Protocol Number: HP-301

Official Title: A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection

NCT Number: NCT04167670

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CLINICAL STUDY PROTOCOL

IND#143190/EUDRACT: 2019-002668-28

A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection

PROTOCOL NO.: HP-301

Sponsor: Phathom Pharmaceuticals, Inc.
70 Willow Road, Suite 200
Menlo Park, CA 94025

Sponsor Contact: [redacted]

Medical Monitor: [redacted]

Version of Protocol: Version 3.0, Protocol Amendment 2

Date of Protocol: 11 May 2020

Previous Date and Version: 05 Nov 2019, Version 2.0 (Amendment 1)

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6 R2: Good Clinical Practice.

Protocol Approval – Sponsor Signatory

Study Title	A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection
Protocol Number	HP-301
Protocol Date	11 May 2020

Protocol accepted and approved by:

Chief Operating Officer

[redacted]

Protocol Approval – Principal/Coordinating Investigator

Study Title A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection

Protocol Number HP-301

Protocol Date 11 May 2020

Protocol accepted and approved by:

Principal/Coordinating Investigator

[redacted]

Protocol Approval – Lead Statistician

Study Title	A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection
Protocol Number	HP-301
Protocol Date	11 May 2020

Protocol accepted and approved by:

Lead Statistician

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 3.0, Protocol Amendment 2, dated 11 May 2020, the International Council for Harmonisation harmonised tripartite guideline E6 R2: Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with Phathom Pharmaceuticals, Inc. or implement protocol changes without Institutional Review Boards/Independent Ethics Committee approval except to eliminate an immediate risk to subjects. I agree to administer study drug only to subjects under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Phathom Pharmaceuticals, Inc.

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Summary of Changes

Protocol Amendment History and Reasons for Amendment

Version	Date	Reasons for Amendment
Version 1.0	19 Aug 2019	Original Protocol
Version 2.0 (Protocol Amendment 1)	05 Nov 2019	• To change the primary objective and primary endpoint to exclude subjects who have a clarithromycin or amoxicillin resistant strain of *Helicobacter pylori* at baseline • To make CYP2C19 genotyping optional • To remove wording allowing a subject's legally acceptable representative as a party capable of giving consent for the study • To clarify that contraception must be double barrier and that adequate double barrier contraception must be used from the signing of informed consent until Day -2 and 2 forms of adequate contraception must be used from Day -1 until 4 weeks after the last dose of study drug • To allow rescreening of subjects with approval from the Medical Monitor • To clarify that subjects who discontinue study drug or withdraw from the study prematurely will undergo early termination assessments • To redefine noncompliance as taking either less than 75% or more than 120% of study drug during any evaluation period • To exclude the use of CYP3A4 substrates with a narrow therapeutic index from 14 days prior to Day 1 through the End of treatment visit • To update the resistance breakpoint for amoxicillin to > 0.125 µg/mL from > 0.03 µg/mL • To add overall study stopping criteria in Section 6.2.1.15

Version	Date	Reasons for Amendment
		• To remove the requirement for at least one dose of study drug to be taken as a condition for inclusion in the modified intent-to-treat analysis set • To add smoking status and alcohol use in the Schedule of Events and to include smoking status, alcohol use, and clinical condition as variables for subgroup analyses • To redefine the 4-week post-treatment period in the Schedule of Events to be Days 42 to 70 • To remove the requirement that the early termination visit be conducted within 14 days of the last dose being taken • To clarify that testing for ^{13}C-UBT for HP infection status should be performed at least 4 weeks after the last dose of study medication
Version 3.0 (Protocol Amendment 2)	11 May 2020	• Addition of pre-screen optional fingerstick test to evaluate for HP+ status • Clarify at screening negative urine drug test results for cannabinoids/tetrahydrocannabinol and non-prescribed medications. • Addition to Schedule of Events to include a Week 1 phone call visit to remind subjects about study drug compliance and other assessments. • Addition to Schedule of Events to include pharmacokinetic samples on Day 15 • To clarify that PTE and AE collection and reporting time windows include PTEs/AEs that are considered SAEs. • To clarify that SAE eCRF forms must be completed and submitted within 24 hours of the investigator first becoming aware of the SAE (including SAEs that are PTEs).

For details of Protocol Amendment 1 and Amendment 2, see Appendix 4 (Section 13.4).

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Protocol Synopsis

Protocol Number:	HP-301
Title:	A Phase 3 Randomized Multicenter Study to Evaluate the Efficacy and Safety of Open-Label Dual Therapy with Oral Vonoprazan 20 mg or Double-Blind Triple Therapy with Oral Vonoprazan 20 mg Compared to Double-Blind Triple Therapy with Oral Lansoprazole 30 mg Daily in Patients with *Helicobacter Pylori* Infection
Sponsor:	Phathom Pharmaceuticals, Inc. 70 Willow Road, Suite 200 Menlo Park, CA 94025
Study Phase:	3
Study Sites:	Approximately 150 sites in US and Europe
Indication:	*Helicobacter pylori* infection
Rationale:	The purpose of this study is to compare the efficacy and safety of vonoprazan open-label dual therapy (vonoprazan and amoxicillin) and vonoprazan double-blind triple therapy (vonoprazan, amoxicillin, and clarithromycin) administered for 14 days compared to lansoprazole double-blind triple therapy (lansoprazole, amoxicillin, clarithromycin) administered for 14 days in subjects with *Helicobacter pylori* (HP) infection.
Objectives:	**Primary Objective** To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects who do not have a clarithromycin or amoxicillin resistant strain of HP at baseline **Secondary Objectives** • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in subjects infected with a clarithromycin resistant strain of HP • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in all subjects **Safety Objectives** To compare the safety of vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects

Study Population: Subjects aged ≥18 years of age with confirmed HP infection not previously treated with any regimen to attempt to eradicate HP.

Study Design: This is a Phase 3 randomized study to compare the efficacy and safety of vonoprazan open-label dual therapy (vonoprazan and amoxicillin) and vonoprazan double-blind triple therapy (vonoprazan, amoxicillin, and clarithromycin) administered for 14 days compared to lansoprazole double-blind triple therapy (lansoprazole, amoxicillin, clarithromycin) administered for 14 days in HP+ subjects.

Approximately 975 subjects will be randomized in a 1:1:1 ratio to receive:

- Vonoprazan dual therapy arm: vonoprazan 20 mg twice daily (BID) in conjunction with amoxicillin 1 g three times daily (TID) for 14 days
- Vonoprazan triple therapy arm: vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days
- Lansoprazole triple therapy arm/control arm: lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days.

