**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: 18 July 2024**

# CLINICAL STUDY PROTOCOL
# IND 143190/144399

# 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

## PROTOCOL NO. VONO-401

| | |
|---|---|
| Sponsor: | Phathom Pharmaceuticals, Inc.<br>2150 E. Lake Cook Road<br>Suite 800<br>Buffalo Grove, IL 60089 USA |
| Sponsor Contact: | [redacted]<br>Telephone: [redacted] |
| Medical Monitor: | [redacted] Medical Monitor<br>[redacted]<br>SAE Hotline (24 hour): [redacted]<br>SAE Fax: [redacted] |
| Version of Protocol: | Version 2.0 |
| Date of Protocol: | 18 July 2024 |

## CONFIDENTIAL



The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

# SIGNATURE PAGE

**PROTOCOL 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

**PROTOCOL NUMBER:** VONO-401

[redacted]

Phathom Pharmaceuticals, Inc.

[redacted]

Phathom Pharmaceuticals, Inc.

[redacted]

Clinical Pharmacology Consultant
Phathom Pharmaceuticals, Inc.

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "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" in accordance with the guidelines and all applicable government regulations including United States Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

| | |
|---|---|
| Signature of Principal Investigator | Date |
| Printed Name of Principal Investigator | |

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# 1. INTRODUCTION

## 1.1 BACKGROUND

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.

Vonoprazan was developed by Takeda Pharmaceutical Company Limited. Phathom Pharmaceuticals, Inc. (Phathom) has licensed the exclusive rights from Takeda to develop and commercialize vonoprazan in the United States (US), Europe, and Canada.

In the US, vonoprazan is 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 relief of heartburn associated with nonerosive 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 other countries, vonoprazan has been studied in additional acid-related diseases including healing of gastric ulcer/duodenal ulcer and for the prevention of recurrence of peptic ulcer during nonsteroidal anti-inflammatory drugs or aspirin administration. Vonoprazan is approved in Japan and other countries in Asia, Latin America, and Russia for a variety of these indications in adults.

Further information on the study drug can be found in the investigator's brochure (Takeda Pharmaceutical 2024).

## 1.2 RATIONALE FOR STUDY

Breastfeeding is crucial in child health and development (Lawrence and Lawrence 2011, Eidelman et al 2012). Immunological and anti-inflammatory agents that are passed on from mother to the infant via breast milk also facilitates development of protective mechanisms against several diseases (DHHS 2011). Despite these benefits, the conflict between the risks of maternal medications needed for postpartum health and ensuring optimal child nutrition through breastfeeding presents a complex challenge in the development of drugs for postpartum women (Clowse et al 2017). Approximately 72% of nursing mothers take medications. Although medication use is not the primary reason for most mothers avoiding or

stopping breastfeeding, it has been reported in up to 10% of mothers (Anderson and Momper 2020).

There are no data available to date on the presence of vonoprazan in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, vonoprazan was shown to be excreted in milk. Although animal data cannot often be directly extrapolated to humans due to physiological differences between animals and humans for excretion into breast milk, there is a potential that the drug may also be present in human milk (Anderson and Momper 2020).

In the US Prescribing Information for Voquezna Triple Pak and Voquezna Dual Pak (Voquezna 2024), it is advised that a woman should pump and discard human milk for the duration of Voquezna Triple Pak or Voquezna Dual Pak therapy, and for 2 days after therapy ends, and feed her infant stored human milk (collected prior to therapy) or formula due to the potential risk of adverse liver effects shown in animal studies with vonoprazan. This study is designed to assess the concentrations of vonoprazan in milk from healthy lactating women using a validated assay.

Breastfeeding women receiving vonoprazan and their treating physicians would benefit from the availability of information about the transfer of vonoprazan into mature breast milk, to better assess the benefits and risks of breastfeeding in their individual situations.

## 1.3 RATIONALE FOR DOSE SELECTION

Per the DHHS 2019 guidelines, this study has been designed to minimize the burden on the lactating mother for data collection while obtaining adequate data.

Voquezna Triple Pak and Voquezna Dual Pak are approved for use in the US for treatment of *H. pylori* infection in adults. Voquezna is approved in the US for the healing of EE and relief of heartburn associated with EE, maintenance of healed EE and relief of heartburn associated with EE, and for relief of heartburn associated with GERD in adults.

