Protocol Number: VONO-401

Official Title: A Phase 1, Open-label Study to Evaluate Vonoprazan Concentrations in Breast Milk of Healthy Lactating Women Receiving Vonoprazan 20 mg Once Daily or Vonoprazan 20 mg Twice Daily

NCT Number: NCT06391177

Document Date: 30 August 2024

16.1.9 Documentation of Statistical Methods

16.1.9.1 Statistical Analysis Plan

This section contains the following document:

Final Statistical Analysis Plan Version 1.0, dated 28 August 2024

Phathom Pharmaceuticals, Inc.

VONO-401

A PHASE 1, OPEN-LABEL STUDY TO EVALUATE VONOPRAZAN CONCENTRATIONS IN BREAST MILK OF HEALTHY LACTATING WOMEN RECEIVING VONOPRAZAN 20 MG ONCE DAILY OR VONOPRAZAN 20 MG TWICE DAILY

28Aug2024
Final Statistical Analysis Plan

Version 1.0

Prepared by:

[redacted]

TABLE OF CONTENTS

List of Abbreviations

AE	adverse event
AUC	area under the drug concentration-time curve
AUC_{0-24}	area under the drug concentration-time curve from time 0 to 24 hours following the last dose
BLQ	below the limit of quantification
BMI	body mass index
C_{avg}	average drug concentration in milk
C_{max}	maximum drug concentration in milk
C_{min}	minimum drug concentration in milk
CSR	clinical study report
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
ICF	informed consent form
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic(s)
PT	preferred term
PTE	pretreatment event
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed milk concentration
WHODrug	World Health Organization Drug Dictionary

1. Introduction

Vonoprazan (TAK-438) is a member of a class of compounds referred to as potassium-competitive acid blockers (PCABs) that suppress gastric acid secretion by competitively inhibiting gastric hydrogen, potassium–adenosine triphosphatase (H+, K+-ATPase). Vonoprazan is formulated and administered orally as its fumarate salt, vonoprazan fumarate. Following oral administration, the fumarate salt is rapidly converted to the free base form, and vonoprazan fumarate is not detectable in human plasma.

Further information on the study drug can be found in the investigator's brochure.

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 VONO-401, version 2.0, dated 18 July 2024 .

2. Objectives and Endpoints

2.1 Primary Objective and Endpoints

Primary objective	Endpoint
• To determine the pharmacokinetics (PK) of vonoprazan in breast milk of healthy lactating women who have received vonoprazan 20 mg administered once daily or vonoprazan 20 mg administered twice daily for 4 consecutive days	• Area under the drug concentration-time curve from time 0 to 24 hours following the morning dose (AUC_{0-24}) on Day 4, maximum drug concentration in milk (C_{max}), minimum drug concentration in milk (C_{min}), and average drug concentration in milk (C_{avg}), time to maximum observed concentration in milk (T_{max})

2.2 Secondary Objectives and Endpoints

Secondary objective	Endpoints
• To determine total drug excreted in milk	• Total amount of drug excreted in milk (mg) • Amount of drug excreted in milk relative to the total dose received (%)
• To estimate the relative infant dose of vonoprazan	• Estimated infant daily dose (mg/kg/day) • Estimated relative infant dose to the total maternal dose received (%)

2.3 Safety Objectives and Endpoints

Safety objective	Endpoint
• To evaluate the safety and tolerability of vonoprazan 20 mg administered once daily or vonoprazan 20 mg administered twice daily for 4 consecutive days	• Adverse events (AEs) • Clinical laboratory test values (hematology, serum chemistry, urinalysis) • Vital signs

3. Study Design

This is a Phase 1, nonrandomized, open-label study in healthy lactating women who have been actively breastfeeding or pumping for at least 4 weeks postpartum. Approximately 15 subjects will be enrolled. No formal sample size estimation was performed.

