Individual plasma concentrations and time deviation data will be presented in data listings. Plasma concentrations will be summarized separately by time point for each treatment using the following descriptive statistics: number of observations, arithmetic mean, standard deviation (SD), CV, median, minimum, and maximum.

Individual plasma concentrations will be plotted by actual time on both linear and semi-logarithmic scales with all treatments overlaid on the same plots. 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 concentration.
T_{max}	Time of maximum observed concentration.
AUC_{0-t}	AUC from time 0 to the last measurable observed concentration (C_{last}), calculated using the linear trapezoidal rule.
AUC_{0-inf}	AUC from time 0 extrapolated to infinity, calculated as [AUC_{0-t} + (C_{last} / λ_z)] where C_{last} is the last observed measurable concentration.
$\%AUC_{ext}$	Percentage of AUC_{0-inf} due to extrapolation; AUC_{0-inf}, CL/F and V_z/F values will be flagged and excluded from summary statistics and statistical analysis (as applicable) where $\%AUC_{ext}$ > 20%.
$t_{1/2}$	Apparent terminal elimination half-life, calculated as: ln (2) / λ_z.
CL/F	Apparent total body clearance after oral (extravascular) administration, calculated as: Dose / AUC_{0-inf}.
V_z/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as: Dose / [λ_z * AUC_{0-inf}].

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed and summarized to document the selection of data points used to estimate t1/2z 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); λ_z and all associated parameters will only be reported where $r^2 \geq 0.80$.

Actual sampling times will be used for the estimation of all plasma PK parameters, and all concentrations will be included in the analysis (including concentrations collected outside predefined collection windows).

Individual plasma PK parameters will be presented and summarized by treatment using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum). T_{max} will be summarized using number of observations, median, minimum, and maximum only.

8.4 Pharmacokinetic Statistical Analyses

8.4.1 Bioequivalence Assessment

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} to assess the relative bioavailability (BA) of the test dose form (vonoprazan sprinkle capsule [either sprinkled on pudding, Treatment A, or on applesauce, Treatment B]) to the reference dose form (vonoprazan tablet, Treatment C). The geometric least square means 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 least square means from the linear mixed-effect model on 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/C or B/C) of the geometric means and its corresponding CIs for AUC_{0-t}, AUC_{0-inf}, and C_{max} PK parameters. Bioequivalence will be concluded if the 90% CI for the geometric mean ratio (GMR) between the test treatments (20 mg sprinkle capsule, either sprinkled on pudding or on applesauce) and the reference treatment (20 mg tablet) are wholly contained within 0.80 and 1.25 for the vonoprazan PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max}.

In addition, the GMR and corresponding 90% CIs for AUC_{0-t}, AUC_{0-inf}, and C_{max} will be summarized in forest plots to visually assess bioequivalence.

Nonparametric methods (Wilcoxon signed-rank test) will be used to examine the differences in T_{max} between treatments for vonoprazan. 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 Analysis

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

9.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject enrolled in this study regardless of its causal relationship to study drug.

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

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.

The AE's relationship to study treatment will be evaluated as related or 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 AE
- Any TEAE
- Any PTE
- 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 SAE
- Any treatment-related SAE
- Any TEAE leading to early discontinuation
- Any death

All AEs will be coded using MedDRA (version 25.0). The TEAEs will also be summarized by system organ class (SOC), preferred term (PT), by severity and relationship to study treatment. Treatment-related TEAEs will be summarized by SOC and PT.

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.

In summaries of TEAEs by treatment, TEAEs will be summarized according to the most recent treatment received prior to the TEAE onset. For example, a TEAE that occurred on or after administration of the study drug on Day 1 of Period 1 but before the administration of study drug on Day 1 of Period 2 will be summarized for study drug administered in Period 1.

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

9.2 Clinical Laboratory Evaluations

The hematology, serum chemistry, and urinalysis tests will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 13).

All clinical laboratory test results will be presented in the data listings and identified whether the test results are clinically significant or not. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

Actual results and change from baseline for continuous variables at each time point will be summarized for the safety population. Shift from baseline categorical variables will be summarized for the safety population.

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 assessments (schedules of assessments can be found in Section 13).

All vital sign, body weight, and height measurements will be presented in a data listing. The actual values and change from baseline values at each time point will be summarized for the safety population.

