Protocol Number: VONO-103

Official Title: A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Vonoprazan (20 mg) and Lansoprazole (30 mg) in Healthy Subjects

NCT Number: NCT04729101

Document Date: 15-Apr-2021

[redacted]

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Clinical Protocol

A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Vonoprazan (20 mg) and Lansoprazole (30 mg) in Healthy Subjects

Celerion Project No.: CA32534

Sponsor Project No.: VONO-103

US IND No.: 079212

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
15APR2021 by [redacted]	Final Protocol, Amendment 2 **Purpose of Amendment** The protocol is amended to broaden the age and body mass index criteria to improve subject recruitment for the study. **Changes to the Study Protocol:** **Section 11.1 (Inclusion Criteria)** For Inclusion Criterion #1, the upper age range has been increased from 50 to 55 years of age. For Inclusion Criterion #3, the body mass index has been increased from 30.0 to 32.0 kg/m^2.
08MAR2021 by [redacted]	Final Protocol, Amendment 1 **Purpose of Amendment** The protocol is amended to incorporate the changes as approved in the Protocol Clarification Letter (PCL), dated 22Feb2021 and to update inclusion and exclusion criteria. **Changes to the Study Protocol:** **Section 11.1 (Inclusion Criteria)** For Inclusion Criterion #1, the upper age range has been increased. For Inclusion Criterion #5, the acceptable range for the cited clinical laboratory parameters has been updated. In addition one recheck will be allowed. **Section 11.2 (Exclusion Criteria)** For Exclusion Criterion #18, the reference range for serum creatinine has been clarified and post PCL production the Principal Investigator (PI) and Sponsor agreed to remove blood urea nitrogen from the criterion and the parameter will be assessed at the PI's discretion. **Section 13.1 (Screening)** Statement has been added to state rescreening is permissible. **Other** The address of [redacted] Institutional Review Board was updated (Section 15.1.1 - Institutional Review Board).

	Minor formatting and editorial changes have been applied.
30DEC2020 by [redacted]	Final Protocol

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Vonoprazan (20 mg) and Lansoprazole (30 mg) in Healthy Subjects

CELERION CLINICAL SITE AND PRINCIPAL INVESTIGATOR:

[redacted]

[redacted]

Signature: [redacted] Date: 15-Apr-2021 | 14:20:06 PDT

Printed name: _____

A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Vonoprazan (20 mg) and Lansoprazole (30 mg) in Healthy Subjects

SPONSOR AND SPONSOR'S REPRESENTATIVE:

Phathom Pharmaceuticals, Inc.
2150 East Lake Cook Road, Suite 800
Buffalo Grove, Illinois 60089, USA

Signature: [redacted] Date: 15-Apr-2021 | 15:22:39 CDT

E-mail: [redacted]

Signature: [redacted] Date: 15-Apr-2021 | 15:36:18 CDT

E-mail: [redacted]

Signature: [redacted] Date: 15-Apr-2021 | 15:36:59 CDT

E-mail: [redacted]

Signature: [redacted] Date: 15-Apr-2021 | 15:19:14 CDT

E-mail: [redacted]

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	[redacted] Clinical and Patient Safety [redacted]
Protocol Author	[redacted] Senior Scientist, Protocol and Medical Writer [redacted]
Certified Clinical Laboratory	[redacted]
Bioanalytical Laboratories	Vonoprazan: [redacted] Lansoprazole: [redacted]
Pharmacokinetic and Statistical Analyses	[redacted]

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5 SYNOPSIS

Compound:	Vonoprazan
Clinical Indication:	Potassium competitive acid blocker (PCAB) for 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* (*H. pylori)* infection.
Study Phase and Type:	Phase 1 – Pharmacokinetic (PK), pharmacodynamic (PD), and safety and tolerability study
Study Objectives:	**Primary Objective:** To evaluate the PK and PD of vonoprazan (20 mg) and lansoprazole (30 mg) following single (Day 1) and multiple doses (Day 7). **Secondary Objective:** To evaluate the safety and tolerability of vonoprazan (20 mg) following single (Day 1) and multiple doses (Day 7).
Summary of Study Design:	This is a Phase 1, open-label, randomized, 2-period, crossover study to evaluate the PK, PD, and safety and tolerability of vonoprazan in comparison to lansoprazole in healthy subjects. The study will be conducted at a single site. In each period, multiple doses of either vonoprazan or lansoprazole will be administered once daily (QD) for 7 consecutive days. Gastric pH will be measured continuously over a 24-hour period at Baseline (Day -1 of Period 1 only) and on Days 1 and 7 of Periods 1 and 2. PK samples will be collected at predose and for 24 hours following dosing on Days 1 and 7 of Periods 1 and 2. Gastrin samples will be collected over a 24-hour period at Baseline (Day -1 of Period 1 only), at predose and for 24 hours following dosing on Days 1 and 7 of Period 1 only, and at predose (single sample) on Day 1 of Period 2. Safety will be monitored throughout the study by repeated clinical safety tests and laboratory evaluations. There will be a washout period of at least 7 days between the last dose in Period 1 and the first dose in Period 2. The clinical research unit (CRU) will attempt to contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) via a phone call approximately 14 days after the last dose to determine if any adverse event (AE) has occurred and if any concomitant medication has been taken since the last study visit.

Number of Subjects:	Forty (40), healthy, adult male and female subjects will be enrolled.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A: Vonoprazan (1 x 20 mg tablet) administered QD on Days 1 through 7 Treatment B: Lansoprazole (1 x 30 mg capsule) administered QD on Days 1 through 7 On Days 2 through 7, the study drug will be administered within ± 1 hour of the dosing time established on Day 1 of each period. All study drugs will be administered orally with approximately 240 mL of water under fasting conditions.
Key Assessments:	**Pharmacodynamics** The following PD parameters will be calculated for vonoprazan and lansoprazole (Baseline [Day -1 of Period 1] and Days 1 and 7 of each period): integrated acidity, mean gastric pH, time and the percentage of time (i.e., the holding time ratio [HTR]) during which the pH is >4, >5, and >6 over the 24 hour period following dosing and for the approximate time intervals as follows: 0-24 hours, 0-2 hours, 0-4 hours, 4-9 hours, 9-12 hours, and 12-24 hours. For each 15 minute interval within a pH collection time interval, the median pH, the mean pH, and the standard deviation of the pH values will be calculated for each subject. For gastric pH >4, >5, and >6 HTRs and mean gastric pH on Days 1 and 7, the point estimate of the difference in changes from baseline between the study medications (vonoprazan – lansoprazole) will be calculated along with the 2-sided 95% confidence interval (CI), using an analysis of variance (ANOVA) with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Gastric pH >4, >5, and >6 HTRs, mean gastric pH, and their changes from baseline will be summarized with descriptive statistics and 2-sided 95% CIs for each study treatment. The gastrin area under the curve over the 0-24 hour period (AUC0-24) will be calculated for Day -1 of Period 1 (Baseline) and Days 1 and 7 of Period 1.