The study will consist of a Screening Period (up to 28 days prior to Baseline), Baseline (Day 1, predose), Treatment Period (4 days of treatment with study drug from Days 1 through 4 and 24 hours of postdose assessments after the morning dose of study drug on Day 4), and a 7-day safety follow-up after the last dose. Since vonoprazan exhibits time-independent PK and steady-state concentrations are achieved by Days 3 to 4, a once-daily or twice daily dose of vonoprazan 20 mg administered for 4 consecutive days will ensure that breast-milk sampling occurs when drug exposure in plasma is at steady state.

During the Screening Period, subjects will be evaluated to determine if they meet the inclusion/exclusion criteria; information on their current breastfeeding practice will also be obtained. After screening, eligible subjects will visit the clinical research unit on Day 1 for the baseline assessment to confirm protocol eligibility and to obtain baseline data.

Subjects who complete the baseline assessment and meet the criteria for inclusion and exclusion will enter the Treatment Period and will be administered vonoprazan 20-mg tablet once daily or twice daily for 4 days (Days 1 through 4). On the mornings of Days 1 through 3, subjects will present in the clinical research unit for an outpatient visit, and for administration of vonoprazan 20 mg orally with 240 mL of room temperature water, at approximately the same time each day and under direct observation of clinical research unit staff (without regard to food intake). Those assigned to receive vonoprazan 20 mg twice daily will self-administer a second dose of vonoprazan 20 mg orally with 240 mL of room temperature water at home approximately 12 hours after the first dose on Days 1 through 3. The evening dose should be taken at the time instructed by the clinic staff, but can be taken late if no more than 4 hours have elapsed since the prescribed dosing time. If more than 4 hours have elapsed since the prescribed evening dosing time, the evening dose should not be taken. On Day 4, the morning and evening doses of vonoprazan 20 mg will be administered in the clinic. On Day 4, subjects will be admitted to the

clinical research unit at least 2 hours prior to their scheduled dose administration for check-in procedures. Milk samples for PK assessments will be collected at prespecified intervals from predose (0 hour) and at pooled intervals up to 24 hours (0-4 hours, 4-8 hours, 8-12 hours, 12-18 hours, and 18-24 hours) after the morning dose of study drug on Day 4. During each sampling interval, the sample collections will be done using a standardized electric pump for efficient milk extraction, emptying both breasts. The time of starting and finishing milk expression will be recorded. All milk within each prespecified sampling interval will be carefully combined and mixed, and the total volume recorded. After recording the volume, each milk sample will be mixed with a stabilizing solution in 1:1 ratio to ensure stability of vonoprazan in the milk sample. Details of this process will be provided in a separate document. Two equal aliquots from each of these stabilized interval collections will be appropriately labelled and stored immediately at or below -70 °C until analyzed for vonoprazan concentrations.

Safety will be assessed by monitoring AEs, clinical laboratory test results (hematology, serum chemistry, and urinalysis), and vital signs. In the event of early termination, subjects should return to the clinical research unit for final safety assessments. These subjects may be replaced at the investigator's discretion.

Subjects will be confined to the clinical research unit from the morning of Day 4 until discharge on Day 5. All subjects will be followed up via a phone call on Day 11 (±2 days) for follow-up safety assessments of AEs, concomitant medication use, and to reassess breastfeeding practices (eg, frequency, duration of feeds, use of formula supplementation), along with a description of any challenges the subject experienced and any need for lactation consultation. Information will also be obtained to determine whether reinitiation of breastfeeding was established for subjects who planned to continue breastfeeding after Day 9.

The duration of the study for individual subjects, excluding Screening Period, is approximately 13 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.

All tables, listings, and figures will be presented by treatment. The treatments below will be used for presentations:

Vonoprazan 20 mg tablet once daily;

Vonoprazan 20 mg tablet twice daily;

All data listings will be sorted by treatment and 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, 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 number of subjects is based on clinical and practical considerations and not on a formal statistical power calculation. The total sample size of 15 subjects is considered sufficient for the objectives of the study.