Vonoprazan is absorbed rapidly following oral administration, with median time to maximum observed plasma concentrations typically occurring 1.5 to 2 hours after once-daily dosing and 2.5 to 4 hours after twice-daily dosing. The rate of elimination from the plasma allows for once- or twice-daily dosing, with mean $t_{1/2z}$ values typically 7 to 8 hours. Vonoprazan exhibits time-independent pharmacokinetics (PK) and steady-state concentrations are achieved by Day 3 to 4. In this study, a once-daily dose of vonoprazan 20 mg or twice-daily dose of vonoprazan 20 mg will be administered for 4 consecutive days ensuring that

breast-milk sampling occurs when drug exposure in plasma is at steady state. A dose of vonoprazan 20 mg once daily is selected as it is the highest dose approved for the healing of EE and vonoprazan 20 mg twice daily is selected as it is the highest approved dose for the treatment of *H. pylori* infection.

# 2. STUDY OBJECTIVES

**Table 2-1 Study Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To determine the 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 | • $AUC_{0-24}$, $C_{max}$, $C_{min}$, $C_{avg}$, and $T_{max}$ |
| **Secondary** | |
| • To determine total drug excreted in milk | • Total amount of drug excreted in milk (mg)<br>• 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)<br>• Estimated relative infant dose to the total maternal dose received (%) |
| **Safety** | |
| • To evaluate the safety and tolerability of vonoprazan 20 mg administered once daily or vonoprazan 20 mg administered twice daily for 4 consecutive days | • AEs<br>• Clinical laboratory test values (hematology, serum chemistry, urinalysis)<br>• Vital signs |

AEs: adverse events; $AUC_{0-24}$: area under the milk drug concentration-time curve from time 0 to 24 hours following the morning dose on Day 4; $C_{avg}$: average drug concentration in milk; $C_{max}$: maximum drug concentration in milk; $C_{min}$: minimum drug concentration in milk; PK: pharmacokinetics; $T_{max}$: time to maximum observed concentration in milk.

# 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 is planned.

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 must agree to discontinue breastfeeding for the duration of the Treatment Period and until at least 5 days after the last dose of the study drug to ensure that the infant is not exposed to vonoprazan (ie, the subject must agree to not breastfeed or use breast milk that is pumped from Day 1 of dosing with vonoprazan until 5 days after the last dose). Subjects will be encouraged to have stored breast milk available for feeding their infants for a duration of 9 days. 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). Subjects will have access to a lactation consultant throughout the duration of the study to provide lactation support.

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 adverse events (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. All assessments will be conducted per the schedule of events (SOE, Section 3.1).

## 3.1 SCHEDULE OF EVENTS

| 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 | | |
| Dispense study drug for at-home administration in the evenings of Days 1 to 3 (l) | | | X | | | | | |
| Dispense Study Dosing Card (l) | | | X | | | | | |
| Review Study Dosing Card/Drug Accountability | | | | 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. 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) Subjects will be assigned to either once-daily or twice-daily doses of vonoprazan. Each subject will receive vonoprazan 20-mg tablet in the morning from Day 1 through Day 4 at the clinic. Those assigned to receive vonoprazan 20 mg twice daily will self-administer a second dose of vonoprazan 20 mg at home approximately 12 hours after the first dose on Days 1 through 3. Date and time of self-administered doses will be documented on the Study Dosing Card. 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 the morning and evening doses of vonoprazan 20 mg will be administered in the clinic. All doses of vonoprazan will be administered with 240 mL of room temperature water.

(m) Breast milk samples for PK analyses will be collected predose on Day 4, and at regularly scheduled intervals through 24 hours after the morning 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.

# 4. STUDY POPULATION

Up to 15 healthy lactating women subjects will be enrolled at a single center in the US.

## 4.1 INCLUSION CRITERIA

Each subject must meet all the following criteria to be enrolled in this study:

1. The subject is a healthy lactating woman at least 18 years of age at the time of signing the informed consent form (ICF).

2. The subject has delivered a normal term infant (at least 37 weeks gestation) and has been breastfeeding or actively pumping breast milk for at least 4 weeks postpartum prior to the first dose.

3. The subject is willing to not breastfeed or otherwise use her breast milk during administration of vonoprazan and until at least 5 days after the last dose of the study drug.