	Pharmacokinetics: The following PK parameters will be calculated for vonoprazan and lansoprazole in plasma: Day 1: AUC0-24, AUC0-t, AUC0-inf, Cmax, Tmax, Kel, t½, CL/F, and Vz/F; Day 7: AUCtau, Cmax,ss, Cavg, Tmax,ss, RA,AUC, and RA,Cmax. Additional parameters may be assessed as appropriate. All PK parameters will be summarized by treatment using descriptive statistics. **Safety:** Safety will be monitored through AEs, 12-lead electrocardiograms (ECGs), vital sign measurements, clinical laboratory tests, and physical examinations. AEs will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

Study Procedures [a]	Screening [b]	Study Days in Period 1 and 2 [c]																						
Days →		-2 (P1)/-1 (P2)	-1 (P1)	1																2	3	4	5	6
Hours →		Check-In [d]		Pre	0	0.25	0.5	0.75	1	1.5	2	3	4	5	9	10	12	13	16	24	0	0	0	0
Administrative Procedures																								
Informed Consent	X																							
Inclusion/Exclusion Criteria	X	X [e]																						
Medical History	X																							
Safety Evaluations																								
Full Physical Examination [f]	X																							
Height	X																							
Weight	X	X																						
12-Lead Safety ECG	X	X																						
Vital Signs (heart rate, blood pressure, and temperature) [g]	X	X	X	X																X	X	X	X	X
Vital Signs (respiratory rate)	X																							
Hematology, Serum Chemistry [h], and Urinalysis	X	X																						
Serum Pregnancy Test (females only)	X	X [e]																						
Serum FSH (postmenopausal females only)	X																							
Urine Drug and Alcohol Screen	X	X [e]																						
COVID-19 Monitoring [i]	X	X	X										X											
HIV/Hepatitis Screen	X																							
AE Monitoring	X	X	X								X													
Concomitant Medication Monitoring	X	X	X								X													
Study Drug Dosing / Pharmacokinetics																								
Randomization				X [e]																				
Study Drug Dosing					X															X	X	X	X	X
Blood for Vonoprazan and Lansoprazole PK (Per Randomization Schedule)				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [r]				

Study Procedures [a]	Screening [b]	Study Days in Period 1 and 2 [c]																						
Days →		-2 (P1)/-1 (P2)	-1 (P1)	1																2	3	4	5	6
Hours →		Check-In [d]		Pre	0	0.25	0.5	0.75	1	1.5	2	3	4	5	9	10	12	13	16	24	0	0	0	0
Other Procedures																								
Lower Esophageal Sphincter Determination		X [e]																						
Gastric pH Probe Insertion [j]			X	X																				
Gastric pH Monitoring (24 hour) [k]			X	X																				
CYP2C19 Genotyping test																				X [e]				
H. pylori Test	X																							
Gastrin Profile [l]			X	X [m]							X		X	X	X	X	X	X		X [n]				
Confinement in the CRU		X																						
Visit	X																							

Study Procedures [a]	Study Days in Period 1 and 2 [c]																FU [q]
Days →	7															8	
Hours →	Pre	0	0.25	0.5	0.75	1	1.5	2	3	4	5	9	10	12	13	16	24	
Safety Evaluations																		
Full Physical Examination [f]																	X [o]	
12-Lead Safety ECG																	X [o]	
Vital Signs (heart rate, blood pressure, and temperature) [g]	X																X [o, p]	
Vital Signs (respiratory rate)																	X [o]	
Hematology, Serum Chemistry [h] and Urinalysis																	X [o]	
COVID-19 Monitoring [i]	X																	
AE Monitoring	X																	X
Concomitant Medication Monitoring	X																	X
Study Drug Dosing / Pharmacokinetics																		
Study Drug Dosing		X																
Blood for Vonoprazan and Lansoprazole PK (Per Randomization Schedule)	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Procedures [a]	Study Days in Period 1 and 2 [c]																	FU [q]
Days →	7																8	
Hours →	Pre	0	0.25	0.5	0.75	1	1.5	2	3	4	5	9	10	12	13	16	24	
Other Procedures																		
Gastric pH Probe Insertion [j]	X																	
Gastric pH Monitoring (24 hour) [k]		X																
Gastrin Profile [l]	X							X		X	X	X	X	X	X		X [n]	
Confinement in the CRU	X																	

a For details on Procedures, refer to Section 13.

b Within 28 days prior to the first dosing.

c There will be a washout period of at least 7 days between the last dose in Period 1 and the first dose in Period 2.

d Subjects will be admitted to the CRU on Day -2 (Period 1) at the time indicated by the CRU and will remained confined during the study including the washout period. Subjects may be asked to check-in earlier to undergo COVID-19 screening assessment.

e To be performed in Period 1 only.

f Symptom-driven physical examinations may be performed at other times, at the PI's or designee's discretion.

g Vital signs (temperature, heart rate, and blood pressure) will be measured at screening, check in, approximately 1 hour before and after pH probe placement on Day -1 (Period 1 only) and on Days 1 and 7 of Periods 1 and 2, and approximately 1 hour prior to each dose on Days 2 through 6 of Periods 1 and 2. The vital signs assessment following removal of the pH probe used for monitoring on Day -1 of Period 1 will be the same as the vital signs assessment prior to dosing on Day 1 of Period 1.

h Samples for serum chemistry will be obtained after a fast of at least 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.

i COVID-19 related safety assessments will be detailed in a separate document following up-to-date local regulations.

j Gastric pH probe insertion will occur within approximately 2 hours prior to the start of each 24-hour monitoring period for Baseline on Day -1 (Period 1 only) and Days 1 and 7 of Periods 1 and 2.

k Gastric pH will be measured continuously over a 24-hour period at Baseline on Day -1 (Period 1 only) and on Days 1 and 7 of Periods 1 and 2.

l Blood samples for the profile measurement of gastrin will be taken on Day -1 of Period 1 only (0, 2, 4, 5, 9, 10, 12, 13, and 24 hours) and will be time matched to postdose sampling on Day 1 and Day 7 of Period 1 only. The samples collected at 4, 9, and 12 hours postdose should be collected prior to starting meal/snack consumption. The 0-hour (predose) sample on Day 1 of Period 1 will be the same as the 24-hour sample on Day -1; only one sample will be collected.

m In Period 2, a gastrin sample will be collected only at predose on Day 1 (approximately 15 minutes prior to dosing).

n The 24 hour gastrin sample on Day -1 of Period 1 is to be taken approximately 15 minutes prior to dosing on Day 1 of Period 1 (this sample will also serve as the predose sample on Day 1 of Period 1), and the 24 hour postdose gastrin sample on Day 1 and Day 7 of Period 1 is to be taken approximately 15 minutes prior to pH probe removal on Day 2 and Day 8 of Period 1, respectively.

o To be performed at the end of Period 2 only or prior to early termination from the study.

p To be performed after pH probe removal.

q The CRU will attempt to contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) via a phone call approximately 14 days after the last dose to determine if any AE has occurred and if any concomitant medications has been taken since the last study visit.

r To be performed prior to dosing.