4.2. Randomization and Blinding

This is a nonrandomized and open-label study. The first 5 subjects will be assigned to receive vonoprazan 20 mg once daily and the next 10 subjects will be assigned vonoprazan 20 mg twice daily.

4.3. Analysis Population

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

The PK population will include all subjects who received sufficient doses of vonoprazan and have sufficient concentration data in milk to support accurate estimation of at least 1 PK parameter in milk.

5. Subject Disposition

5.1 Disposition

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

The following will be summarized for the screened population for all:

- The number of subjects who screen failed (both overall and according to reason for screen failure)
- The number of subjects who received treatment
- The number of subjects who completed the study
- The number of subjects treated 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.

Significant protocol deviations will be summarized in a table 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.

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 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 27.0) 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 Vonoprazan 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 2024-March (Global B3)) and presented in a data listing.

7.2 Study Treatment

The study drug administration data as collected on electronic case report form (eCRF) will be presented in a data listing.

8. Pharmacokinetics

All PK listings will be presented using the safety population, and subjects not included in the PK population will be highlighted. Individual PK concentrations, amounts, and parameters will be presented using the safety population, and subjects not included in the PK population will be highlighted. Subjects without any estimable PK parameters will not be presented in the listing of PK parameters. PK tables and mean figures will be presented using the PK population.

8.1 Breast Milk Concentrations and Amounts

Breast milk samples will be collected at the following time points for PK assessment:

Prior to the morning dose on Day 4 and at regularly scheduled intervals through 24 hours after the morning dose (0-4 hours, 4-8 hours, 8-12 hours, 12-18 hours, and 18-24 hours)

Individual breast milk concentrations, amounts (concentration * volume), and cumulative amounts will be presented in data listings and summarized separately by dosing scheme (once daily or twice daily) and collection interval.

Individual breast milk concentrations will be plotted by actual mid-point of the collection interval on a linear scale. Arithmetic mean breast milk concentrations will be plotted by nominal mid-point of the collection interval on a linear scale. Individual and arithmetic mean amounts, and cumulative amounts will be plotted by collection interval on a linear scale.

8.2 Breast Milk Pharmacokinetic Parameters and Infant Exposure Measures

Breast milk vonoprazan concentration-time data and excretion parameters will be derived from vonoprazan amount data using SAS® (SAS Institute Inc., Cary, North Carolina) Version 9.4 or higher. The following PK parameters and infant exposure measures will be calculated for vonoprazan, where data permit:

Parameter	Definition
C_{min}	Minimum observed concentration.
C_{max}	Maximum observed concentration.
C_{avg}	Average concentration, calculated as: AUC_{0-24} / tau (tau = 24 hours)
T_{max}	Time to maximum observed concentration (actual midpoint of the interval in which C_{max} is observed).
AUC_{0-24}	AUC from time 0 to 24 hours post-dose, calculated as: the sum of the product of the concentration of the interval and the width of the interval i.e. Σ interval concentration × interval width The actual interval width will be used in the derivation.
Total amount of drug excreted (mg)	Total amount of drug excreted in breast milk over 24 hours; calculated as the sum of drug concentration × expressed milk volume in each collection interval over 24-hour period.
Relative amount excreted (%)	Total amount of drug excreted over 24 hours relative to total dose administered; calculated as the sum of (total amount of drug excreted in each collection interval / total dose received over 24-hour period) * 100.
Daily maternal dose (mg/kg)	Maternal dose received; calculated as: 20 mg / mother's body weight in kg (once daily dosing) or 40 mg / mother's body weight in kg (twice daily dosing).
Daily infant dose (mg/kg/day)	Estimated weight adjusted daily dose consumed by the infant through breast milk; calculated as total amount of drug excreted over 24-hour period / weight of infant. Calculation will use the nominal infant weight of 6.0 kg which is the approximate 50th percentile for a 3-month old infant.

