Protocol Number: VPED-101

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

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CLINICAL STUDY PROTOCOL
IND 079212

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

VPED-101

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Version of Protocol:	Amendment 1 (Version 2.0)
Date of Protocol:	25 April 2022

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, Randomized, Single-Dose, Crossover Study to Determine the Bioavailability of Vonoprazan Sprinkle Capsules on Pudding or on Applesauce Relative to a Vonoprazan Tablet in Healthy Subjects

PROTOCOL NUMBER: VPED-101

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled "A Phase 1, Open-Label, Randomized, Single-Dose, Crossover Study to Determine the Bioavailability of Vonoprazan Sprinkle Capsules on Pudding or on Applesauce Relative to a Vonoprazan Tablet in Healthy Subjects" in accordance with the guidelines and all applicable government regulations including US 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

Vonoprazan belongs to a novel class of acid suppressants known as potassium-competitive acid blockers (PCABs) that suppress gastric acid secretion by competitively inhibiting gastric hydrogen, potassium-adenosine triphosphatase (H+, K+-ATPase). Vonoprazan is formulated and administered orally as its fumarate salt, vonoprazan fumarate (MW 461.46). Following oral administration, the fumarate salt is rapidly converted to the free base form (MW 345.39), and vonoprazan fumarate is not detectable in human plasma. Vonoprazan fumarate is also referred to as TAK-438, and the free base form of vonoprazan is also referred to as TAK-438F. Vonoprazan was discovered and developed by Takeda Pharmaceutical Company, Japan and is being developed by Phathom Pharmaceuticals (Phathom) in the United States, Europe, and Canada for the treatment of heartburn in patients with symptomatic non-erosive gastroesophageal reflux disease (sGERD), healing of all grades of erosive esophagitis (EE) and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn, and treatment of *Helicobacter pylori* infection. Vonoprazan has been studied in a number of other gastric 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.

1.1 BACKGROUND

The gastric H+, K+-ATPase, also known as the proton pump, is responsible for acid secretion from parietal cells in the stomach. It is inactive in cytoplasmic vesicles but relocates from the cytosol to the secretory membrane of parietal cells when food is present in the stomach, thereby becoming active and pumping H+ ions out of cells and into the canaliculi in exchange for K+ ions. The gastric proton pump represents an attractive pharmacological target because it is the final step of the acid secretion process. Two classes of pharmaceuticals, with distinct mechanisms of action for inhibiting the gastric proton pump, have been developed for clinical application: proton pump inhibitors (PPIs) and PCABs. As a PCAB, vonoprazan has a unique mechanism of action and pharmacokinetics (PK) relative to PPIs, as follows:

- Acid activation and stability: Conventional PPIs are prodrugs that are activated by acid and covalently bind H+, K+-ATPase; however, activated PPIs are not stable under acidic conditions. In contrast, vonoprazan does not require acid activation, is stable under acidic conditions, and does not require enteric-coated formulations; thus, vonoprazan has a more durable effect than conventional PPIs. Furthermore, vonoprazan is rapidly

protonated in the parietal cell canaliculi, which concentrates the drug proximal to H+, K+-ATPase (Scarpignato and Hunt 2019).

- Activity against active and inactive proton pumps: Vonoprazan inhibits acid secretion by competitively inhibiting the binding of potassium ions to H+, K+-ATPase. Vonoprazan selectively concentrates in parietal cells in both resting and stimulated states, binds to active pumps, and remains associated with active and inactive pumps. In contrast, PPIs covalently bind H+, K+-ATPase only when the pump is active, as an acidic environment is required for the activation and accumulation of PPIs in parietal cells (Scott et al 2015).

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

- Extended half-life: The plasma half-life of vonoprazan is typically 7 to 8 hours after single and multiple once daily administration. This is significantly longer than the half-life of conventional PPIs (<2 hours) (Shin and Kim 2013).