Abbreviations: AE = Adverse event(s), COVID-19 = Coronavirus disease 2019, CRU = Clinical research unit, CYP2C19 = Cytochrome P450 2C19, ECG = Electrocardiogram, FSH = Follicle-stimulating hormone, FU = Follow-up, *H. pylori* = Helicobacter pylori, HIV = Human immunodeficiency virus, P1 = Period 1, P2 = Period 2, Pre = predose, PI = Principal Investigator, and PK = Pharmacokinetics.

7 ABBREVIATIONS

AE	Adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATPase	Adenosine triphosphatase
AUC	Area under the concentration-time curve
AUC0-24	Area under the concentration-time curve, from time 0 to the 24-hour time point
AUC0-inf	Area under the concentration-time curve, from time 0 extrapolated to infinity
AUC0-t	Area under the concentration-time curve, from time 0 to the last observed non-zero concentration (t)
AUCt,ss	Area under the concentration-time curve at steady-state
AUCtau	Area under the concentration-time curve during a dosing interval (tau), at steady state
BMI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
Cavg	Average concentration during a dosing interval
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
cm	Centimeter
Cmax	Maximum observed concentration
Cmax,ss	Maximum observed concentration at steady-state
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRU	Clinical Research Unit
CYP	Cytochrome P450
dL	Deciliter

DU	Duodenal ulcer
ECG	Electrocardiogram
EE	Erosive esophagitis
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GERD	Gastroesophageal reflux disease
g	Gram
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GU	Gastric ulcer
h	Hour
H. pylori	Helicobacter Pylori
H+	Hydrogen ion
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTR	Holding time ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
K+	Potassium ion
Kel	Apparent terminal elimination rate constant
kg	Kilogram
L	Liter
LES	Lower esophageal sphincter
m^2	Meters squared
M-IV-Sul	Sulfate of oxidative metabolite of vonoprazan
MedDRA®	Medical Dictionary for Regulatory Activities®
mg	Milligram

mL	Milliliter
mM	Millimolar
mmHg	Millimeter of mercury
mmol	Millimole
msec	Millisecond
No.	Number
oz	Ounce
PCAB	Potassium competitive acid blockers
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic(s)
PPI	Proton-pump inhibitor
PTE	Pre-treatment event
QA	Quality Assurance
QD	Once daily
QTcF	Fridericia's correction to the QT interval
RA,AUC	Accumulation ratio based on AUC
RA,Cmax	Accumulation ratio based on Cmax
SAE	Serious adverse event
SAP	Statistical analysis plan
t½	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to reach maximum observed concentration
Tmax,ss	Time to reach maximum observed concentration at steady state
UK	United Kingdom
US	United States
USA	United States of America
Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration

8 INTRODUCTION

8.1 Background

Vonoprazan is a member of a class of compounds referred to as PCABs that suppress gastric acid secretion by competitively inhibiting gastric hydrogen, potassium adenosine triphosphatase (H+, K+-ATPase), an enzyme that catalyzes the final step in the acid secretion pathway. Vonoprazan does not require activation by acid and is a strong base with a high affinity for the acid pump of gastric cells inhibiting gastric acid production. Vonoprazan is being investigated in the US and Europe for the healing of EE, maintenance of healed EE, and treatment of *H. pylori* infection.

Clinical Studies

As of 25 December 2019, a total of 6096 subjects have been exposed to vonoprazan in the completed Phase 1 to 3 studies through to the cutoff date: 893 subjects in Phase 1, 762 subjects in Phase 2, and 4441 subjects in Phase 3. An additional 466 subjects were participating in ongoing Phase 3 and Phase 4 clinical studies.

Pharmacodynamics

In healthy subject studies, vonoprazan administration indicated a dose-dependent increase in gastric pH across the doses tested. From the multiple rising dose studies, mean maximum pH >4 HTRs following the 40 mg dose of vonoprazan were 85.3% (Japan-based study) and 85.6% (United Kingdom [UK]-based study) on Day 1, 94.0% (UK only) on Day 4, and 100% (Japan) and 93.2% (UK) on Day 7. Also, in Japanese subjects, the 24-hour pH ≥4 HTR after a dose of 10 mg vonoprazan following food intake was higher than after an overnight fast. In contrast, 24-hour pH ≥4 HTR after a dose of 40 mg vonoprazan was similar between fed and fasting conditions.

Efficacy

The results of large Phase 3 clinical studies conducted in Japan and China have shown that vonoprazan, at a dose of 20 mg, was beneficial for the treatment of several acid-related diseases including EE healing and maintenance, gastric ulcer (GU) and duodenal ulcer (DU), and the eradication of *H pylori* in combination with antibiotics.

Pharmacokinetics

The plasma concentrations of a 20 mg single-dose vonoprazan reaches a peak by approximately 1.5 hours (mean) under fasting conditions and 3 hours (mean) under fed conditions. The mean apparent t½ was 7.7 hours. Following 7 day repeat QD doses of vonoprazan at doses of 10-40 mg, in healthy adult male subjects, AUCt,ss and Cmax,ss increased in a slightly greater than dose-proportional manner. Steady state was reached by Day 3 of administration.

Vonoprazan is metabolized mainly by hepatic drug-metabolizing enzyme cytochrome P450 (CYP) 3A4 and partially by CYP2B6, CYP2C19, and CYP2D6. Metabolism is also

mediated by sulfotransferase 2A1 and followed by CYP2C9 to form the sulfate of oxidative metabolite of vonoprazan (M-IV-Sul). Vonoprazan was shown to exhibit a time-dependent inhibitory effect on CYP2B6, CYP2C19, and CYP3A4/5 (in vitro). In addition, vonoprazan shows a slight concentration-dependent inductive effect on CYP1A2, but it shows little inductive effect on CYP2B6 and CYP3A4/5 (in vitro). When radioactive labeled 15 mg vonoprazan was orally administered to healthy adult male subjects, 98.5% of the radioactivity administered was shown to be excreted into urine and feces by 168 hours after administration (67.4% into urine and 31.1% into feces).

Safety

Overall, vonoprazan has been well tolerated in healthy subjects in Phase 1 studies, as well as in completed Phase 2 and 3 studies of Japanese, Asian, and Western subjects with acid-related diseases. The most common AEs in Phase 2 through 4 studies for vonoprazan were nasopharyngitis, followed by upper respiratory tract infection and diarrhea.

Refer to the Investigator's Brochure (IB) for detailed background information on vonoprazan (IB, 2020).

8.2 Lansoprazole

Lansoprazole has been administered previously as a comparator in vonoprazan studies. Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.

Lansoprazole is approved for the treatment of DU, GU, and EE, maintenance of healed DU and EE, eradication of *H. pylori* to reduce the risk of DU recurrence, healing of nonsteroidal anti-inflammatory drug--associated GU, treatment of symptomatic gastroesophageal reflux disease (GERD), and treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

After oral administration, lansoprazole was shown to significantly decrease the basal acid output and significantly increase the mean gastric pH and percent of time the gastric pH was >3 and >4 (pH >3 and pH >4 HTR). Lansoprazole also significantly reduced meal stimulated gastric acid output and secretion volume, as well as pentagastrin-stimulated acid output. In patients with hypersecretion of acid, lansoprazole significantly reduced basal and pentagastrin-stimulated gastric acid secretion. After the initial dose, increased gastric pH was observed within one to two hours following administration of 30 mg lansoprazole. After multiple daily dosing, increased gastric pH was observed within the first hour following administration of 30 mg lansoprazole.