Relative infant dose (%)	Daily infant dose relative to the daily maternal dose; calculated as (daily infant dose / daily maternal dose) * 100.

Actual sampling times will be used for the estimation of all breast milk PK parameters, and all concentrations associated with scheduled sampling times will be included in the analysis. Unscheduled PK samples will not be included in the estimation of PK parameters.

Breast milk PK parameters and exposure measures will be presented in data listings and summarized descriptively by dosing scheme (once daily or twice daily).

8.3 Data Handling

8.3.1 Pharmacokinetic Profile Exclusions

Where subjects experience issues pertaining to a specific administration of study drug which may affect exposure to study drug during PK sample collections (eg, dosing errors, etc), individual PK results will be reviewed and evaluated by the study pharmacokineticist on a case-by-case basis for potential exclusion from treatment summaries and/or the PK population. All exclusions will be documented throughout the affected data listings.

8.3.2 Data Rounding

Concentration data will be reported in the listings to the same precision as received in the raw bioanalytical data. Amounts, PK parameter estimates, and infant exposure measures will be reported to 3 significant figures. Associated concentration, amount, parameter, and measure summary statistics will be reported to 3 significant figures except number of non-missing observations (n), which will be reported as an integer.

8.3.3 Below the Limit of Quantification

Breast milk concentrations that are below the limit of quantification (BLQ) will be treated as zero for the calculation of amounts, concentration descriptive statistics, and estimation of all PK parameters.

8.3.4 Missing Data

All missing concentration data will be presented as missing in concentration data listings and excluded from the estimation of amounts, concentration summary statistics, and PK parameters. No imputation for missing data will be performed.

8.3.5 Summary Statistics

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

Breast milk concentrations and amounts: n, arithmetic mean, standard deviation (SD), percent coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum.

Breast milk concentration and amount data will be summarized according to nominal time windows.

Breast milk PK parameters and infant exposure measures: n, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum; only n, median, minimum, and maximum will be presented for T_{max}.

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

Where breast milk concentrations are BLQ (handled as zero for amount calculation, summary statistics, and parameter generation), geometric mean and geometric CV will be reported as not applicable (NA).

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 associated with the use of a drug in humans, whether or not considered drug related.

A pretreatment 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 ICF to participate in a study; it does not necessarily have to have a causal relationship with study participation.

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 the study drug.

A serious AE (SAE) is defined as any untoward medical occurrence at any dose that meets one of the following criteria:

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 9.1 of protocol)
   - Exposes the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization

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

The AEs that are evaluated as related will be considered treatment-related AEs for summary purpose.

The severity of AEs will be classified by the investigator as mild, moderate, or severe.
An overall TEAE summary will be generated presenting the frequency and percentage of subjects and the number of AEs for the following:

Any AE
Any PTE
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 SAE
Any treatment-related SAE
Any TEAE leading to early discontinuation
Any death

All AEs will be coded using MedDRA (version 27.0). The TEAEs will also be summarized by system organ class (SOC), preferred term (PT), by severity and relationship to study treatment.

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, treatment-emergent AEs, PTEs, and SAEs, and AEs leading to study treatment discontinuation.

9.2 Clinical Laboratory Evaluations

The following laboratory tests will be performed:

Hematology	Absolute neutrophil count and differential count, hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocytes count (basophils, eosinophils, lymphocytes, monocytes, neutrophils), mean corpuscular volume, platelet count, red blood cell count, and red blood cell distribution width
Serum chemistry	Alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen, calcium, carbon dioxide, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), creatinine, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, triglycerides, and uric acid
Urinalysis	Appearance, bilirubin, color, glucose, ketones, leukocyte esterase, reflex microscopy (performed if dipstick is positive for protein or the blood value is 1+ or greater; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen
Serology	Hepatitis B surface antigen, hepatitis C virus antibody, and HIV antibody types 1 and 2 (Screening only)
Other analyses	Urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, methylenedioxymethamphetamine, and opiates [including heroin, codeine, and oxycodone]), COVID-19 screening (SARS-CoV-2 testing will be conducted as per clinical research unit's standard processes), serum and urine pregnancy test (human chorionic gonadotropin), international normalized ratio (INR) (to be done when follow-up laboratory tests are required for elevated ALT or AST levels per Section 9.3.1 of protocol), and an alcohol breath test