HP+ subjects whose eligibility is confirmed by ^{13}C-urea breath test (^{13}C-UBT) during the Screening Period will have an endoscopy performed to collect gastric mucosal biopsy specimens to document HP infection by histology and for culture and susceptibility testing to determine resistance to bacteria to clarithromycin, amoxicillin and metronidazole antibiotics. At Week 6 (4 weeks after the last dose of study drug), HP eradication status will be assessed by ^{13}C-UBT. Subjects who remain HP+ should have a follow-up endoscopy with repeat bacteriological testing for resistant bacteria to the antibiotics used in the study, and the subjects should be treated as per the standard clinical care.

Estimated Study Duration: The study will consist of a ≤34-day Screening Period, a 14-day Treatment Period and a 4-week Follow-up Period.

Efficacy Assessments: The study will evaluate HP infection status as determined by a ^{13}C-UBT.

If the subject's ^{13}C-UBT test is positive at 4 weeks after the last dose of study drug, an endoscopy will be performed, and gastric mucosal biopsy specimens will be taken for antibiotic susceptibility testing.

Pharmacokinetic or Pharmacodynamic Assessments:	For pharmacokinetic analysis of drug concentrations, blood samples will be collected at the Week 2 Visit, unless prohibited by local regulations. In order to determine the subject's metabolizer status, an optional blood sample will be obtained for CYP2C19 genotype testing, unless prohibited by local regulations.
Safety Assessments:	Safety assessments will include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory assessments, physical examinations, electrocardiograms and vital signs.
Study Drug, Dosage, and Route of Administration:	The vonoprazan dual therapy arm will consist of vonoprazan 20 mg BID in conjunction with amoxicillin 1 g TID for 14 days. The vonoprazan triple therapy arm will consist of vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days. The lansoprazole triple therapy arm/control arm will consist of lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days. All study drugs will be administered orally starting on Day 1 (the day after randomization).
Sample Size:	325 subjects per arm.
Statistical Methods:	The primary endpoint (proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, in subjects who do not have a clarithromycin or amoxicillin resistant strain of HP at baseline) will be calculated as a percentage of subjects in each treatment group. Noninferiority of vonoprazan triple therapy to lansoprazole triple therapy, and vonoprazan dual therapy to lansoprazole triple therapy, will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in HP eradication rates between treatments. For each noninferiority comparison that yields statistical significance, superiority will then be assessed via the Farrington and Manning test of the null hypothesis difference ≤ 0 versus the alternative hypothesis difference >0. The secondary endpoints will be evaluated in a similar manner as the primary endpoint for superiority of vonoprazan triple therapy to lansoprazole triple therapy and of vonoprazan dual therapy to lansoprazole triple therapy.

Version and Date of Protocol:	Version 3.0 (Protocol Amendment 2); 11 May 2020

List of Abbreviations

Abbreviation	Definition
^{13}C-UBT	carbon 13-urea breath test
ACG	American College of Gastroenterology
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
CYP	cytochrome P450 isoenzymes
ECG	electrocardiogram
eCRF	electronic case report form
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HP	*Helicobacter pylori*
HP+	*Helicobacter pylori* positive
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response system
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
NSAID	nonsteroidal anti-inflammatory drug
PCAB	potassium-competitive acid blocker
PD	pharmacodynamic
PP	per protocol
PPI	proton pump inhibitor
PT	Preferred Term
PTE	pretreatment adverse event
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SoE	schedule of events
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	three times daily
UEG	United European Gastroenterology
ULN	upper limit of normal

1 Introduction

Vonoprazan belongs to a new class of acid-inhibitory agents called "potassium-competitive acid blockers" (PCAB), and in combination with antibiotics, is being developed for the eradication of *Helicobacter pylori* (HP) infection which is an important cause of peptic ulcer disease and gastric cancer (see Section 1.2).

The gastric hydrogen, potassium–adenosine triphosphatase (H+, K+-ATPase), also known as the proton pump, is responsible for acid secretion from parietal cells in the stomach. It is inactive in the cytosol but relocates from the cytosol to the secretory membrane of the parietal cells when food is present in the stomach, thereby becoming active and pumping H+ ions out of the cells and into the canaliculi in exchange for K+ ions. It represents an attractive pharmacological target, since 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 relative to PPIs:

- Acid activation and stability: Conventional PPIs are prodrugs, which are activated by acid and covalently bind the H+, K+-ATPase; however, activated PPIs are not stable in acidic conditions. In contrast, vonoprazan does not require acid activation, is stable in acidic conditions, and does not require enteric-coated formulations, enabling a more durable effect. Further, vonoprazan is rapidly protonated in the parietal cell canaliculi, which concentrates the drug proximal to the H+, K+-ATPase.

- Activity against active and inactive proton pumps: Vonoprazan inhibits acid secretion by competitively inhibiting the binding of potassium ions to the H+, K+-ATPase. Vonoprazan can bind to the pump while it is either active or inactive; 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 the parietal cell. Pumps are constantly switching between the active and inactive state throughout the day, therefore multiple doses of PPIs are required to control acid compared with a single dose of vonoprazan. Vonoprazan can also be dosed in the presence or absence of food, while most PPIs require dosing before a meal to stimulate activation of the pumps.

- Extended half-life: The plasma half-life of vonoprazan (20 mg) is 5.7 and 7 hours after the first dose and after the seventh day of once daily dosing in humans, respectively

(Jenkins et al 2015). 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, which lacks a high degree of genetic polymorphism compared with CYP2C19, which is the primary enzyme responsible for the metabolism of PPIs.

These unique aspects of the vonoprazan mechanism relative to PPIs translate into greater magnitude and duration of gastric acid suppression, which are reflected in the pharmacodynamic (PD) profile.

In Japan, the Phase 1 Study TAK-438/CPH-010 evaluated the anti-secretory effect of vonoprazan 20 mg compared with esomeprazole 20 mg or rabeprazole 10 mg in healthy adult male Japanese subjects who were CYP2C19 extensive metabolizers. In this study, gastric pH was consistently higher after administration of vonoprazan than after administration of esomeprazole or rabeprazole. The difference was first notable 2 hours after the study drug administration and persisted until Day 7. Whereas the gastric pH level on Day 1 was consistently lower over 24 hours than that on Day 7 after administration of esomeprazole or rabeprazole, they were similar after administration of vonoprazan (Sakurai et al 2015).

Furthermore, in a Phase 1 study conducted in the United Kingdom, vonoprazan at doses ≥20 mg demonstrated a rapid onset of action after the first dose and near maximal PD effect within 24 hours of dosing, which was maintained with repeat dosing (TAK-438 107, Jenkins et al 2015).

Vonoprazan was developed by Takeda Pharmaceutical Company Limited (Takeda). Phathom has licensed the exclusive rights from Takeda to develop and commercialize vonoprazan in the United States (US), Europe, and Canada. Phathom is developing vonoprazan for the eradication of *Helicobacter pylori* (HP) infection in combination with amoxicillin (dual therapy) or in combination with amoxicillin and clarithromycin (triple therapy).