The Tmax of lansoprazole occurs at approximately 1.7 hours. After a single-dose administration of 15 mg to 60 mg of oral lansoprazole, the Cmax and AUC values of lansoprazole were approximately proportional to the administered dose. Lansoprazole does

not accumulate and its PK is unaltered by multiple dosing. The absolute bioavailability is over 80%. In healthy subjects, the mean t½ was 1.5 (±1.0) hours. Both the Cmax and AUC are diminished by about 50% to 70% when lansoprazole is given 30 minutes after food. Lansoprazole is extensively metabolized in the liver, specifically through the CYP3A and CYP2C19 enzymes.

Most commonly reported adverse reactions with lansoprazole administration are diarrhea, abdominal pain, nausea, and constipation. Observational studies did not definitely establish or exclude any drug-associated risk during pregnancy and based on preclinical data, lansoprazole was shown to possibly cause adverse effects on fetal bone growth and development (Prevacid, 2020).

8.3 Rationale

8.3.1 Rationale for this Study and Study Design

In vitro studies conducted at pH 6.5 demonstrated that vonoprazan is a potent inhibitor of K+ stimulated porcine gastric H+, K+-ATPase activity and >300 times more potent than the comparator proton-pump inhibitors (PPIs) lansoprazole and esomeprazole. Similarly, the results of in vivo studies involving both rats and dogs indicated that dose-dependent effects were observed for both drugs vonoprazan and lansoprazole and vonoprazan exhibited greater inhibitory potency compared with lansoprazole. In Phase 1 studies in Japan, the PD of vonoprazan 20 mg has been compared to PPIs (esomeprazole 20 mg and rabeprazole 20 mg) in healthy subjects. The acid-inhibitory effect of vonoprazan was greater than that of esomeprazole or rabeprazole. While after all treatments the mean 24-hour pH ≥4 HTRs increased from baseline to Day 1 and from Day 1 to Day 7, the mean 24-hour pH ≥4 HTRs were higher after administration of vonoprazan on Day 1 than after administration of esomeprazole or rabeprazole on Day 7. Elevation of gastric pH is important for the treatment of gastrointestinal (GI) disorders.

In the clinical developmental program with vonoprazan for healing of EE, maintenance of healed EE and treatment of *H. pylori* infection, lansoprazole is an active comparator and thus is more suited as a comparator product in this study. Phase 1 studies have evaluated the PD of vonoprazan compared to esomeprazole and rabeprazole in healthy Japanese subjects. There is no comparative PD data available in healthy Western subjects between vonoprazan and a PPI. This study will provide these data. In this study, the Day 1 and Day 7 PD (gastric acid pH) of vonoprazan will be compared to that of lansoprazole following dosing in healthy subjects. Safety and tolerability, and PK will also be monitored. Healthy subjects are appropriate for comparison of changes in intragastric pH and collecting PK.

Subjects will be randomized to treatment sequences to minimize assignment bias. A crossover design is used to reduce the residual variability as every subject will act as their own control. The washout period between doses is considered sufficient to prevent carryover effects of the preceding treatment.

The study will be conducted in *H. pylori* negative healthy subjects as determined by the urea breath test and in non-smoking subjects, to minimize the influence of *H. pylori* infection and

smoking on gastric pH. Metabolizing status of CYP2C19 enzyme will also be evaluated in Period 1 to identify genetic polymorphism.

8.3.2 Rationale for the Dose Selection

The dose selected for this study is 20 mg vonoprazan. Vonoprazan has been previously safely administered in studies in doses up to 40 mg QD for a duration of 8 weeks and doses of 10 mg and 20 mg for up to 52 weeks with a safety profile similar to lansoprazole (IB, 2020). Vonoprazan (20 mg) is currently being evaluated in the US and Europe for the healing of EE and treatment of *H pylori* infection. Lansoprazole 30 mg is the approved dose for these indications (Prevacid, 2020).

8.4 Risks and/or Benefits to Subjects

The doses of vonoprazan and lansoprazole administered in this study are consistent with the indicated full prescribing information for lansoprazole and as indicated in the IB for vonoprazan (IB, 2020; Prevacid, 2020).

The safety monitoring practices employed by this protocol (i.e., AEs, 12-lead ECG, vital sign measurements, clinical laboratory tests, and physical examination) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

9 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective: To evaluate the PK and PD of vonoprazan (20 mg) and lansoprazole (30 mg) following single (Day 1) and multiple doses (Day 7).	**Primary Endpoints:** PD parameters: gastric pH >4 HTR and mean gastric pH over 24 hours on Days 1 and 7. PK parameters as appropriate: following Day 1: AUC0-24, AUC0-inf, Cmax, and Tmax, and following Day 7: AUCtau, Cmax,ss, and Tmax,ss.
Secondary Objective: To evaluate the safety and tolerability of vonoprazan (20 mg) following single (Day 1) and multiple doses (Day 7).	**Safety Assessments:** AEs, 12-lead ECGs, vital signs, clinical laboratory tests, and physical examinations.

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a Phase 1, open-label, randomized, 2-period, crossover study to evaluate the PK, PD, and safety and tolerability of vonoprazan in comparison to lansoprazole in healthy subjects. The study will be conducted at a single site.

Forty (40), healthy, adult male and female subjects will be enrolled.

Screening of subjects will occur within 28 days prior to the first dosing.

In each period, multiple doses of either vonoprazan or lansoprazole will be administered QD for 7 consecutive days. Gastric pH will be measured continuously over a 24-hour period at Baseline (Day -1 of Period 1 only) and on Days 1 and 7 of Periods 1 and 2. PK samples will be collected at predose and for 24 hours following dosing on Days 1 and 7 of Periods 1 and 2. Gastrin samples will be collected over a 24-hour period at Baseline (Day -1 of Period 1 only), at predose and for 24 hours following dosing on Days 1 and 7 of Period 1 only, and at predose (single sample) on Day 1 of Period 2. Safety will be monitored throughout the study by repeated clinical safety tests and laboratory evaluations.

There will be a washout period of at least 7 days between the last dose in Period 1 and the first dose in Period 2.

Discontinued subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement and Follow-Up

Subjects will be housed on Day -2 (Period 1) at the time indicated by the CRU until after the 24-hour blood draw and/or study procedures on Day 8 of Period 2 (subjects will be housed throughout the washout period). Subjects may be asked to check-in earlier to undergo Coronavirus disease 2019 (COVID-19) screening assessment. At all times, a subject may be required to remain at the CRU for longer at the discretion of the Principal Investigator (PI) or designee.

The CRU will attempt to contact all subjects who received at least one dose of study drug (including subjects who terminate the study early) via a phone call approximately 14 days after the last dose to determine if any AE has occurred and if any concomitant medication has been taken since the last study visit.