4. The subject has confirmed that her breastfed infant is able to feed from a bottle.

5. The subject agrees to collect all breast milk from predose to 24 hours after the morning dose administration on Day 4, using an electric pump.

6. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings at Screening.

7. Subjects of childbearing potential must use an acceptable method of birth control (ie, diaphragm with spermicide, intrauterine device, condom with foam or vaginal spermicide, oral contraceptives, or abstinence) or be surgically sterile (ie, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy). All subjects must have a negative pregnancy test at Screening and before the first dose of study drug (Baseline).

8. The subject agrees to comply with all protocol requirements.

9. The subject is able to provide written informed consent.

## 4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has a positive pregnancy test at Screening or Baseline, is planning to become pregnant before, during, or within 4 weeks after participating in this study, or intends to donate ova during this time period, or is of childbearing potential and not using an effective contraceptive method.

2. The subject has a history of breast implants, breast augmentation, or breast reduction surgery that significantly impacts breastfeeding or collection of milk from one or both breasts.

3. The subject has signs or symptoms of mastitis or other condition that would prevent the collection of milk from one or both breasts.

4. The subject has undergone prior esophageal and/or gastrointestinal surgeries that may affect study drug absorption.

5. The subject has undergone surgery (other than cesarean section) within 30 days before the first dose of study drug.

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

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

8. The subject has used any prescription (excluding hormonal birth control) and/or over-the-counter medications (including cytochrome P450 3A4 inducers), including herbal or nutritional supplements, within 14 days before the first dose of study drug, and/or is expected to require any such medication during the course of the study until end of the Treatment Period. Use of multivitamins and acetaminophen (up to 2 g per day) is permissible.

9. The subject has consumed grapefruit and/or grapefruit juice, Seville orange, or Seville orange-containing products (eg, marmalade) within 7 days before the first dose of study drug and/or is expected to be unable to abstain through the study.

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

11. The subject has a history of alcohol abuse or drug dependency within 12 months before the first dose of study drug.

12. The subject has a positive test result for drugs of abuse, alcohol, or cotinine (indicating active current smoking) at Screening, Baseline, or Day 4 (Check-in).

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

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

15. The subject has received study drug in another investigational study (including vonoprazan) within 30 days prior to start of the Screening Period.

16. The subject has a history of hypersensitivity or allergies to vonoprazan or any of its formulation excipients (D-mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, ascorbic acid, croscarmellose sodium, magnesium stearate, hypromellose, polyethylene glycol 8000, titanium dioxide, or ferric oxide red).

17. In the opinion of the investigator, the subject is not suitable for entry into the study.

## 4.3 WITHDRAWAL CRITERIA

General criteria for subject withdrawal and the handling of withdrawals can be found in Appendix 2.

## 4.4 SUBJECT REPLACEMENT

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws before completing the study may be replaced to retain the target of up to 15 subjects.

## 4.5 SCREEN FAILURES

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

# 5. STUDY TREATMENTS

## 5.1 TREATMENTS ADMINISTERED

All subjects will receive the study treatment as described in Section 3 and according to the SOE (Section 3.1). Five subjects will receive vonoprazan 20 mg once daily and 10 subjects will receive vonoprazan 20 mg twice daily (total daily dose of 40 mg).

## 5.2 INVESTIGATIONAL PRODUCTS

The study drug that will be used is as follows:

| Product | Supplied Formulation |
|---|---|
| Vonoprazan | 20-mg tablet |

Vonoprazan tablets contain 20 mg vonoprazan free base (MW 345.39) and the following inactive excipients: D-mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, ascorbic acid, croscarmellose sodium, magnesium stearate, hypromellose, polyethylene glycol 8000, titanium dioxide, and ferric oxide red.

Further information on the study drug can be found in the investigator's brochure (Takeda Pharmaceutical 2024).

### 5.2.1 Study Drug Preparation and Storage

Phathom will provide the investigator and clinical research unit with adequate quantities of vonoprazan tablets. The tablets will be packaged in high-density polyethylene bottles. The clinical research unit pharmacy will provide the study drug for each subject according to the SOE (Section 3.1) and the pharmacy standard procedures for in-clinic dosing. The clinical

research unit pharmacy will provide the study drug for each subject who will self-administer the evening dose at home.