1.1 Study Rationale

Vonoprazan has been studied in a number of acid-related diseases including eradication of HP infection, erosive esophagitis healing and maintenance, gastric ulcer/duodenal ulcer healing, and for the prevention of recurrence of a gastric or duodenal ulcer during

nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin administration. Vonoprazan has received regulatory approval in Japan and other countries in Asia and Latin America for these indications.

For the eradication of HP, a Phase 3 study in Japan tested vonoprazan 20 mg twice daily (BID) in combination with clarithromycin and amoxicillin and demonstrated noninferiority (pre-specified) and superiority (post hoc) compared with lansoprazole in combination with clarithromycin and amoxicillin (TAK-438/CCT-401, Murakami et al 2016). The eradication rate for the vonoprazan triple regimen was 92.6% compared to 75.9% for the lansoprazole triple therapy regimen.

Study HP-301 will compare the efficacy and safety of vonoprazan open-label dual therapy (vonoprazan and amoxicillin) and vonoprazan double-blind triple therapy (vonoprazan, amoxicillin, and clarithromycin) administered for 14 days compared to lansoprazole double-blind triple therapy (lansoprazole, amoxicillin, clarithromycin) administered for 14 days in subjects with HP infection.

1.2 Background

Helicobacter pylori is a gram-negative, microaerophilic bacterium found on human gastric mucosa. Its causal relationship to gastrointestinal diseases has been extensively studied (O'Connor 1994) since it was isolated from the gastric mucosa of a patient with chronic gastritis in 1983 (Warren and Marshall 1983). The current prevalence of HP infection in the US is estimated at 30% (Crowe 2019) and is between 20% and 40% in Europe (O'Connor and O'Morain 2013). The incidence of HP is lower in Northern and Western Europe than in Eastern and Southern Europe. As a result of the chronic inflammation induced by HP infection (Brawner et al 2014), approximately 20% of infected patients will develop a range of pathologies including peptic ulcer disease and gastric cancer.

According to the 2017 American College of Gastroenterology (ACG) guidelines, HP infection is a chronic bacterial infection and, if left untreated, it can ultimately lead to gastric cancer in a subset of infected patients (Chey et al 2017). Gastric cancer is the third most common cause of cancer-related death worldwide and over 80% of gastric cancers are attributed to HP infection (Plummer et al 2015). Globally there are more than one million new cases of gastric cancer and approximately 780,000 deaths each year (IARC).

In a study conducted in Japan with a mean follow-up of 7.8 years, gastric cancer developed in 29% of patients with peptic ulcer, dyspepsia, or gastric hyperplasia who also had HP infection, whereas no cases were detected in uninfected patients with these conditions (ie, those without HP infection) (Nomura et al 1991; Parsonnet et al 1991; Uemura et al 2001). Additionally, immigrants who grew up in regions of the world with a high incidence of HP infection (eg, Eastern Europe, Latin America, and East Asia) and who now reside in the US or Western Europe have a higher prevalence of the infection than people born in Western Europe or the US. These individuals are also at increased risk of gastric cancer (Crowe 2019). Recently, the World Health Organization included HP among the 16 antibiotic-resistant bacteria that pose the greatest threat to human health, and previously designated it as a class 1 carcinogen (Graham and Dore 2018).

Recently the ACG and the Maastricht IV/Florence Consensus Report updated treatment guidelines for HP infection (Chey et al 2017; Malfertheiner et al 2017) and recommended using anti-secretory agents, such as PPIs, in conjunction with antibiotics to improve their efficacy against HP infection. The use of an anti-secretory agent enhances the effect of antibiotics in 2 ways. First, anti-secretory agents increase gastric pH, which in turn increases the stability of the antibiotics. For example, amoxicillin and clarithromycin are chemically unstable at the low pH typically found in the human stomach. Clarithromycin, in particular, is rapidly degraded at pH 2 (Erah et al 1997). Second, several antibiotics, including amoxicillin and clarithromycin, are most potent against HP at the time of maximum bacterial replication, which occurs at pH 6 to 7 (Marcus et al 2012). In contrast, HP is in a dormant state at lower pH values, which reduces the effectiveness of the antibiotics (Hassan et al 1999; Scott et al 2015). As a result, increasing the pH reduces the minimum inhibitory concentration (MIC) of antibiotics against HP (Table 1-1).

Table 1-1 *H. pylori* MIC Values as a Function of pH

	MIC_{90} (mg/L)		
Agent	**pH 7.5**	**pH 6.0**	**pH 5.5**
Penicillin	0.03	0.5	0.5
Ampicillin	0.06	0.25	0.5
Cephalexin	2	16	32
Erythromycin	0.06	2	8
Clarithromycin	0.03	0.06	0.25
Ciprofloxacin	0.12	0.5	2
Tetracycline	0.12	0.25	0.5

Abbreviations: MIC, minimum inhibitory concentration.
Source: Erah et al 1997.

PPIs have been the recommended anti-secretory agent in combination with antibiotics for the eradication of HP; combination regimens have been approved in various countries around the world. A triple therapy regimen (PPI, clarithromycin, and either amoxicillin or metronidazole) is most common. However, HP eradication rates with PPI triple therapy have fallen from >90% in the 1990s to current levels of <80%, which may be accounted for by the increased resistance of HP to clarithromycin and metronidazole (Shiota et al 2015). A recent meta-analysis suggests that in the US, the resistance rates measured from 2012 to 2016 for clarithromycin, metronidazole, and levofloxacin were 20%, 29%, and 19%, respectively (Savoldi et al 2018). These figures represent a marked increase from 2009 to 2011 for both clarithromycin and metronidazole, where resistance was 9% for clarithromycin, 21% for metronidazole, while at 11% for levofloxacin (Savoldi et al 2018). A similar trend was seen in Europe where resistance rates measured from 2012 to 2016 for clarithromycin, and metronidazole were 28% and 46%, respectively (Savoldi et al 2018) and also represent an increase from 2009 to 2011, where resistance was 23% for clarithromycin and 33% for metronidazole (Savoldi et al 2018). *Helicobacter pylori* resistance to amoxicillin remains low despite its extensive use in most triple therapy regimens of 7, 10, or 14 days duration, and a wide range of other clinical infections. Resistance levels to amoxicillin are generally <2% among isolates in the US (Meyer et al 2002) and Europe (Megraud 2012). Given the declining eradication rates for HP, quadruple therapy (eg, PPI, clarithromycin, amoxicillin, and metronidazole, or PPI, bismuth salt, tetracycline, and metronidazole) is recommended as first-line treatment in areas with high rates of clarithromycin or metronidazole resistance. However, regimens with multiple drugs dosed at multiple times throughout the day may pose compliance challenges for patients (Vakil 2005). Further, geographic patterns of resistance are poorly understood, and treatment is largely empiric, with susceptibility testing rarely conducted before first-line treatment. As such, there is a clear need for simpler, more effective first-line treatment options.