10.1.2 End of Study Definition

The end of study is defined as the date of the follow-up visit as outlined in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

11.1 Inclusion Criteria

Subjects must fulfill all the following inclusion criteria to be eligible for participation in the study:

1. Healthy, adult, male or female 18 - 55 years of age, inclusive, at screening.

2. Continuous nonsmoker who has not used nicotine-containing products for at least 3 months prior to the first dosing and throughout the study, based on subject self-reporting.

3. Body mass index (BMI) $\geq$ 18.0 and $\leq$ 32.0 kg/m^2 at screening.

4. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles, vital signs, or ECGs, as deemed by the PI or designee.

5. Alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) $\leq$upper limits of the clinical laboratory reference range (one recheck is permissible).

6. A female of childbearing potential is either sexually inactive (abstinent as a life style) for 28 days prior to the first dosing and throughout the study or is using one of the following acceptable birth control methods:

   - hormonal oral contraceptives, vaginal ring, transdermal patch, or hormone releasing intrauterine device for at least 3 months prior to the first dosing and with either a physical (e.g., condom, diaphragm, or other) or a chemical (e.g., spermicide) barrier method from the time of screening and throughout the study.
   - Depot/implantable hormone (e.g., Depo-Provera®, Implanon®) for at least 3 months prior to the first dosing and throughout the study.

   In addition, female subjects of childbearing potential will be advised to remain sexually inactive or to keep the same birth control method for at least 28 days after the last dose.

7. A female of non-childbearing potential has undergone one of the following sterilization procedures at least 6 months prior to the first dosing:

   - hysteroscopic sterilization;
   - bilateral tubal ligation or bilateral salpingectomy;
   - hysterectomy;
   - bilateral oophorectomy;

   or be postmenopausal with amenorrhea for at least 1 year prior to the first dosing and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status.

8. A non-vasectomized, male subject must agree to use a condom with spermicide or abstain from sexual intercourse during the study until 90 days after the last dosing. (No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to the first dosing. A male who has been vasectomized less than 4 months prior to study first dosing must follow the same restrictions as a non-vasectomized male).

9. If male, must agree not to donate sperm from the first dosing until 90 days after the last dosing.

10. Understands the study procedures in the informed consent form (ICF), and be willing and able to comply with the protocol.

11.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

1. Is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

2. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee.

3. History of any illness that, in the opinion of the PI or designee, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. History or presence of alcohol or drug abuse within the past 2 years prior to the first dosing.

5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug(s), its excipients, related compounds, or lidocaine.

6. Clinically significant GI disorder (e.g., GU, GERD, impaction, chronic constipation, inflammatory bowel disease, ischemic colitis, vascular intestinal atherosclerosis, previous bowel resection, bowel obstruction, bariatric surgery, cholecystitis [including history of cholecystectomy), and/or appendectomy).

7. Positive result for *H. pylori* breath test at screening.

8. Had diarrhea or vomiting within 48 hours prior to check-in.

9. Has nasal abnormalities that could affect pH probe insertion.

10. Cannot tolerate placement of the pH probe.

11. Female subjects with a positive pregnancy test at screening or check-in or who are lactating.

12. Positive urine drug or alcohol results at screening or check-in.

13. Positive results at screening for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV).

14. Seated blood pressure is less than 90/40 mmHg or greater than 140/90 mmHg at screening.

15. Seated heart rate is lower than 40 bpm or higher than 99 bpm at screening.

16. QTcF interval is >460 msec (males) or >470 msec (females) or has ECG findings deemed abnormal with clinical significance by the PI or designee at screening.

17. Estimated creatinine clearance <80 mL/min at screening.

18. The subject has serum creatinine >1.22 mg/dL at screening or check-in.

19. Unable to refrain from or anticipates the use of:

    - Any drug, including prescription and non-prescription medications, herbal remedies, or vitamin supplements beginning 14 days prior to the first dosing and throughout the study. Medication listed as part of acceptable birth control methods will be allowed (refer to Section 11.1). After randomization, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee. Topical lidocaine may be administered for pH probe insertion. Hormone replacement therapy will also be allowed.

    - Any drugs known to be significant inducers of CYP3A4/5, CYP1A2, and/or CYP2C19 for 28 days prior to the first dosing and throughout the study. Appropriate sources will be consulted by the PI or designee to confirm lack of PK/PD interaction with study drug.

20. Has been on a diet incompatible with the on-study diet, in the opinion of the PI or designee, within the 30 days prior to the first dosing and throughout the study.

21. Donation of blood or significant blood loss within 56 days prior to the first dosing.

22. Plasma donation within 7 days prior to the first dosing.

23. Participation in another clinical study within 30 days prior to the first dosing. The 30 day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of Period 1 of the current study.

11.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test.
- Positive urine drug or alcohol test.
- Inability to tolerate pH probe

A subject may be withdrawn by the PI (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

11.4 Study Restrictions

11.4.1 Prohibitions and Concomitant Medication

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 48 hours prior to the first dose until check-out (small amounts of caffeine derived from normal foodstuffs e.g., 250 mL/8 oz/1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz chocolate bar, per day, would not be considered a deviation to this restriction);
- Alcohol: 48 hours prior to the first dose and until check-out;
- Grapefruit/Seville orange: 14 days prior to the first dose and until check-out;
- Vegetables from the mustard green family [kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard] and charbroiled meats): 7 days prior to the first dose and until check-out.

Concomitant medications will be prohibited as listed in the exclusion criteria in Section 11.2. After randomization, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee. Topical lidocaine may be administered for pH probe insertion. Acceptable birth control methods as described in Section 11.1 and hormone replacement therapy will be allowed.

If deviations occur, the PI or designee in consultation with the Sponsor if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

All medications taken by subjects during the course of the study will be recorded.

11.4.2 Meals

On Days 1 and 7, water (except water provided with each dosing) will be restricted 1 hour prior to and 2 hours after each dosing. On Days 1 and 7, a small amount of water to facilitate the insertion of the pH probe will be allowed, subjects will also be encouraged to take approximately 120 mL of water each hour during waking hours; time and amount of water intake will be recorded. On Days 2 to 6, water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after each dosing but will be allowed ad libitum at all other times. On Day -1 of Period 1, subjects will follow a similar time matched (± 15 minutes) water administration schedule as planned for Day 1. Only water will be given as part of meals and snacks throughout the confinement periods.

Subjects will fast overnight for at least 10 hours prior to each dosing. On Days 1 and 7 of Periods 1 and 2, subjects will continue the fast for 4 hours postdose when they will be given a meal, the next meal will be served at 9 hours postdose, and a snack will be served at 12 hours postdose. On Day -1 of Period 1, subjects will follow a similar time matched (± 15 minutes) food administration schedule as planned for Day 1. Subjects will receive identical meals on Day -1 of Period 1 and Days 1 and 7 of Periods 1 and 2 and should be consumed within 30 minutes. Any food not consumed on Day -1 of Period 1 and Days 1 and 7 of Periods 1 and 2 will be documented. On all other days, subjects will begin their meals at the scheduled time and are permitted to finish their meal at their own pace.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snack served at the CRU will be standardized and will be similar in caloric content and composition and will be taken at the same time relative to dosing in each period. Subjects will receive identical meals on Days -1 of Period 1 and Days 1 and 7 of Periods 1 and 2.