- Metabolism: Vonoprazan is predominantly metabolized by cytochrome P450 (CYP)3A4/5, which lacks a high degree of genetic polymorphisms compared with CYP2C19, the primary enzyme responsible for the metabolism of PPIs (Shin and Kim 2013). Therefore, vonoprazan can be administered without regard to CYP2C19 metabolizer status.

These unique aspects of vonoprazan's mechanism of action and PK relative to those of PPIs translate into a greater magnitude and duration of gastric acid suppression, which are reflected in the pharmacodynamic profile (Jenkins et al 2015; Sakurai et al 2015).

Vonoprazan is absorbed rapidly following oral administration, with the median time of peak plasma concentrations (T_{max}) typically occurring 1.5 to 2 hours after once daily dosing. Vonoprazan exhibits time-independent pharmacokinetics, and steady state concentrations are achieved by Day 3 to 4. There is little accumulation of vonoprazan in plasma after multiple once daily doses, with an accumulation ratio index based on an area under the plasma concentration versus time curve (AUC) of <1.2 for doses ranging from 10 to 40 mg. Overall, vonoprazan has been well tolerated in healthy subjects in Phase 1 studies, as well as in

subjects with gastric acid-related diseases who completed Phase 2 and 3 studies in the United States, Europe, Japan, and Asia (outside of Japan).

Further information on the study drug can be found in the investigator's brochure (IB) (Takeda Pharmaceutical 2022).

1.2 RATIONALE FOR STUDY

Phathom is developing vonoprazan in pediatrics for the healing of all grades of EE and relief of heartburn, maintenance of healing of all grades of EE and relief of heartburn and treatment of heartburn associated with sGERD.

The current adult formulation and size of vonoprazan tablets are appropriate for administration in pediatric subjects 12 years of age or older, who are capable of swallowing tablets. However, different strengths and formulations will need to be developed to support the pediatric clinical program for the pediatric age group <12 years of age and for pediatric patients incapable of swallowing tablets. Phathom is investigating a sprinkle capsule formulation for these pediatric patients. Therefore, this study will investigate the bioavailability (BA) of vonoprazan in healthy adult subjects when administered as 20 mg sprinkle capsules on pudding or on applesauce relative to 20 mg tablets, in accordance with the Food and Drug Administration (FDA) Guidance for industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations (DHHS 2014). The use of healthy adult subjects is appropriate for the BA study prior to initiation of studies in pediatric patients.

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

1.3 RATIONALE FOR DOSE SELECTION

A single 20 mg dose of vonoprazan, either as a sprinkle capsule or a tablet, was selected because this is the highest planned clinical dose strength. Oral dosing will be used for vonoprazan sprinkle capsules and tablets as this is the intended route of clinical administration for both formulations. Multiple oral doses of vonoprazan 20 mg tablets have

been shown to be safe and well tolerated in patients and a single dose of up to 120 mg in healthy adult subjects.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

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

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are as follows:

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

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

3. STUDY DESIGN

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

The study will consist of a screening period, a Check-in, 3 treatment periods, and a follow-up (telephone call). The treatment periods will include administration of single doses of vonoprazan 20 mg (tablet/sprinkle capsule) on Day 1 of each period. There will be a washout interval of a minimum of 7 days between study drug dosing in each period.

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

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

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

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

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

Table 3-1 Study Treatment Sequence

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

In each period, subjects will fast overnight (nothing to eat or drink except water) for at least 10 hours before study drug administration. Subjects will remain fasted for 4 hours after dosing with study drug, excluding the pudding and applesauce used for dosing. Water (other than the water consumed with the administration of vonoprazan tablets or sprinkle capsule) is permitted as desired except for 1 hour before and 1 hour after administration of vonoprazan.

For Treatment A, vonoprazan sprinkle capsule administration on pudding, the following should be done:

- Open sprinkle capsule.
- Sprinkle pellets on 1 tablespoon of pudding.
- Administer pudding with pellets and have the subject swallow it immediately.
- The subject should not chew the pellets.
- Immediately follow with swish/swallow of 240 mL of room temperature water.