The clinical laboratory 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. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

Actual results and change from baseline for hematology, serum chemistry, and urinalysis quantitative data at post-dose time point will be summarized for the safety population. Shift from baseline in terms of low/normal/high for hematology and serum chemistry tests, and in terms of normal/abnormal for urinalysis tests will be summarized for the safety population.

9.3 Vital Sign Measurements

Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature 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, 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 (Visit 1), and abbreviated physical examinations will be performed at the timepoints indicated in the schedule of assessments (schedules of assessments can be found in Section 13).

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

9.5 Electrocardiograms

Single 12-lead (electrocardiogram) 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. Assessments will 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.

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).

All ECG data will be presented in a data listing.

9.6 Breastfeeding

Subjects will be asked about their intentions for continuing breastfeeding and information will be obtained regarding their current breastfeeding practices (eg, frequency, duration of feeds, use of formula supplementation).

Breastfeeding practices will be reassessed, along with a description of any challenges the subject experienced and any need for a lactation consultant. (schedules of assessments can be found in Section 13).

All breastfeeding data will 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 clinical study report (CSR) for this study.

12. References

None.

13. Schedule of Assessments

Period	Screening	Baseline	Treatment					Safety Follow-up Telephone Call/ EOS
Procedure **Day**	**–28 to –1**	**1 (Predose)**	**1**	**2**	**3**	**4**	**5/ET**	**11 (±2 Days)**
Admission to clinical research unit						X		
Discharge from clinical research unit [a]							X	
Outpatient visit[b]	X	X	X	X	X			
Telephone call[c]								X
Informed consent	X							
Demographics	X							
Serology[d]	X							
Inclusion/exclusion criteria	X	X						
Medical history	X	X						
Urine drug/alcohol/cotinine screen[e]	X	X				X		
Height, weight, and BMI[f]	X	X					X	
Physical examination[g]	X	X					X	
Vital sign measurements[h]	X	X				X	X	
12-lead ECG[i]	X	X						
Clinical laboratory testing[j]	X	X					X	
Pregnancy test[k]	X	X				X	X	
Study drug administration[l]			X	X	X	X		
Milk PK sample collection[m]						X	X	
Lactation consultation[n]	X	X	X	X	X	X	X	X
Breastfeeding discussion[o]	X	X						X
PTEs monitoring[p]	X	X						
AEs[q]			←				X	→
Prior/concomitant medications	←					X		→

Abbreviations: AEs, adverse events; BMI, body mass index; ECG, electrocardiogram; EOS, end of the study; ET, early termination; ICF, informed consent form; PK, pharmacokinetic; PTE, pretreatment event; QTcF, QT interval corrected for heart rate using Fridericia's formula.

Notes:

[a] Discharge on Day 5 following 24-hour milk PK sample collection. Note: Subjects who withdraw before completion of the study should return to the clinical research unit for ET assessments.

[b] Outpatient visits will occur at the clinical research unit at Screening and on Days 1 through 3; subjects will be administered vonoprazan tablet in the morning at the same time each day.

(c) Safety follow-up/EOS telephone call: Subjects will receive a telephone call from the clinical research unit 7 days (±2 days) after their last dose of study drug to assess for AEs and concomitant medication use. Information will also be obtained to determine whether reinitiation of breastfeeding was established for subjects who planned to continue breastfeeding after Day 9). Breastfeeding practices (eg, frequency, duration of feeds, use of formula supplementation) will be reassessed, along with a description of any challenges the subject experienced and any need for a lactation consultant.