11.4.3 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours after initiation of pH monitoring on Day -1 of Period 1 and Days 1 and 7 of each period, except when they are supine or semi-reclined for study procedures.

However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Subjects will be instructed to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

12 TREATMENTS

12.1 Treatments Administered

Treatment A (vonoprazan) will be supplied as 20 mg tablets.

Treatment B (lansoprazole) will be supplied as 30 mg capsules.

Subjects will be instructed not to crush, split, or chew the study drugs.

Treatments A and B are described as follows:

Treatment A: Vonoprazan (1 x 20 mg tablet) administered QD on Days 1 through 7

Treatment B: Lansoprazole (1 x 30 mg capsule) administered QD on Days 1 through 7

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject and for each study period, as per the randomization scheme.

On Days 2 through 7, the study drug will be administered within ± 1 hour of the dosing time established on Day 1 of each period.

The exact time of dosing will be recorded.

All study drugs will be administered orally with approximately 240 mL of water under fasting conditions.

12.2 Dose Modification

The dose and administration of the study drug to any subject may not be modified. If necessary, a subject must be discontinued for the reasons described in Section 11.3.

12.3 Method of Treatment Assignment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product, according to a randomization scheme.

Eligible subjects will be randomized to 1 of the 2 sequences in a 1:1 ratio. The sequences to be used in the randomization will be AB and BA.

If replacement subjects are allowed, the replacement subject number will be 100 plus the original (e.g., Subject No. 101 will replace Subject No. 1), with the same treatment sequence assignment.

12.4 Blinding

This is an open label study.

12.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral doses. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the PD measurements for pH assessment and the blood collections for vonoprazan and lansoprazole PK are the critical parameters and will be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

13.1 Screening

Within 28 days prior to the first dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and history of tobacco use will be recorded. Each subject will have a 12-lead ECG, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), *H. pylori* breath test, clinical laboratory tests, and additional tests as noted in Section 13.2.6, and physical examination. Rescreening is permissible.

13.2 Safety Assessments

13.2.1 Physical Examination

A full physical examination will be performed as outlined in the Study Events Flow Chart (Section 6). Symptom-driven- physical examinations may be performed at other times, if deemed necessary by the PI or designee.

13.2.2 Vital Signs

Single measurements of temperature, respiratory rate, blood pressure, and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6). Additional vital signs may be taken at any other times, if deemed necessary.

Vital sign measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g. nausea, dizziness) or if deemed necessary by the PI or designee.

When scheduled post dose, vital sign measurements will be performed within approximately 15 minutes of the scheduled time point.

13.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position. All ECG tracings will be reviewed by the PI or designee.

When scheduled postdose, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Body Weight

Body weight (kg) will be reported as outlined in the Study Events Flow Chart (Section 6).

13.2.5 *Helicobacter pylori* Test

An *H. pylori* breath test will be performed as outlined in the Study Events Flow Chart (Section 6) and according to the instructions provided with the breath test kit. A negative *H. pylori* result is required for subject eligibility.

13.2.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee.

Hematology

- Hematocrit
- Hemoglobin
- Red blood cell count
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Red blood cell distribution width
- Leukocytes and leukocyte differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
- Platelet count

Serum Chemistry *

- ALT
- Albumin
- ALP
- AST
- Bilirubin (total and direct)
- BUN
- Calcium
- Carbon dioxide
- Chloride
- Cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein)
- Creatine kinase
- Creatinine**
- GGT
- Globulin
- Glucose (fasting)
- Lactate dehydrogenase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Total protein
- Triglycerides (fasting)
- Uric acid

Urinalysis

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Leukocyte esterase***
- Nitrites***
- Occult blood***
- pH
- Protein***
- Specific gravity
- Turbidity
- Urobilinogen

Additional Tests

- HIV test
- HBsAg
- HCV
- Urine drug screen
  - Opiates
  - Opioids
  - Amphetamines
  - Cocaine
  - Cannabinoids
- Urine alcohol screen
- Serum pregnancy test (for females only)
- FSH (for at least 12 months postmenopausal females only)
- COVID-19 Test
- Gastrin

*Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours prior to the serum chemistry sample being taken.

**At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

***If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, crystals, and epithelial cells) will be performed.

13.2.7 Adverse Events

13.2.7.1 Adverse Event (AE) Definition

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

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 (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.

13.2.7.2 Adverse Event Monitoring

Subjects will be monitored from the signing the ICF and throughout the study for adverse reactions to the study drugs and/or procedures. On each study day and prior to check out, subjects will be asked how they are feeling. During the follow-up phone call, as applicable, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?'

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI or designee and treated and/or followed up until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI or designee.

Treatment of serious adverse events (SAEs) will be performed by a physician, either at Celerion or at a nearby hospital emergency room where appropriate medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal, or unknown.

13.2.7.3 Reporting

All AEs that occurred during this clinical study will be recorded. The PI or designee will review each event and assess its relationship to drug treatment 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.

Each sign or symptom reported will be graded on a 3-point severity scale (mild, moderate, or severe), and the date of onset, time of onset, and outcome of each event will be noted.

The following definitions will be used for rating the severity of AEs:

- 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.

13.2.7.4 Serious Adverse Event

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or email within one working day of becoming aware of the event, whether or not the serious events are deemed drug related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012. The Sponsor is responsible for reporting all Suspected Unexpected Serious Adverse Reaction and any other applicable SAEs to regulatory authorities, investigators and Institutional Review Boards (IRBs) or Independent Ethics Committees, as applicable, in accordance with national regulations in the countries where the study is conducted.

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 (see Table 1)
    - Exposes the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization

Table 1: Medically Significant Adverse Events 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

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.

For this study, the following contact information is to be used for SAE reporting:

Sponsor / Medical Monitor:

Phathom PV Inbox:

A special interest AE (serious or nonserious) is one of scientific and medical concern specific to the compound or program for which ongoing monitoring and rapid communication by the investigator to Phathom Pharmaceuticals 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 Pharmaceuticals. There are no special interest AEs for this study.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

13.2.8 Reporting of Pregnancy to the Sponsor

Although pregnancy is not considered an AE, it is the responsibility of the PI or designee to report any pregnancy in a subject that occurs during the study (from the time of enrollment). All subjects who become pregnant from the time of enrollment through completion of the study must be followed to the completion/termination of the pregnancy. The PI will follow up with the subject every 3 months throughout the pregnancy.

Pregnant partners of male subjects will not be followed.

Such events must be reported within one working day of becoming aware of the pregnancy to the Sponsor.