For Treatment B, vonoprazan sprinkle capsule administration on applesauce, the following should be done:

- Open the sprinkle capsule.
- Sprinkle pellets on 1 tablespoon of applesauce.
- Administer applesauce with pellets and have the subject swallow it immediately.
- The subject should not chew the pellets.
- Immediately follow with swish/swallow of 240 mL of room temperature water.

For Treatment C, vonoprazan tablet administration with water, the following should be done:

- Administer the tablet whole with 240 mL of room temperature water and swallow immediately.
- The subject should not chew the tablet.

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

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

3.1 SCHEDULE OF EVENTS

Phase	Screening	Check-in	Treatment Periods 1 to 3[b]																Follow-up (Phone Call)/EOS
Day	–28 to –2	–1	Day 1													Day 2		Day 3 (ET)	Day 31 (±2)
Procedure[a] Hours	—	—	Predose	0	0.25	0.5	1	1.5	2	4	6	8	10	12	16	24	36	48	
Admission to clinic		X																	
Discharge from clinic[c]																		X	
Telephone call																			X
Informed consent	X																		
Demographics	X																		
Serology[d]	X																		
COVID-19 screening	X	X																	
Serum FSH[e]	X																		
Inclusion/exclusion criteria	X	X																	
Medical history	X	X																	
Urine drug/alcohol/cotinine screen[f]	X	X																	
Height, weight, and BMI[g]	X	X																X	
Physical examination[h]	X	X																X	
Vital sign measurements[i]	X	X	X															X	
12-lead ECG[j]	X	X																X	
Clinical laboratory testing[k]	X	X																X	
Pregnancy test[l]	X	X																X	
Guidance on avoidance of pregnancy	X	X																X	
Randomization[m]			X																
Study drug administration[n]				X															
PK sample collection[o]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CYP genotyping		X																	
Fasting period[p]		X	X	X	X	X	X	X	X	X									
Non-fasting period[q]											X	X	X	X	X	X	X	X	
PTEs monitoring[r]	X	X	X																
AEs[s]				← X →															
Prior/concomitant medications	← X →																		

Abbreviations: AE, adverse event; BMI, body mass index; COVID-19, coronavirus disease 2019; CYP, cytochrome P450; ECG, electrocardiogram; EOS, end of study; ET, end-of-treatment period phase; FSH, follicle stimulating hormone; ICF, informed consent form; PK, pharmacokinetic; PTE, pre-treatment event; QTcF, QT interval corrected for heart rate using Fridericia's formula.

Notes:

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

(b) There will be a washout interval of a minimum of 7 days between study drug dosing in each period.

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

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

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

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

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

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

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

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

(k) Clinical laboratory testing will occur at Screening, Check-in, and ET. A complete list of assessments is provided in Section 6.2.2. Blood and urine samples will be collected and prepared per the clinic's standard procedures; blood sample will be collected under fasted conditions.

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

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

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

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

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

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

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

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

4. STUDY POPULATION

Approximately 27 healthy male and female subjects will be enrolled at a single center in the United States to achieve at least 24 evaluable subjects.

4.1 INCLUSION CRITERIA

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

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

4.2 EXCLUSION CRITERIA

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

1. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at Screening.
2. The subject has a positive test result for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at Screening or Check-in.

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

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

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

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

7. The subject has consumed grapefruit and/or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or other food products that may be CYP3A4 inhibitors (eg, vegetables from the mustard green family [kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard] and charbroiled meats) within 7 days (or 5 half-lives) before the first dose of study drug and/or is expected to be unable to abstain through the study.

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

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

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

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

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

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

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

15. The subject has received a study drug in another investigational study within 30 days of dosing.

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

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

4.3 WITHDRAWAL CRITERIA

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

4.4 SUBJECT REPLACEMENT

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

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws before completing the study may be replaced to retain the target of 24 evaluable subjects (8 in each treatment sequence). Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

All subjects will receive the study treatments as described in Section 3 and according to the schedule of events (SOE; Section 3.1). Additional instructions for dosing, fasting periods, and non-fasting periods can be found in the SOE.