9.4 Physical Examination

A full physical examination will include, 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 include, at minimum, assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Full physical examinations will be performed at Screening, and brief physical examinations will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 13).

All physical examination results will be presented in a data listing.

9.5 Electrocardiograms

Single 12-lead ECGs will be obtained after the subject has been in the supine position for at least 5 minutes.

Heart rate, PR interval, QRS width, RR interval, QT interval, QT interval corrected for heart rate using Fridericia's formula (QTcF), and interpretation of ECG will be captured on the eCRF.

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

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

All ECG data will be presented in a data listing.

9.6 Other Tests

A serology test, COVID-19 test, urine drug screen, pregnancy test (female only) and serum follicle stimulating hormone (FSH) test (female only) will be performed at the timepoints indicated at schedules of assessments (schedules of assessments can be found in Section 13).

The test results will be presented in a data listing.

9.7 COVID-19 Vaccine, Infection History and Impact

The status of coronavirus disease 2019 (COVID-19) including vaccine and infection history will be collected and presented in a data listing.

The visits impacted by COVID-19 will also be presented in a data listing.

10. Interim Analysis.

No formal interim analyses are planned.

11. Changes in the Planned Analysis

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

12. References

1. Department of Health and Human Services (DHHS), Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Guidance for industry. Bioavailability Studies Submitted in NDAs or INDs – General Considerations. April 2022. Available from: https://www.fda.gov/media/121311/download.

13. Schedule of Assessments

Phase	Screening	Check-in	Treatment Periods 1 to 3[b]															Follow-up (Phone Call)/EOS
Day	–28 to –2	–1	Day 1													Day 2		Day 3 (ET)	Day 31 (±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																	
Discharge from clinic[c]																		X	
Telephone call																			X
Informed consent	X																		
Demographics	X																		
Serology[d]	X																		
COVID-19 screening	X	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	X	X																X	
Randomization[m]			X																
Study drug administration[n]				X															
PK sample collection[o]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CYP genotyping		X																	
Fasting period[p]		X	X	X	X	X	X	X	X	X									
Non-fasting period[q]											X	X	X	X	X	X	X	X	
PTEs monitoring[r]	X	X	X																
AEs[Error! Reference source not found.]				←											X			→	
Prior/concomitant medications	←														X			→	

Abbreviations: AE, adverse event; BMI, body mass index; COVID-19, coronavirus disease 2019; CYP, cytochrome P450; ECG, electrocardiogram; EOS, end of study; ET, end-of-treatment period phase; 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 7 days between study drug dosing in each period.

(c) Discharge will occur following the last study assessment on Day 17 (ET, ie, Day 3 of Period 3).

(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) Females 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 ET.

(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 ET (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 ET. 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 ET 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; morphology; 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 ET. A complete list of assessments is provided in Section **Error! Reference source not found.**. Blood and urine samples will be collected and prepared per the clinic's standard procedures; blood sample will be collected under fasted conditions.

(l) All women will have a serum pregnancy test performed at Screening. At Check-in and ET, a urine pregnancy test will be performed, and if the test result is positive, a serum pregnancy test will be performed for confirmation.

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

(n) The time of vonoprazan dosing will be called "0" hour in each period and is denoted with gray shading. Vonoprazan sprinkle capsule sprinkled on 1 tablespoon of pudding will be swallowed and will be followed with swish/swallow of 240 mL of room temperature water; vonoprazan sprinkled on 1 tablespoon of applesauce will be swallowed and will be followed with swish/swallow of 240 mL of room temperature water. Vonoprazan tablet will be administered and swallowed whole with 240 mL of room temperature water. Subjects will maintain an upright (ie, seated or standing) position for at least 4 hours after dosing.

(o) 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 will be ±30 minutes.

(p) During fasting periods, subjects should have nothing to eat or drink except water for 10 hours prior to vonoprazan dosing until 4 hours after dosing. Water (other than the water consumed with the administration of vonoprazan tablet or sprinkle capsule) is permitted as desired except for 1 hour before and 1 hour after administration of vonoprazan.

(q) During non-fasting periods, subjects should receive standardized meals per the clinic's standard procedures that will be scheduled at the same time in each period of the study.

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

(s) 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.