For this study, the following contact information is to be used for Pregnancy Reporting:

Sponsor / Medical Monitor:
[redacted]
Phathom PV Inbox: [redacted]

13.3 Pharmacodynamic Assessments

13.3.1 Gastric pH Monitoring

Gastric pH will be measured and recorded continuously for a 24-hour period on scheduled days as per the Study Events Flow Chart (Section 6) using a pH and pressure sensitive probe and ambulatory pH recording system (Sleuth/ZepHr™ Software from Sandhill Scientific). A pH recording will be taken every 5 seconds. After each 24-hour recording period, the flashcard will be removed from the recorder and transferred to the computer. It will then be placed back to start the next 24-hour collection, as appropriate. Once the recording is complete for Day -1 of Period 1 and Days 1 and 7 of Periods 1 and 2, the data will be transferred on a SAS data file and sent for analyses as specified in Section 14.3.1.

On Day -2 (Period 1) the lower esophageal sphincter (LES) will be identified and the distance from the upper border of LES to the nares will be recorded to facilitate the placement of the microelectrode probe for pH monitoring.

Prior to pH monitoring, the pH probe will be inserted nasogastrically so that it will be positioned in the gastric fundus (i.e., 10 cm below the LES). The microelectrode will record pH values over a 24-hour time frame.

A new probe will be inserted within approximately 2 hours prior to the start of each 24-hour monitoring period. Baseline pH monitoring will start in the morning of Day -1 of Period 1 and will continue for approximately 24 hours. On Days 1 and 7 of Periods 1 and 2, the continuous pH recording session will commence 30 to 60 minutes prior to treatment administration (Hour 0). Gastric pH will be sampled and recorded every 5 seconds and will conclude at the end of the 24-hour continuous monitoring period. Start time and stop time will be recorded. Study personnel will check and document the operation of the monitor every 2 hours during waking hours and every 4 hours overnight to ensure that it is functioning properly. On Day -1 of Period 1, continuous pH recording will follow a similar time matched (± 15 minutes) scheduled as planned for Day 1. Any interruptions in pH monitoring will be captured in the source document and appropriate case report form (CRF). Following completion of the 24-hour pH monitoring, the probe will be gently removed from the subject.

To minimize the discomfort of probe insertion, administration of a topical anesthetic (lidocaine) will be permitted.

13.3.2 Gastric pH Pharmacodynamic Parameters

The following PD parameters will be assessed:

Integrated acidity: The acid concentration (mM) is calculated as 1000×10^{-pH}. The integrated acidity is the time-weighted average of the acid concentration expressed as mM - the units are mmol.h/L. It is also the area under the acid concentration-time curve.

Integrated acidity will be computed over the following intervals:

- Hour 0 to approximately Hour 24;
- Hour 0 to approximately Hour 2;
- Hour 0 to approximately Hour 4;
- Hour 12 to approximately Hour 24.

To measure Integrated acidity for food intake, Integrated acidity will be computed over the following intervals:

- Hour 4 to approximately Hour 9;
- Hour 9 to approximately Hour 12.

Gastric pH: Measure of the immediate effect on gastric pH and duration of effect on gastric pH.

Measure of the average gastric pH will be computed over the following intervals:

- Hour 0 to approximately Hour 24;
- Hour 0 to approximately Hour 2;

- Hour 0 to approximately Hour 4;
- Hour 12 to approximately Hour 24.

To measure average gastric pH for food intake, gastric pH will be computed over the following intervals:

- Hour 4 to approximately Hour 9;
- Hour 9 to approximately Hour 12.

Time pH >4:	Calculated time that the gastric pH >4 over the course of the 24-hour monitoring period within the intervals described above.
pH >4 HTR:	pH >4 holding time ratio: the percentage of time gastric pH >4 over the course of the 24-hour monitoring period within the intervals described above.
Time pH >5:	Calculated time that the gastric pH >5 over the course of the 24-hour monitoring period within the intervals described above.
pH >5 HTR	pH >5 holding time ratio: the percentage of time gastric pH >5 over the course of the 24-hour monitoring period within the intervals described above.
Time pH >6:	Calculated time that the gastric pH >6 over the course of the 24-hour monitoring period within the intervals described above.
pH >6 HTR	pH >6 holding time ratio: the percentage of time gastric pH >6 over the course of the 24-hour monitoring period within the intervals described above.

13.3.3 Gastrin Sampling

For all subjects, blood samples for determination of serum gastrin concentrations will be drawn starting at 0, 2, 4, 5, 9, 10, 12, 13, and 24 hours on Day -1 of Period 1 for baseline determination and on Days 1 and 7 of Period 1. Sampling times on Day -1 will be time matched to postdose sampling on Day 1 and Day 7. The samples collected at 4, 9, and 12 hours postdose should be collected prior to starting meal/snack consumption. The 0-hour (predose) sample on Day 1 of Period 1 will be the same as the 24-hour sample on Day -1; only one sample will be collected. A single gastrin sample will also be drawn in Period 2 at Day 1 predose.

The 24-hour gastrin sample on Day -1 of Period 1 is to be taken approximately 15 minutes prior to dosing on Day 1 of Period 1, and the 24-hour postdose gastrin sample on Day 1 and Day 7 of Period 1 is to be taken approximately 15 minutes prior to pH probe removal on Day 2 and Day 8 of Period 1, respectively.

Instructions for gastrin blood sampling collection will be provided separately.

13.3.4 Gastrin Pharmacodynamic Parameters

PD parameters for plasma gastrin will be calculated as follows:

Gastrin AUC0-24:	The area under the curve over the 24-hour postdose period (AUC0-24) for Day -1 of Period 1 (Baseline) and Days 1 and 7 of Period 1, as calculated by the linear trapezoidal method.

13.4 Pharmacokinetic Assessments

13.4.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of plasma vonoprazan and lansoprazole concentrations will be collected in blood collection tubes at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

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

13.4.2 Plasma Pharmacokinetic Parameters

PK parameters for plasma vonoprazan and lansoprazole will be calculated as follows, as appropriate:

Day 1:

AUC0-t:	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.
AUC0-24:	The area under the concentration-time curve, from time 0 to the 24-hour time point, as calculated by the linear trapezoidal method.
AUC0-inf:	The area under the concentration-time curve from time 0 extrapolated to infinity. AUC0-inf is calculated as the sum of AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/AUC0-inf.
Cmax:	Maximum observed concentration.
Tmax:	Time to reach Cmax. If the maximum value occurs at more than one time point, Tmax is defined as the first time point with this value.
Kel:	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (e.g., three or more non-zero plasma concentrations).

t½:	Apparent first-order terminal elimination half-life will be calculated as 0.693/Kel.
Vz/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as Dose/(AUC0-inf x Kel).

Day 7:

AUCtau:	The area under the concentration-time curve during a dosing interval (tau) at steady state.
Cmax,ss:	Maximum observed concentration at steady-state.
Cavg:	Ratio of AUCtau to the dosing interval, tau.
Tmax,ss	Time to reach Cmax at steady state
RA,AUC	Accumulation ratio calculated from AUCtau at steady-state (ss), calculated as: note: sd = single dose on Day 1. $$R_{A,AUC} = \frac{AUC_{\tau,ss}}{AUC_{\tau,sd}}$$
RA,Cmax	Accumulation ratio calculated from Cmax at steady-state, calculated as: $$R_{A,Cmax} = \frac{C_{max,ss}}{C_{max,sd}}$$

No value for Kel, AUC0-inf, CL/F, Vz/F, or t½ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

13.4.3 Future Research

No additional analysis is planned to be performed on the PK blood samples for possible future research. Any additional research on these samples unspecified by this protocol will require approval from the subjects.