In Japan, vonoprazan has shown the potential to restore the effectiveness of the most common triple therapy antibiotic combination regimen to historical cure rates of greater than 90% and has also shown promising results as a dual therapy combined with high dose amoxicillin. The vonoprazan dual therapy regimen has the potential for improved convenience and compliance over triple or quadruple therapy regimens. Further, this regimen

spares the use of clarithromycin, metronidazole, and levofloxacin, representing an opportunity both for effective treatment and for sound antibiotic stewardship through the avoidance of antibiotics to which HP is known to acquire resistance. Less frequent use of these antibiotics, which have important uses aside from the treatment of HP infection, may help to limit the spread of resistance among other pathogenic bacteria within populations.

1.3 Justification for Dose

The current ACG guideline and the Maastricht IV/Florence Consensus Report recommend a number of treatment regimens including triple therapy consisting of a PPI, clarithromycin (500 mg BID), and amoxicillin (1 g BID) for 14 days (Chey et al 2017; Malfertheiner et al 2017). The guidelines stress the importance of increasing clarithromycin resistance and suggests alternative regimens when local resistant rates are known to be high. Therefore, for the purposes of this study, PPI-based triple therapy is a reasonable comparator to use empirically because the clarithromycin resistance rate will vary across countries and investigative sites, and clarithromycin resistance in a particular subject is not known at the time of treatment initiation.

Lansoprazole is the PPI in the active comparator arm of this study, as it is a well-established regimen used globally. The lansoprazole regimens proposed in this study are consistent with the approved dosing recommendation in the US and Europe (PREVACID 2018; eMC 2018).

As described in Section 1, vonoprazan provides more rapid and potent acid suppression than PPIs. The combination regimen of vonoprazan, amoxicillin, and clarithromycin studied in Japan has been shown to be highly efficacious in the treatment of HP infection with an eradication rate of 92.6% (Murakami et al 2016). The vonoprazan triple therapy regimen will use the same doses and treatment duration of amoxicillin and clarithromycin being used in the lansoprazole triple therapy active control to allow a direct comparison of the 2 regimens. Although the doses of amoxicillin and clarithromycin are higher than those used in the Japan development program, they reflect the differences in standard of care between Japan and Western countries and are appropriate for use in the proposed Study HP-301 to be conducted in the US and Europe.

Dual therapy with PPI and high dose amoxicillin is approved for the eradication of HP in many regions; however, the eradication rates are now unacceptably low (Graham et al 2017).

The use of vonoprazan and high dose amoxicillin as dual therapy is supported by the results of 2 Japanese investigator-initiated studies that demonstrated that vonoprazan dual therapy achieves eradication rates similar to those of triple therapy with a PPI, and triple therapy with vonoprazan.

One study of 61 subjects assessed vonoprazan 20 mg BID in combination with amoxicillin 500 mg three times daily (TID) for 7 days compared with vonoprazan 20 mg BID in combination with amoxicillin 750 mg BID and clarithromycin 200 mg BID for 7 days. In this study, vonoprazan dual therapy was as efficacious as vonoprazan triple therapy (93.3% versus 90.3%) (Furuta et al 2018).

A second study enrolled 81 subjects, 41 of whom had failed standard first-line therapy. Subjects assigned to dual therapy were treated with vonoprazan 20 mg BID in combination with amoxicillin 500 mg TID for 7 days. Subjects assigned to triple therapy were treated first-line with esomeprazole 20 mg or rabeprazole 10 mg BID, amoxicillin 750 mg BID, and clarithromycin 200 mg BID, or second-line with esomeprazole 20 mg or rabeprazole 10 mg BID, amoxicillin 750 mg BID, and metronidazole 250 mg BID for 7 days. Dual therapy with vonoprazan was as efficacious as both first- and second-line therapy with eradication rates of 95% (19 of 20) and 90% (18 of 20), respectively, versus 81% (17 of 21) and 85% (17 of 20) for PPI-based triple therapies (Furuta et al 2016).

2 Study Objectives and Endpoints

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects who do not have a clarithromycin or amoxicillin resistant strain of HP at baseline	• Proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug in subjects who do not have a clarithromycin or amoxicillin resistant strain of HP at baseline
Secondary • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in subjects infected with a clarithromycin resistant strain of HP • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in all subjects	• Proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT at 4 weeks after the last dose of study drug, among subjects who had a clarithromycin resistant strain of HP at baseline • Proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug among all subjects
Safety • To compare the safety of vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects	• Adverse events (AEs) • Laboratory test values (hematology, serum chemistry, urinalysis) • Electrocardiogram (ECG) • Vital signs

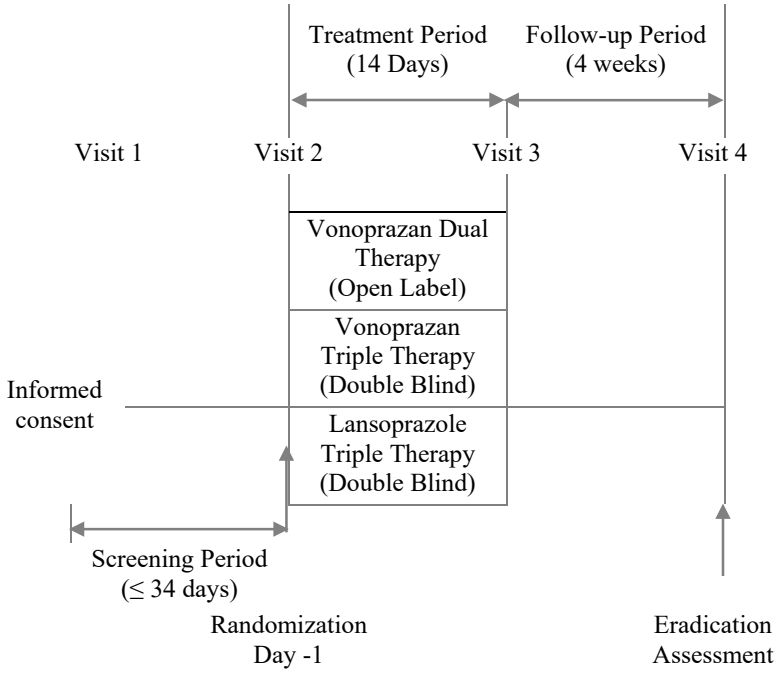
3 Investigational Plan

3.1 Study Design

This is a Phase 3, randomized, parallel group study to compare the efficacy and safety of vonoprazan open-label dual therapy (vonoprazan and amoxicillin) and vonoprazan double-blind triple therapy (vonoprazan, amoxicillin, and clarithromycin) administered for 14 days compared to lansoprazole double-blind triple therapy (lansoprazole, amoxicillin, clarithromycin) administered for 14 days in HP+ subjects.