At the clinical site, all study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinical research unit personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions. For study drug dispensed for at-home administrations, subjects should follow the labeled storage conditions.

### 5.2.2 Study Drug Accountability

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

## 5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

This is a nonrandomized study. Subjects who meet all inclusion and none of the exclusion criteria will receive study treatments according to their assigned treatment and the SOE (Section 3.1). 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.

## 5.4 BLINDING

This is an open-label study.

# 6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an ICF as outlined in Section 9.4.2.3.

Details of additional standard study procedures can be found in Appendix 2.

The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

## 6.1 PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS

The following milk PK parameters for vonoprazan will be estimated (if data permit) as endpoints for each subject using standard noncompartmental methods: $AUC_{0-24}$, $C_{max}$, $C_{min}$, $C_{avg}$, and $T_{max}$. In addition, the total amount of drug excreted in milk (mg), the amount of drug excreted in milk relative to the total dose received (%), the estimated infant daily dose (mg/kg/day), and the estimated relative infant dose to the total maternal dose received (%) will be derived.

The timing and frequency of PK sample collection is listed in the SOE (Section 3.1).

### 6.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical research unit separately.

### 6.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay for vonoprazan in human milk. Assay results and validation details will be provided in a separate bioanalytical report.

## 6.2 SAFETY ASSESSMENTS AND ENDPOINTS

The timing and frequency of all safety assessments is listed in the SOE (Section 3.1).

Safety and tolerability endpoints will include monitoring and recording of AEs, clinical laboratory test results (hematology, serum chemistry, and urinalysis), and vital sign measurements.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE reported on the AE page of the subject's electronic case report form (eCRF). The investigator will monitor the subject until the result has reached the reference range or the result at Screening, or until the investigator determines that follow-up is no longer medically necessary.

### 6.2.1 Adverse Events

Definitions and procedures for reporting of AEs can be found in Appendix 3. For this study, the following contact information is to be used for SAE reporting:

[redacted] Medical Monitor: [redacted]

SAE Hotline (24 hour): [redacted]
SAE: [redacted]
Safety Email Address: [redacted]

### 6.2.2 Clinical Laboratory Assessments

The following clinical laboratory assessments 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), and an alcohol breath test |

The clinical laboratory that performs the tests will provide the reference ranges for all clinical laboratory parameters.

Clinical laboratory tests may be repeated at the discretion of the investigator, if necessary, for assessment of inclusion and exclusion criteria or evaluation of clinical laboratory abnormalities.

### 6.2.3 Lactation Consultation and Breastfeeding Practice/Reinitiation

Subjects will have access to a lactation consultant throughout the duration of the study, to provide lactation support, as needed.

At Screening, subjects will be encouraged to have stored breast milk available for feeding their infants for the duration of the Treatment Period and until at least 5 days after the last dose of the study drug. 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 Day 11 (±2 days) safety follow-up telephone call, information will be obtained to determine 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 may have experienced and any need for a lactation consultant.

# 7. STATISTICAL ANALYSIS PLANS

## 7.1 SAMPLE SIZE CALCULATIONS

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.

## 7.2 ANALYSIS SETS

The analysis populations are as follows:

- The PK population will include subjects who receive sufficient doses of vonoprazan and have sufficient concentration data in milk to support accurate estimation of at least 1 PK parameter in milk.
- The safety population will include all subjects who receive at least 1 dose of study drug.

## 7.3 STATISTICAL ANALYSES

Details of all statistical analyses will be described in a separate statistical analysis plan. All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum).

Baseline demographic and background variables will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

### 7.3.1 Pharmacokinetic Analyses

The PK analysis will be based on the PK population. Noncompartmental analysis to determine the milk PK parameters of vonoprazan will be performed. All parameters will be calculated using the latest version of Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) or SAS® software (SAS Institute Inc., Cary, North Carolina).

Individual milk concentration-time data will be presented and summarized for each treatment (once daily and twice daily), both graphically and in tabular form with descriptive statistics (n, arithmetic mean, SD, percent coefficient of variation [CV%], median, minimum, maximum, geometric mean, and geometric CV%). Concentration data will be summarized according to nominal time windows.

The following milk PK parameters will be estimated (if data permit) for each subject: $AUC_{0-24}$, $C_{max}$, $C_{min}$, $C_{avg}$, and $T_{max}$. Pharmacokinetic parameters will be summarized for each treatment (once daily and twice daily) using descriptive statistics (n, arithmetic mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%). A listing of individual PK parameters for each subject will be provided.