5.2 INVESTIGATIONAL PRODUCTS

The study drugs that will be used are as follows:

Product	Supplied Formulation
Vonoprazan	20 mg tablet (reference)
	20 mg sprinkle capsule (test)

Vonoprazan tablets contain 20 mg vonoprazan free base (MW 345.39) and the following inactive excipients: D-Mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, polyethylene glycol 8000, titanium dioxide, red ferric oxide, and printing ink gray F1.

Vonoprazan sprinkle capsules contain 20 mg vonoprazan free base (MW 345.39) and the following inactive excipients: microcrystalline cellulose pellets, hypromellose, AquaPolish®, amino methacrylate copolymer (Eudragit®), sodium lauryl sulfate, stearic acid, talc, and colloidal silicon dioxide in a gelatin capsule.

Further information on the study drug can be found in the IB (Takeda Pharmaceutical 2022).

5.2.1 Study Drug Preparation and Storage

Phathom will provide the investigator and clinical unit with adequate quantities of vonoprazan 20 mg tablets and 20 mg sprinkle capsules (pellets) for the conduct of the study plus required retention samples (DHHS 2020). The study drugs will be provided in 21-count high-density polyethylene bottles. The clinical unit pharmacy will prepare the study treatments for each subject according to the SOE (Section 3.1).

All study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with 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 (DHHS 2020) or destroyed according to applicable regulations.

5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

[redacted] will generate the randomization schedule. Subjects who meet all the inclusion and none of the exclusion criteria will be randomly assigned to a treatment sequence in a 1:1:1 ratio (Section 3). Randomization numbers (in sequential order) will be assigned before the first dose of study drug is administered on Day 1 of Period 1 (Section 3). There will be no stratification.

5.4 BLINDING

This is an open-label study.

6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an informed consent form (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 PK parameters for vonoprazan will be calculated as endpoints using standard noncompartmental methods: $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, terminal elimination rate constant (λ_z), terminal phase half-life ($t_{1/2}$), apparent total body clearance (CL/F), and apparent volume of distribution (V_z/F). Additional PK parameters may be calculated as appropriate.

The primary endpoints will be $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of vonoprazan.

- The timing and frequency of PK sample collection is listed in the SOE (Section 3.1).
- Definitions of the PK parameters can be found in the list of abbreviations, Appendix 1.

6.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical 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 plasma. Assay results and validation details will be provided in a separate bioanalytical report. Plasma remaining after the assays are completed may be stored and used for further exploratory investigation of vonoprazan metabolites.

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 adverse events (AEs), clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead ECG results, and physical examination findings (Section 3.1).

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 serious adverse event (SAE) reporting:

Safety Reporting: [redacted]

SAE Hotline (24 hour): [redacted]

SAE Fax: [redacted]

6.2.2 Clinical Laboratory Assessments

The following clinical laboratory assessments will be performed:

Hematology	Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, absolute and differential leukocyte 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-glutamyl transferase, 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 human immunodeficiency virus antibody types 1 and 2 (Screening only)
Other analyses	All subjects: Urine drug screen (alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, methylenedioxymethamphetamine, and opiates [including heroin, codeine, and oxycodone]); 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) All subjects: coronavirus disease 2019 (COVID-19) screening Female subjects: FSH, serum and urine pregnancy test (human chorionic gonadotropin)

- 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.

6.3 CYP GENOTYPING

Cytochrome P450 enzymes are involved in the metabolism of vonoprazan. A blood sample will be collected on Day -1 as delineated in the SOE (Section 3.1) to determine metabolizer status (i.e., poor, normal, intermediate, or ultra-rapid metabolizer) for certain CYP enzymes.

Instructions for blood sampling, collection, processing, and sample shipment will be provided separately.

These blood samples may be stored and used for future exploratory investigation of CYP enzymes involved in the metabolism of vonoprazan.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

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

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

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The PK population will include subjects who receive at least 1 dose of vonoprazan and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. Subjects who experience vomiting within 2 times the median T_{max} after study drug dosing will be excluded from the PK analysis.