A schematic diagram of the overall study design is presented in Figure 3-1.

Figure 3-1 Study Design



The study will include 3 main periods:

1. Screening Period (Day -35 to Day -2): Subjects will provide informed consent and the subject will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will enter the study.

Subjects may be pre-screened for HP infection using a fingerstick test performed not more than 30 days prior to screening. The subjects will sign a pre-screening ICF for optional fingerstick test of HP status.

An endoscopy will be performed to collect gastric mucosal biopsy specimens (one each from the greater and lesser curve of the gastric body, and one each from the greater and lesser curve of the antrum) at the start of the study for histopathology (Section 6.1.2.2) to document HP infection. Two additional gastric mucosal biopsy specimens will be collected (one from the greater curve of the antrum and one from the lesser curve of the gastric body) for culture and susceptibility testing (Section 6.1.2.1) to determine resistance to bacteria to clarithromycin, amoxicillin and metronidazole antibiotics which are commonly used in the treatment of HP infection. After randomization, as part of the overall analysis, MICs of amoxicillin, clarithromycin, and metronidazole against HP will be determined using the strains isolated from these specimens by the 2-fold agar dilution method. Results from the gastric mucosal biopsy specimens (histology and culture) will be available post-randomization. Any remaining gastric mucosal biopsy samples may be used for future pharmacogenomic evaluation of HP (Section 6.10).

2. Treatment Period (2-week treatment period): HP+ subjects whose eligibility is confirmed by ^{13}C-urea breath test (^{13}C-UBT) during the Screening Period will be randomly assigned in a 1:1:1 ratio to receive vonoprazan 20 mg BID in conjunction with amoxicillin 1 g TID (vonoprazan dual therapy arm) for 14 days, vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID (vonoprazan triple therapy arm) for 14 days, or lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID (lansoprazole triple therapy arm/control arm) for 14 days.

   Subjects will receive a phone call from the site at Week 1 to remind subjects about compliance with study drug and other assessments described in the SoE (Section 13.1).

   Subjects will return at Week 2 for laboratory tests and other assessments described in the SoE (Section 13.1).

3. Follow-up Period: A phone call follow-up will be performed at Week 4 (2 weeks after last dose of study drug) to assess adverse events (AEs) and any concomitant medication usage. At Week 6 (4 weeks after the last dose of study drug), HP eradication status will be assessed by ^{13}C-UBT. Subjects who remain HP+ at the Follow-up Period should have a follow-up endoscopy with repeat bacteriological test for resistant bacteria to the antibiotics used in the study, and the subjects can be treated as per the standard clinical care.

End of study definition: A subject is considered to have completed the study if he/she has completed all phases of the study including Visit 4 performed 4 weeks after the last dose of study drug.

3.1.1 Rationale of Study Design

This Phase 3 randomized, parallel group study, with open-label dual therapy and double-blind triple therapy, is designed to evaluate the efficacy and safety of vonoprazan in HP+ subjects. The parallel group design allows for direct assessment of efficacy and safety of the 2 vonoprazan arms of the study relative to the lansoprazole control arm and of the 2 vonoprazan arms to each other. Further, the primary endpoint for this study is based on an objective measurement via the ^{13}C-UBT, and the UBT testing facility will remain blinded to all 3 treatment assignments ensuring that the evaluation of the efficacy endpoint is not subject to bias.

Diagnosis and eradication of HP by ^{13}C-UBT is a well-accepted method by both the ACG and United European Gastroenterology (UEG).

The antibiotics amoxicillin and clarithromycin are recommended first line use by both the ACG and the UEG guidelines, and the duration of dosing of 14 days is accepted in both regions.

While PPIs require 3 to 5 days to exert their maximum acid-inhibitory effects, vonoprazan is known to exhibit its maximum acid-inhibitory effects in a much shorter time compared with PPIs, and to exert potent and sustained acid-inhibitory effects. The relatively higher pH in the stomach, due to faster and greater acid suppression by vonoprazan, is expected to confer greater efficacy in eradication by optimizing the conditions in the stomach for the antibiotics to work. This should lead to better treatment outcomes and a greater adjunctive effect to HP eradication therapy.

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

This study will be conducted in approximately 150 sites in the US and Europe with an estimated total of 975 randomly assigned subjects (325 subjects per treatment group). Subjects will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1.1 Inclusion Criteria

Subjects are eligible for enrollment in the study if they meet all of the following inclusion criteria:

1. The subject is ≥ 18 years of age at the time of informed consent signing.
2. In the opinion of the investigator or sub-investigators, the subject is capable of understanding and complying with protocol requirements.
3. The subject signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures. The subject is informed of the full nature and purpose of the study, including possible risks and side-effects. The subject has the ability to cooperate with the investigator. Ample time and opportunity should be given to read and understand verbal and/or written instructions.
4. The subject has at least one of the following clinical conditions with confirmed HP infection demonstrated by a positive ^{13}C-UBT during the Screening Period.
    - Dyspepsia (ie, pain or discomfort centered in the upper abdomen) lasting at least 2 weeks
    - A confirmed diagnosis of functional dyspepsia
    - A recent / new diagnosis of (non-bleeding) peptic ulcer
    - A history of peptic ulcer not previously treated for HP infection
    - A requirement for long-term NSAID treatment at a stable dose of the NSAID

5. A female subject of childbearing potential who is or may be routinely sexually active with a nonsterilized male partner agrees to routinely use adequate double barrier contraception from the signing of informed consent until Day -2 and 2 forms of adequate contraception from Day -1 until 4 weeks after the last dose of study drug as detailed in Appendix 2 (Section 13.2) of this protocol.

4.1.2 Exclusion Criteria

Subjects are not eligible for study participation if they meet any of the following exclusion criteria:

1. The subject has previously been treated with any regimen to attempt to eradicate HP.
2. The subject has gastric or duodenal ulcer with endoscopic evidence of current or recent bleeding.
3. The subject has confirmed diagnosis of gastric cancer by biopsy.
4. The subject is receiving colchicine.
5. The subject has received any investigational compound (including those in post-marketing studies) within 30 days prior to the start of the Screening Period. A subject who has screen failed from another clinical study and who has not been dosed may be considered for enrollment in this study.
6. The subject is a study site employee, an immediate family member, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or who may have consented under duress.
7. The subject has cutaneous lupus erythematosus or systemic lupus erythematosus.
8. The subject has had clinically significant upper or lower gastrointestinal bleeding within 4 weeks prior to randomization.
9. The subject has Zollinger-Ellison syndrome or other gastric acid hypersecretory conditions.