In addition, the total amount of drug excreted in milk (mg), the total amount of drug excreted in milk relative to the total dose received (%), the estimated infant dose (mg/kg/day), and the estimated relative infant dose to the total maternal dose received (%) will be calculated for each subject and summarized for each treatment (once daily and twice daily) using descriptive statistics. Additional PK analyses may be performed as appropriate.

### 7.3.2 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in a data listing. Treatment-emergent AEs (TEAEs) will be summarized overall, as well as by severity and relationship to study drug. Serious AEs, AEs leading to discontinuation of study drug, and PTEs will also be presented in the data listings.

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

## 7.4 HANDLING OF MISSING DATA

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

For the PK analysis, BLQ values will be treated as zero.

## 7.5 INTERIM ANALYSES

No formal interim analyses will be performed in this study.

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# 9. APPENDICES

## 9.1 APPENDIX 1: LIST OF ABBREVIATIONS

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the milk concentration versus time curve |
| $AUC_{0-24}$ | area under the milk drug concentration-time curve from time 0 to 24 hours following the morning dose on Day 4 |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| $C_{avg}$ | average drug concentration in milk |
| CFR | Code of Federal Regulations |
| $C_{max}$ | maximum drug concentration in milk |
| $C_{min}$ | minimum drug concentration in milk |
| CV | coefficient of variation |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EE | erosive esophagitis |
| EOS | end of the study |
| ET | early termination |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GERD | gastroesophageal reflux disease |
| H+, K+ ATPase | hydrogen, potassium–adenosine triphosphatase |
| *H. pylori* | *Helicobacter pylori* |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | independent ethics committee |
| INR | international normalized ratio |
| IRB | institutional review board |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PCAB | potassium competitive acid blocker |
| PK | pharmacokinetic(s) |
| PTE | pretreatment event |
| QTcF | QT interval corrected for heart rate using Fridericia's formula |
| SAE | serious adverse event |
| SD | standard deviation |
| SOE | schedule of events |
| SUSAR | suspected unexpected serious adverse reactions |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | time to maximum observed concentration in milk |

| Abbreviation | Term |
|---|---|
| ULN | upper limit of normal |
| US | United States |

# 9.2 APPENDIX 2: STANDARD PROCEDURES

## 9.2.1 Removal of Subjects From Therapy or Assessment

### 9.2.1.1 General Criteria for Withdrawal

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

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

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

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

#### 9.2.1.2 Handling of Withdrawals

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

### 9.2.2 Prior and Concomitant Medications and Therapies

Restrictions for prior and concomitant medications and therapies are provided in Section 4.2. Prior and concomitant medications and therapies will be coded using the WHODrug Global dictionary.

#### 9.2.2.1 Prior Medications

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

#### 9.2.2.2 Concomitant Medications

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

### 9.2.3 Treatment Compliance

All morning doses of study drug and the evening dose on Day 4 (as applicable, for subjects assigned to twice-daily dosing) will be administered in the clinical research unit under direct observation of clinical research unit personnel and will be recorded in the eCRF. Evening doses of study drug on Days 1 through 3 will be self-administered by the subject at home for subjects assigned to twice-daily dosing. Subjects will be provided a Study Dosing Card to record the date and time the evening dose was taken on Study Days 1 to 3.

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

## 9.3 APPENDIX 3: ADVERSE EVENT DEFINITIONS AND REPORTING

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

### 9.3.1 Adverse Event Definitions

A 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.

An AE is defined as any untoward medical occurrence in a subject enrolled in 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 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.

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

**Table 9-1 Medically Significant Adverse Event List**

| Term |
|---|
| Acute respiratory failure/acute respiratory distress syndrome |
| Torsade de pointes/ventricular fibrillation/ventricular tachycardia |
| Malignant hypertension |
| Convulsive seizures |
| Agranulocytosis |
| Aplastic anemia |
| Toxic epidermal necrolysis/Stevens-Johnson syndrome |
| Hepatic necrosis |
| Acute liver failure |
| Anaphylactic shock |
| Acute renal failure |
| Pulmonary hypertension |
| Pulmonary fibrosis |
| Confirmed or suspected endotoxin shock |
| Confirmed or suspected transmission of infectious agent by a medicinal product |
| Neuroleptic malignant syndrome/malignant hyperthermia |
| Spontaneous abortion/stillbirth and fetal death |
| COVID-19 pneumonia |
| COVID-19–related disease |

Abbreviation: COVID-19, coronavirus disease 2019.