(d) Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and HIV types 1 and 2 antibodies. For COVID-19 screening, SARS-CoV-2 testing will be conducted as per clinical research unit's standard processes.

(e) Urine drug/alcohol/cotinine screen will occur at Screening, Baseline, and Day 4/Check-in per the clinical research unit's standard procedures.

(f) Height and weight will be measured, and BMI calculated at Screening only. Only weight will be measured at Baseline and Day 5/ET.

(g) A full physical examination will be performed at Screening (at a minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities). A brief physical examination will be performed at Baseline and Day 5/ET (at a 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.

(h) Vital signs will be measured at Screening and Baseline; within 60 minutes prior to study drug dosing on Day 4; and on the day of discharge (Day 5)/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, heart rate, respiratory rate, and body temperature.

(i) Single 12-lead ECG recordings will be made at Screening and Baseline 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.

(j) Clinical laboratory testing will occur at Screening, Baseline, and on the day of discharge (Day 5)/ET. A complete list of assessments is provided in Section 6.2.2 of protocol. Blood and urine samples will be collected under fasted conditions and prepared per the clinical research unit's standard procedures.

(k) All subjects will undergo a pregnancy test at Screening, Baseline, and Day 4/Check-in, or ET. A serum pregnancy test will be performed at Screening and urine pregnancy test at Baseline and on Day 4/Check-in or ET.

(l) Each subject will receive vonoprazan 20-mg tablet in the morning from Day 1 through Day 4. All doses of vonoprazan will be administered with 240 mL of room temperature water. Subjects will maintain an upright (ie, seated or standing) position for at least 4 hours after dosing.

(m) Breast milk samples for PK analyses will be collected predose on Day 4, and at regularly scheduled intervals through 24 hours after dosing (0-4 hours, 4-8 hours, 8-12 hours, 12-18 hours, and 18-24 hours). During each collection interval, all milk will be collected and at the conclusion of each interval both breasts will be completely emptied using an electric breast pump and milk will be carefully combined with any milk collected previously within that interval. The combined sample will be mixed, and the total volume recorded. After recording the volume, each milk sample will be mixed with a stabilizing solution in a 1:1 ratio to ensure stability of vonoprazan in the milk sample. Aliquots from each of these interval collections will be stored and analyzed for vonoprazan concentrations.

(n) Subjects will have access to a lactation consultant throughout the study to provide lactation support as needed.

(o) At Screening and Baseline, subjects will be encouraged to have stored breast milk available for feeding their infants for the duration of approximately 9 days (from Day 1 till 5 days after the last dose). Subjects will be asked about their intentions for continuing breastfeeding after Day 9 and information will be obtained regarding their current breastfeeding practices (eg, frequency, duration of feeds, use of formula supplementation). At the safety follow-up telephone call, subjects will be asked whether reinitiation of breastfeeding was established for subjects who planned to continue breastfeeding after Day 9. Breastfeeding practices will be reassessed, along with a description of any challenges the subject experienced and any need for a lactation consultant.

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

(q) Adverse events will be assessed from the time of the first study drug dosing until EOS 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:	**VONO-401**

Document Description:	Final Statistical Analysis Plan
SAP Title:	A Phase 1, Open-Label Study to Evaluate Vonoprazan Concentrations in Breast Milk of Healthy Lactating Women Receiving Vonoprazan 20 mg Once Daily or Vonoprazan 20 mg Twice Daily
SAP Version Number:	Final Version 1.0
Effective Date:	30 August 2024

Author(s):

For [redacted], Biostatistician

Approved by:

[redacted]

30-Aug-2024

Date *(DD-MMM-YYYY)*

Biostatistics and Programming,
Phathom Pharmaceuticals, Inc.

[redacted]

30-Aug-2024

Date *(DD-MMM-YYYY)*

Clinical Pl.
Phathom Pharmaceuticals, Inc.