10. The subject has a history of hypersensitivity or allergies to vonoprazan (including the formulation excipients: D-mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 8000, titanium oxide, red or yellow ferric oxide), PPIs, amoxicillin and/or clarithromycin, or any excipients used in the ^{13}C-UBT: mannitol, citric acid or aspartame. Skin testing may be performed according to local standard practice to confirm hypersensitivity.
11. The subject has a history of alcohol abuse, illegal drug use, or drug addiction within the 12 months prior to screening, or who regularly consume >21 units of alcohol (1 unit = 12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine) per week based on self-report. Subjects must have a negative urine drug screen for cannabinoids/ tetrahydrocannabinol and non-prescribed medications at screening.
12. The subject is taking any excluded medications or treatments listed in the protocol (Section 5.8.2).
13. If female, the subject is pregnant, lactating, or intending to become pregnant before, during, or within 4 weeks after participating in this study; or intending to donate ova during such time period.
14. The subject has a history or clinical manifestations of significant central nervous system, cardiovascular, pulmonary, hepatic, renal, metabolic, other gastrointestinal, urological, endocrine or hematological disease that, in the opinion of the investigator, would confound the study results or compromise subject safety.
15. The subject requires hospitalization or has surgery scheduled during the course of the study or has undergone major surgical procedures within 30 days prior to the Screening Visit.
16. The subject has a history of malignancy (including MALToma) or has been treated for malignancy within 5 years prior to the start of the Screening Period (Visit 1) (the subject may be included in the study if he/she has cured cutaneous basal cell carcinoma or cervical carcinoma in situ).
17. The subject has acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection, or tests positive for the hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or HCV RNA. However, subjects who test positive for HCV antibody, but negative for HCV RNA are permitted to participate.

18. The subject has any of the following abnormal laboratory test values at the start of the Screening Period:
    a) Creatinine levels: >2 mg/dL (>177 μmol/L).
    b) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 × the upper limit of normal (ULN) or total bilirubin >2 × ULN.

4.1.3 Lifestyle Considerations

Subjects should be instructed as follows:

- To refrain from excessive drinking and eating, an extreme diet change (eg, change to an extremely high-fat diet) or excessive exercise throughout the study.
- Not to donate blood during the study, and to report on any such donation immediately.

4.1.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

If a suspected erroneous laboratory result is obtained at screening, retesting of that laboratory parameter will be allowed at investigator discretion with medical monitor approval.

Rescreening of subjects is permitted if approved by the Medical Monitor. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

4.2 Withdrawal of Subjects From Study Drug and/or the Study

The duration of the study is defined for each subject as the date signed written informed consent is provided through the last Follow-up Visit performed 4 weeks after the last dose of study drug.

4.2.1 Reasons for Withdrawal/Discontinuation

Subjects may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. Every effort should be made to keep subjects in the study. The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF). For screen failure subjects, refer to Section 4.1.4. A subject may be withdrawn from the study for any of the following reasons:

1. Adverse events or SAE: The subject has experienced a pretreatment adverse event (PTE), AE or SAE that requires early termination because continued participation imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the PTE, AE or SAE.

   Note: If a subject is discontinued from study participation due to a PTE, AE, or SAE, the event will be followed until it is fully resolved.

2. Liver Function Test (LFT) abnormalities: Appropriate clinical follow-up (including repeat laboratory tests) is to be done until a subject's laboratory profile has returned to normal/baseline status. See Appendix 3 (Section 13.3) for the criteria of liver function abnormalities for temporary and permanent discontinuation of study drug.

3. Significant protocol deviation: The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.

4. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented (3 documented telephone contact attempts and 1 certified letter, at a minimum) within 6 weeks of the most recent planned visit.

5. Voluntary withdrawal: The subject wishes to withdraw from the study. The reason for the withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).

6. Study termination: The sponsor, Institutional Review Boards (IRB), Independent Ethics Committees (IEC), or regulatory agency terminates the study.

7. Pregnancy: The subject is found to be pregnant. Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 6.4.
8. Lack of efficacy: The investigator has determined that the subject is not benefiting from investigational treatment and continued participation would pose an unacceptable risk to the subject.
9. Other: The subject is discontinued from the study for any reason other than those listed above. The specific reason(s) for subject discontinuation should be recorded in the "specify" field of the eCRF.

4.2.2 Handling of Withdrawals

Subjects are free to withdraw from the study or study drug at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

Subjects who discontinue study drug or active participation in the study will no longer receive study drug. When a subject withdraws from the study drug or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will undergo all early termination assessments. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any subject withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified safety follow-up procedures.

See the SoE (Section 13.1) for data to be collected at the time of discontinuation of study drug and follow-up and for any further evaluations that need to be completed.

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 4.2.1.

4.2.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter (or local equivalent methods) to the subject's last known mailing address). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study due to being lost to follow-up.

4.2.4 Replacements

Discontinued or withdrawn subjects will not be replaced.

5 Study Drugs

5.1 Method of Assigning Subjects to Treatment Groups

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomly assigned at the baseline/randomization visit (Visit 2/Day -1) to receive vonoprazan dual therapy, vonoprazan triple therapy, or lansoprazole triple therapy for 14 days using a 1:1:1 allocation ratio.

An interactive response system (IRT) will be used to administer the randomization schedule. Biostatistics will generate the randomization schedule using SAS software Version 9.4 or later (SAS Institute Inc, Cary, North Carolina) for IRT, which will link sequential subject randomization numbers to treatment codes. It will also use an appropriate block size, which will not be revealed.

5.2 Treatments Administered

Subjects randomly assigned to vonoprazan dual therapy will receive vonoprazan 20 mg BID in conjunction with amoxicillin 1 g TID for 14 days.

Subjects randomly assigned to vonoprazan triple therapy will receive vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days.

Subjects randomly assigned to lansoprazole triple therapy will receive lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days.

All study drugs will be administered orally starting on Day 1 (the day after randomization, Table 13-1).

Study drug administration will be as presented in Table 5-1.

Table 5-1 Study Drugs Timings

Study Drugs	Vonoprazan Dual Therapy			Vonoprazan Triple Therapy			Lansoprazole Triple Therapy		
	Mor	Aft	Eve	Mor	Aft	Eve	Mor	Aft	Eve
Vonoprazan 20 mg	X	-	X	X	-	X	-	-	-
Lansoprazole 30 mg	-	-	-	-	-	-	X	-	X
Amoxicillin 1 g	X	X	X	X	-	X	X	-	X
Clarithromycin 500 mg	-	-	-	X	-	X	X	-	X

Abbreviations: Aft, afternoon; Eve, evening; Mor, morning.

Subjects should be instructed as follows:

- To take study drug(s) 30 minutes before breakfast, lunch and dinner (for subjects enrolled in the dual-therapy arm) or breakfast and dinner (for subjects enrolled in the triple-therapy arm) at about the same time as he/she usually does with approximately 240 mL (8 oz) water.
- To present to the clinic in a fasting state when he/she is scheduled for laboratory tests and/ or an endoscopy. On such study visit days, subjects will be instructed to take their dose of study drug(s) (if appropriate) after study procedures are completed.