13.4.4 Analytical Method

Samples from all subjects will be assayed even if the subjects do not complete the study.

Samples will be analyzed for vonoprazan and lansoprazole using validated bioanalytical methods.

13.5 Cytochrome P450 2C19 Genotyping

A blood sample will be collected as delineated in the Study Events Flow Chart (Section 6) to determine CYP2C19 status (i.e., poor, intermediate, or extensive metabolizer).

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

13.6 Blood Volume Drawn for Study Assessments

Table 2: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, and serology), FSH (for postmenopausal female subjects only) and serum pregnancy (for female subjects only).	1	12.5	12.5
CYP2C19 Genotyping test	1	10	10
On-study hematology, serum chemistry (this includes serum pregnancy for female subjects only when scheduled at the same time)	3	12.5	37.5
Blood for gastrin profile	27	3.5	94.5
Blood for vonoprazan pharmacokinetics	32	4	128
Blood for lansoprazole pharmacokinetics	32	4	128
		Total Blood Volume (mL)→	410.5 **

* Represents the largest collection tube that expected be used for this (a smaller tube may be used).

** If additional safety or PK or PD analysis is required to obtain sufficient plasma/serum for analysis, additional blood may be obtained (up to a maximum of 50 mL).

14 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

14.1 Sample Size Determination

It is planned to enroll 40 subjects in this study, 20 subjects per sequence group (AB, BA), to provide 90% power to detect a difference of at least 10% in the change from baseline in pH >4 HTR on Day 7 between the treatment groups, assuming a common standard deviation of 17% and that the correlation coefficient between periods is 0.5. The sample size allows for 4 dropouts.

14.2 Population for Analyses

PD Population: All subjects who received at least one dose of the study drug and have at least one postdose pH measurement will be included in the PD analysis.

PK Population: All subjects who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment, availability of measurements and absence of major protocol violations) will be included in the PK analysis.

Safety Population: All subjects who received at least one dose of the study drug will be included in the safety analysis.

14.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

14.3.1 Pharmacodynamic Analysis

The PD parameters listed in Section 13.3.2 and Section 13.3.4 will be summarized using the appropriate descriptive statistics which will be fully outlined in the SAP.

14.3.1.1 Analysis of Variance – Pharmacodynamics

For gastric pH >4, pH >5, and pH >6 HTRs and mean gastric pH on Days 1 and 7, the point estimate of the difference in changes from baseline between the study medications (vonoprazan - lansoprazole) will be calculated along with the 2-sided 95% CI, using an ANOVA with treatment, sequence, and period as fixed effects and subject within sequence as a random effect. Gastric pH >4, pH >5, and pH >6 HTRs, mean gastric pH, and their changes from baseline will be summarized with descriptive statistics and 2-sided 95% CIs for each study treatment.

14.3.2 Pharmacokinetic Analyses

14.3.2.1 Descriptive Statistics

The vonoprazan and lansoprazole concentrations and the PK parameters listed in Section 13.4.2 will be summarized using the appropriate descriptive statistics which will be fully outlined in the SAP.

14.3.3 Safety Analyses

All safety data will be populated in the individual CRFs.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by treatment for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Safety data including ECGs, vital signs assessments, and clinical laboratory results will be summarized by treatment and time point of collection.

Quantitative safety data as well as the difference to baseline, when appropriate, will be summarized using the appropriate descriptive statistics. In addition, a shift table describing out of normal range shifts will be provided for clinical laboratory results.

Concomitant medications will be listed by subject and coded using the most current version of World Health Organization drug dictionary available at Celerion.

Medical history will be listed by subject.

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 Institutional Review Board

This protocol will be reviewed by [redacted] IRB, and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is compliant to International Council for Harmonisation (ICH) guidelines, and may be reached at:

[redacted]

This protocol will be reviewed by an IRB and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is ICH compliant.

15.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6[R2] Good Clinical Practice: Integrated Addendum to E6 [R1], November 2016).

15.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. If any 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 study, all active participating subjects must sign the revised IRB approved consent form.

Subjects will be given a copy of their signed ICF.

15.1.4 Confidentiality

All members of the PI's staff have signed confidentiality agreements with Celerion. By signing this protocol, the PI and Celerion staff will regard all information provided by the Sponsor and all information obtained during the course of the study as confidential.

The PI must guarantee the privacy of the subjects taking part in the study. Subjects will be identified throughout documentation and evaluation by a unique subject study number. Throughout the study, a subject's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. If subject name appears on any study document, it must be redacted before the copy of the documents is supplied to the Sponsor. Any information concerning the subjects (clinical notes, identification numbers, etc.) must be kept on file by the PI who will ensure that it is revealed only to the Sponsor, IRB, or regulatory authorities for the purposes of trial monitoring, auditing or official inspections. As required, in the case of an event where medical expenses are the responsibility of the Sponsor, personal information i.e., full name, social security details etc. may be released to the Sponsor. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information in strictest confidence and in accordance with local data protection laws.

15.2 Termination of the Study

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

15.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, and GCP requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

15.4 Direct Access to Source Data/Documents

Celerion will ensure that the Sponsor, IRB, and domestic and foreign regulatory authorities will have direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6][R2] 5.1.2 & 6.10). In the event that other study related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

15.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of vonoprazan tablets 20 mg to allow completion of this study. The vonoprazan tablets 20 mg will be packaged in 50-count high-density polyethylene bottles. Celerion will provide sufficient quantities of lansoprazole capsules 30 mg to allow completion of the study. The lot numbers and expiration dates (where available) of the study drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by Celerion, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Any remaining supplies that were purchased by Celerion will be destroyed, if appropriate. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

15.6 Data Handling and Record Keeping

Celerion standard CRFs will be supplied. CRFs are produced, stored electronically, and are available to the designated study team members. Each CRF is reviewed and signed by the PI. The final signed CRFs are provided to the Sponsor in the format as decided between Celerion and the Sponsor (e.g., compact disc, flash drive, secure file transfer protocol). This will be documented in the data management plan (if applicable).

The Investigator will maintain adequate case histories for the subjects treated as part of the research under this protocol. The Investigator will maintain accurate CRFs and source documentation as part of the case histories. The study will be collected in a validated study database which has an audit trail to log all subsequent changes to the data. The database is compliant with 21 CFR Part 11 guidelines. All queries will be resolved within the study database.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 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 at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

15.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

16 REFERENCES

Investigator's Brochure, Vonoprazan fumarate (TAK-438), Edition 10, 23 February 2020.

Prevacid® (lansoprazole) Capsules, full prescribing information (electronic monograph) document revised: November/2020. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=71ba78cb-7e46-43eb-9425-fa130f537f84