- 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 overall for all subjects. 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

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

Vonoprazan PK parameters will be calculated using actual sampling times. All parameters will be calculated using the latest version of Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) or SAS® (SAS Institute Inc., Cary, North Carolina). The individual PK parameters will be presented in data listings and summarized by treatment using the following descriptive statistics: number of subjects, mean, SD, CV, median, minimum, and maximum. Geometric means and geometric CV will be included for $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}.

A linear mixed model with fixed effects for treatment, sequence, and period and subject within sequence as a random effect will be performed on the natural log-transformed values of $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} to assess the relative BA of the test dose form (vonoprazan sprinkle capsule [either sprinkled on pudding, Treatment A, or on applesauce, Treatment B]) to the reference dose form (vonoprazan tablet, Treatment C). The geometric least square

means and corresponding 90% confidence intervals (CIs) will be computed for AUC_{0-t}, AUC_{0-inf}, and C_{max} by taking the antilog of the least square means from the linear mixed-effect model on the natural logarithms of the corresponding PK parameters. No adjustment will be made for multiplicity.

Relative BA will be reported as the test to reference ratios (A/C or B/C) of the geometric means and its corresponding CIs for AUC_{0-t}, AUC_{0-inf}, and C_{max} PK parameters. Bioequivalence will be concluded if the 90% CI for the geometric mean ratio (GMR) between the test treatments (20 mg sprinkle capsule, either sprinkled on pudding or on applesauce) and the reference treatment (20 mg tablet) are wholly contained within 0.80 and 1.25 for the vonoprazan PK parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}.

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

7.3.2 Safety Analyses

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

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Physical examination findings will be presented in a data listing.

7.4 HANDLING OF MISSING DATA

Plasma concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations

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

7.5 INTERIM ANALYSES

No formal interim analyses will be performed in this study.

8. REFERENCE LIST

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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 plasma concentration versus time curve
$AUC_{0\text{-inf}}$	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
$AUC_{0\text{-t}}$	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
BA	bioavailability
BLQ	below the limit of quantification
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease 2019
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
EE	erosive esophagitis
EOS	end of study
ET	end-of-treatment period phase
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GMR	geometric mean ratio
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
H^+, K^+-ATPase	hydrogen, potassium-adenosine triphosphatase
λ_z	terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
PCAB	potassium-competitive acid blocker
PK	pharmacokinetic(s)
PPI	proton pump inhibitor

Abbreviation	Term
PTE	pre-treatment event
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SD	standard deviation
sGERD	symptomatic non erosive gastroesophageal reflux disease
SOE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal phase half-life
T_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution

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 × 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 pre-treatment event (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 ET assessments. Any subject who fails to return for final assessments will be contacted by the site in a reasonable attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

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 latest version of the World Health Organization Drug 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 doses of study drug will be administered in the clinical unit under direct observation of clinic personnel and will be recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug.

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 informed consent 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 treatment-emergent AE 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.

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. There are no special interest AEs for this study.

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, γ-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 informed consent 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 visit 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 Pre-Treatment Events and Adverse Events

An untoward finding generally may involve the following:

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

Pre-treatment 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.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECGs, etc) 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 pre-existing 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 changes 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 of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be 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.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

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

Changes in the severity of an AE should be documented to allow 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.
- Dose reduced: The dose is reduced due to the particular AE.
- Dose increased: The dose is increased due to the particular AE.
- Drug interrupted: The dose is interrupted due to the particular AE.

9.3.6.6 Outcome

- Recovered/resolved: The subject returns to 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 not available at the time of the first report becomes available at a later date, the investigator should update the SAE eCRF form 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 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 trial. 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 case report forms 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 Section 10.2 of 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 is 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): GCP 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 he or 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 his or 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 time line 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 is 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): GCP; 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 will 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 EOS is defined as the date on which the last subject completes the last visit (including the EOS visit 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.