5.3 Identity of Investigational Product

Vonoprazan

Vonoprazan study medication will be supplied as 20 mg capsules. The tablet drug product will be over-encapsulated into Swedish Orange DB-AAel capsules containing microcrystalline cellulose at the contract manufacturing organization, PCI, Rockford, IL, USA. Takeda Pharmaceutical Company, Ltd, Hikari, Japan manufactures the vonoprazan drug substance and tablet drug product.

The over-encapsulated vonoprazan 20 mg will be packaged in a blister card.

Lansoprazole

Commercially available lansoprazole 30 mg capsules will be supplied by Delpharm Novaro, Cerano, Italy in plain white capsules. The capsule product will be over-encapsulated into Swedish Orange DB-AAel capsules containing microcrystalline cellulose at the contract manufacturing organization, PCI, Rockford, IL, USA.

The over-encapsulated lansoprazole will be packaged in a blister card.

Amoxicillin and Clarithromycin

Commercially available amoxicillin and clarithromycin will be supplied in their commercial packaging.

Each blister card/bottle will bear a label that includes the pertinent study information and local regulatory requirements. Labels will be in the appropriate language for the area in which the study medication is dispensed.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

Over-encapsulated vonoprazan and over-encapsulated lansoprazole will be prepared in blister cards and shipped by PCI. Each blister card will contain a (randomized) dosage for 1 subject and will contain a sufficient quantity for dispensing during the Treatment Period.

Commercially available amoxicillin and clarithromycin will be supplied in their commercial packaging. The commercial product may be packaged in study-specific secondary packaging, for patient convenience.

Study supplies must be stored in a secure area (eg, a locked cabinet), protected from moisture, and kept at controlled room temperature 20° to 25°C (68° to 77°F); excursions allowed between 15°to 30°C (59° to 86°F) until they are used, or returned to the sponsor or designee for destruction.

5.4.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, 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, to satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled and retained or destroyed according to applicable regulations.

5.5 Overdose Management

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

Cases of overdose without manifested signs or symptoms are not considered AEs. Adverse events associated with an overdose will be documented on AE eCRF(s) according to Section 6.2.1.14.1. The SAEs associated with overdose should be reported according to the procedure outlined in Section 6.2.1.14.2.

5.5.1 Treatment of Overdose

In the event of drug overdose, the subject should be treated symptomatically.

5.6 Blinding

The study treatment blind for the triple therapy groups will be maintained using the IRT. The dual therapy group will be open-label.

The latest Good Manufacturing Practice Guidance for non-penicillin beta-lactam drugs, recommending segregated manufacturing facilities, has resulted in clinical supply manufacturers no longer able to handle drugs such as amoxicillin. Therefore, only commercially available amoxicillin can be used, and amoxicillin dosing will not be blinded. Given that the dual therapy arm uses a different amoxicillin regimen than the two triple therapy arms, the dual therapy arm will be considered open label for this study.

A double-blind design is employed for the triple therapy regimens so that both the investigators and the subjects will be unaware of the treatment assignment during the whole study. Although the dual therapy regimen will be open-label, the primary endpoint for this study is based on an objective measurement via the ^{13}C-UBT, and the UBT testing facility will remain blinded to all 3 treatment assignments ensuring that the evaluation of the efficacy endpoint is not subject to bias. Moreover, [redacted] personnel and the Phathom Pharmaceuticals, Inc. team including the study statistician will be blinded to the triple therapy treatment regimens. The dual therapy group will be open-label; therefore, the site, subjects, some [redacted] personnel and potentially Phathom Pharmaceuticals, Inc. team will be unblinded to the dual therapy regimen. No summary of study data by the open-label dual therapy arm will be done

during the study and data management and clean-up will be done on blinded data sets as if the study were a completely blinded study. The final study report will include all data including all endpoints after all subjects have completed the study, database is locked, and the study is unblinded.

5.6.1 Breaking the Blind

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, the investigator will be able to access the IRT to determine the subject's treatment group assignment. The investigator will, whenever possible, discuss options with the medical monitor before unblinding. The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents, and the same information (except the time) must be recorded on the eCRF. If any site personnel are unblinded, investigational drug must be stopped immediately, and the subject must be withdrawn from the study.

5.7 Treatment Compliance

As subjects will self-administer study drug(s) at home, compliance with study drug will be assessed at each visit. For on-site visits, compliance will be assessed by direct questioning and counting returned tablets/capsules during the site visits. For phone visits, a compliance reminder will be provided to the subjects; compliance will be assessed by direct questioning. Subject treatment compliance assessment results will be record in the source documents and eCRF.

A record of the number of tablets/capsules dispensed to and taken by each subject must be maintained and reconciled with study drug and compliance records. Study drug start and stop dates, including dates for study drug delays and/or dose reductions will also be recorded in the eCRF.

Noncompliance is defined as (taking less than 75% or more than 120% of study drug during any evaluation period [visit to visit]). Subjects exhibiting poor compliance as assessed by tablet/capsule counts should be counseled on the importance of good compliance to the study dosing regimen.

5.8 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment (or has received within 30 days before the time of enrollment) or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Subjects are to be instructed not to take any medications, including over-the-counter medications, without first consulting the investigator or sub-investigators. However, single-use medications for endoscopic examination and topical medications, including liniments, ophthalmic drops, nasal drops, ear drops, inhaled drugs, adhesive skin patches, and gargle (mouthwash), will be allowed, whether or not they are excluded or restricted.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.8.1 Background Medications

Subjects who are being treated with these medications before signing the informed consent, who have no endoscopic evidence of current or recent gastric or duodenal ulcer bleeding (see Section 4.1.2) during the Screening Period, and who are compliant with the dosage as instructed by the medication package insert, the following medications are permitted but the dose and administration method is not permitted to change however, switching between once-daily and weekly regimens is permitted for drugs containing the same active ingredient:

- Corticosteroids
- Bisphosphonates
- Anti-platelets
- Anticoagulants

- Psychotropics
- Antidepressants
- Methotrexate
- NSAIDs

Corticosteroids are permitted for the subjects that are using them before signing the ICF at start of the Screening Period, but the dose and administration will not be changed during the study.

5.8.2 Excluded Medications

A list of excluded medications is provided in Table 5-2.