The PTEs that fulfill one or more of the serious criteria above are also considered SAEs and should be reported and followed up in the same manner.

A special interest AE (serious or nonserious) is one of scientific and medical concern specific to the study drug or program for which ongoing monitoring and rapid communication by the investigator to Phathom may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Phathom.

**Reporting of Abnormal Liver Function Tests:**

If a subject is noted to have an ALT or AST value >3 × ULN and a total bilirubin value >2 × ULN during the treatment or follow-up period for which an alternative etiology has not been identified, the event should be reported as an SAE. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B, other acute liver disease, medical history, or concurrent medical conditions. Study drug should be discontinued immediately as per Section 9.2.1.1. Laboratory tests should be followed up as described in Section 6.2.2. In addition, a Liver Function Test Increase eCRF must be completed and transmitted with the SAE form.

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

If subjects with elevated baseline ALT or AST levels experience ALT or AST >5 × ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, gamma-glutamyl transferase, and INR) should be repeated within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality is found.

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

### 9.3.2 Eliciting and Documenting Adverse Events

Collection of PTEs will commence at the time the subject signs the ICF to participate in the study and will continue until the subject is first administered study drug or until screen

failure. For subjects who discontinue prior to study drug administration, PTEs will be collected until the subject discontinues study participation. Collection of AEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection will continue until the follow-up telephone call or withdrawal from the study.

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

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

### 9.3.3 Reporting Adverse Events

All PTEs and AEs will be documented on the PTE/AE page of the eCRF, regardless of whether the investigator concludes that the event is related to drug treatment. Information to be collected includes event term, start and stop date, seriousness, severity, investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related; not applicable for PTEs), action concerning study drug (not applicable for PTEs), any required treatment or evaluations, and the outcome of the event.

Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if the medical condition deteriorates at any time during the study, it should be recorded as an AE. Section 9.3.4 provides additional details. The MedDRA will be used to code all AEs.

Any AE that is considered serious by the investigator or that meets SAE criteria (Section 9.3.1) must be reported to the sponsor within 24 hours (after the investigator has

confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility that the study drug(s) caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly. Contact information to be used for SAE reporting can be found in Section 6.2.1.

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

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

### 9.3.4 Additional Points to Consider for Pretreatment Events and Adverse Events

An untoward finding generally may involve the following:

- Indicates a new diagnosis or unexpected worsening of a preexisting condition (preexisting conditions or underlying disease should not be considered PTEs or AEs)
- Necessitates therapeutic intervention
- Requires an invasive diagnostic procedure
- Requires discontinuation or a change in dose of study drug or a concomitant medication
- Is considered unfavorable by the investigator for any reason

Pretreatment events/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as PTEs or as AEs.

Laboratory values and ECG findings:

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

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

Preexisting conditions:

- Preexisting conditions (present at the time of signing the ICF) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECGs) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (if the worsening or complication occurs before administration of study drug) or an AE (if the worsening or complication occurs after administration of study drug). Investigators should ensure that the recorded event term captures the change in the condition (eg, “worsening of…”).

- If a subject has a preexisting episodic concurrent medical condition (eg, asthma, epilepsy), any occurrence of an episode should be captured as a PTE/AE only if the condition becomes more frequent, serious, or severe in nature. Investigators should ensure that the recorded AE term captures the change in the condition from baseline (eg, “worsening of…”).

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

Worsening of PTEs or AEs:

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

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

Changes in intensity of AEs/serious PTEs:

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

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing the ICF are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the preexisting condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Overdose:

Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs but instead will be documented on the overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

### 9.3.5 Assessment of Severity

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

- Mild: These events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate: These events result in a low level of inconvenience or require minor therapeutic measures. Moderate events may cause some interference with normal functioning.
- Severe: These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow the duration of the event at each level of intensity to be assessed. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

### 9.3.6 Assessment of Causality

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

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs, and concurrent treatments.

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

#### 9.3.6.1 Relationship to Study Procedures

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

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

#### 9.3.6.2 Start Date

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

#### 9.3.6.3 Stop Date

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

#### 9.3.6.4 Frequency

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

#### 9.3.6.5 Action Concerning Study Drug

- Drug withdrawn: The study drug is stopped due to the particular AE.
- Dose not changed: The particular AE does not require stopping study drug.
- Unknown: Only to be used if it cannot be determined what action was taken.
- Not applicable: Study drug is stopped for a reason other than the particular AE; eg, the study was terminated, the subject died, or dosing with study drug was already stopped before the onset of the AE.

#### 9.3.6.6 Outcome

- Recovered/resolved: The subject returns to the first assessment status with respect to the AE/PTE.
- Recovering/resolving: The intensity is decreased by 1 or more stages, the diagnosis or signs/symptoms have almost disappeared, the abnormal laboratory value has improved but has not returned to the normal range or to baseline, or the subject dies from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving."
- Not recovered/not resolved: There is no change in the diagnosis, signs, or symptoms; the intensity of the diagnosis, signs/symptoms, or laboratory value on the last day of the observed study period is worse than when it started; the condition is an irreversible congenital anomaly; or the subject died from another cause while the particular AE/PTE state was "not recovered/not resolved."
- Resolved with sequelae: The subject recovers from an acute AE/PTE but is left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal: AEs/PTEs that are considered the cause of death.
- Unknown: The course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

### 9.3.7 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

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

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

### 9.3.8 Pregnancy

During the course of the study, human chorionic gonadotropin pregnancy tests will be performed for women, and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Section 3.1).

If any subject is found to be pregnant during the study, she should be withdrawn, and any study drug should be immediately discontinued. If the pregnancy occurs during administration of active study drug or within 4 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 6.2.1. If the female subject agrees that the primary care physician can be informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of the treatment the subject received. All pregnancies in subjects receiving study drug will be followed up to final outcome using the pregnancy notification form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

### 9.3.9 Safety Reporting to Investigators, Institutional Review Boards, Independent Ethics Committees, and Regulatory Authorities

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

# 9.4 APPENDIX 4: STUDY GOVERNANCE

## 9.4.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current International Council for Harmonisation (ICH) guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice (GCP), the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in the clinical study report.

## 9.4.2 Investigator Obligations

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

### 9.4.2.1 Confidentiality

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

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the

study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

#### 9.4.2.2 Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study that are to be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

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

#### 9.4.2.3 Subject Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before she enters the study or before performing any unusual or nonroutine procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and will be allowed to read the approved ICF. Once the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject.

#### 9.4.2.4 Study Reporting Requirements

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

### 9.4.2.5 Financial Disclosure and Obligations

The investigator is required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

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

### 9.4.2.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing essential documents, including but not limited to, the following:

- IRB approval
- An original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that are to be provided to the subject

- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493

#### 9.4.2.7 Study Conduct

The investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki; ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

#### 9.4.2.8 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

#### 9.4.2.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

#### 9.4.2.10 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

#### 9.4.2.11 Investigator's Final Report

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

#### 9.4.2.12 Records Retention

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

#### 9.4.2.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

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

### 9.4.3 Study Management

#### 9.4.3.1 Monitoring

##### 9.4.3.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

##### 9.4.3.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, the FDA, or other regulatory agencies access to all study records.

The investigator should promptly notify the sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

#### 9.4.3.2 Management of Protocol Amendments and Deviations

##### 9.4.3.2.1 Modification of the Protocol

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

#### 9.4.3.2.2 Protocol Deviations

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

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. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

### 9.4.3.3 Premature Termination or Suspension of the Study or Investigational Site

#### 9.4.3.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless one or more of the following criteria that require temporary suspension or premature termination of the study are met:

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

#### 9.4.3.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, the protocol, or contractual agreement or is unable to ensure adequate performance of the study or as otherwise permitted by the contractual agreement.

#### 9.4.3.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Sites

In the event that the sponsor, an IRB, or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for premature termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

### 9.4.3.4 Study Termination

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

The end of the study (EOS) is defined as the date on which the last subject completes the last visit (including the EOS follow-up telephone call and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

### 9.4.3.5 Final Report

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

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

Upon completion of the clinical study report, the investigator(s) will be provided with the final approved clinical study report, as appropriate.