Table 5-2 Excluded Medications and Treatments

Excluded Medications and Treatments	Beginning of Exclusion	End of Exclusion
Other investigational drugs or drugs administered due to participation in another clinical trial	30 days prior to start of Screening Period	4-week Post-Treatment Visit
Medications (excluding PPIs and antibiotics) that may interfere with ^{13}C-UBT (ecabet, sodium hydrate)[a]	14 days prior to Screening ^{13}C-UBT	4-week Post-Treatment Visit
Antibiotics, Bismuth	30 days prior to screening ^{13}C-UBT	4-week Post-Treatment Visit
Antiprotozoals	30 days prior to Day 1	4-week Post-Treatment Visit
H_2 receptor antagonists	14 days prior to Screening ^{13}C-UBT	4-week Post-Treatment Visit
PPIs	14 days prior to Screening ^{13}C-UBT	4-week Post-Treatment Visit
Medications contraindicated with clarithromycin: colchicine, pimozide, ergot derivatives, tadalafil, terfenadine, astemizole, cisapride, simvastatin, lovastatin, atorvastatin, etc. Note: other statins such as fluvastatin, pravastatin, and rosuvastatin may be allowed but used with caution	30 days prior to Day 1	End of treatment
Strong inhibitors or inducers of CYP2C19 (eg, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampicin, ritonavir)	14 days prior to Day 1	End of treatment
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	14 days prior to Day 1	End of treatment
CYP3A4 substrates with a narrow therapeutic index	14 days prior to Day 1	End of treatment
Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy)	30 days prior to Day 1	4-week Post-Treatment Visit
Other agents affecting digestive organs including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth, sucralfate	30 days prior to Day 1	4-week Post-Treatment Visit
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	4-week Post-Treatment Visit

Abbreviations: ^{13}C-UBT, ^{13}C-urea breath test; CYP, cytochrome P450 isoenzymes; H_2, histamine-2 (receptor); HP, *Helicobacter pylori;* PPI, proton pump inhibitor.

[a] Prohibited period is 14 days prior to any ^{13}C-UBT or as otherwise stated in the package insert for the ^{13}C-urea breath testing kit package to be used. The exclusion period is not applicable to proton pump inhibitors and antibiotics; they have a separate exclusion period.

6 Study Assessments and Procedures

- Before performing any study procedures, all potential subjects will sign and date an ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign and date the ICF.
    - An optional pre-screening ICF may be used to evaluate a subject for HP infection using a fingerstick test.
- Study procedures and their timing are summarized in the SoE (Section 13.1).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoE, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1 Efficacy Assessments

6.1.1 ^{13}C-Urea Breath Test

Helicobacter pylori infection status will be measured at Screening to establish HP infection and at Week 6 (4 weeks after the last dose of study drug) to assess HP eradication status.

To establish HP infection status, a ^{13}C-UBT will be performed.

Exhaled air samples will be taken in accordance with instructions for use of centrally provided testing kits for HP infection status determination.

Medications such as PPIs are to be stopped at least 14 days before taking the ^{13}C-UBT in order to exclude false negative results. Antibiotics (particularly those with anti-helicobacter

action, and bismuth preparations) are to be stopped 30 days before taking the test. See Section 5.8.2, Table 5-2.

6.1.2 Endoscopy/Gastric Biopsy for Histopathology and Antibiotic Susceptibility Test

During the Screening Period, an endoscopy will be performed on all subjects to collect biopsy specimens. The screening endoscopy can be performed any time during that period; however, it should be performed after the subject has fulfilled all other admission criteria.

The gastric mucosal biopsy samples for antibiotic susceptibility testing are to be taken FIRST in order to avoid any contamination of the specimens with formalin.

6.1.2.1 Biopsy for Culture and Antibiotic Susceptibility Test

Gastric mucosal biopsy specimens will be taken for culture and subsequent antimicrobial susceptibility testing. The testing is to determine if there are any resistant bacteria to the antibiotics used in the study.

Two biopsy specimens will be obtained, one from the greater curve of the antrum and one from the lesser curve of the gastric body, at the start of study (Visit 1) and sent to a central laboratory.

The subject can be randomized prior to receiving the antibiotic susceptibility test result.

Minimum inhibitory concentrations of amoxicillin, clarithromycin, and metronidazole against HP will be determined using the strains isolated from these specimens by the 2-fold agar dilution method.

Clarithromycin ≥ 1 μg/mL, amoxicillin > 0.125 μg/mL and metronidazole > 8 μg/mL are determined as resistance breakpoints.

If subject's ^{13}C-UBT test is positive at 4 weeks after the last dose of study drug, an endoscopy will be performed and two gastric mucosal biopsy specimens (one from the greater curve of the antrum and one from the lesser curve of the gastric body) will be taken for antibiotic susceptibility testing, and the subjects can then be treated as per the standard of care.

Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

6.1.2.2 Biopsy for Histopathology

Four gastric mucosal biopsy specimens will be obtained, one each from the greater and lesser curve of the gastric body, and one each from the greater and lesser curve of the antrum and sent to a central laboratory at the start of study to document HP infection.

The biopsies will be placed in 10% buffered formalin and shipped to the central pathology laboratory for subsequent staining and analysis. All biopsies will be evaluated for the presence or absence of HP infection.

Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

6.2 Safety Assessments

6.2.1 Pre-treatment Adverse Events and Adverse Events

6.2.1.1 Definitions of Pre-treatment Adverse Events

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

6.2.1.2 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a subject enrolled into this study regardless of its to study drug. An AE can therefore be any 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.

6.2.1.3 Serious Adverse Events

An SAE is defined as any untoward medical occurrence at any dose for which the following occurs:

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 expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.
    - Includes any event or symptom described in the Medically Significant AE List (Table 6-1).

Table 6-1 Medically Significant Adverse Event List

Term
Acute respiratory failure/acute respiratory distress syndrome
Torsade de pointes / ventricular fibrillation / ventricular tachycardia
Malignant hypertension
Convulsive seizure 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

The PTEs that fulfill one or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Section 6.2.1.14.2 and Section 6.2.1.14.3).

If a subject is noted to have an ALT or AST value of >3 × ULN and a total bilirubin value of >2 × ULN, for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported (see Section 6.2.1.14.2). 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 or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 6.5 must also be performed. In addition, if the LFT increases are SAEs, a Liver Function Test Increase Form must be completed and transmitted (see Section 6.2.1.14.2).

6.2.1.4 Adverse Events of Special Interest

An AE of special interest (AESI) is defined as a noteworthy event for the particular product or class of products that a sponsor may wish to monitor carefully. It could be serious or non-serious (eg, hair loss, loss of taste, impotence), and could include events that might be potential precursors or prodromes for more serious medical conditions in susceptible individuals.

AESI includes any event described in the AESI list (Table 6-2).

Table 6-2 Adverse Events of Special Interest List

Term
Hepatotoxicity
Severe cutaneous adverse reactions
Clostridioides difficile infections and *Pseudomembranous colitis*
Hypergastrinemia
Bone fracture

For additional details on liver function monitoring see Section 13.3.

6.2.1.5 Additional Points to Consider for PTEs and AEs

An untoward finding generally may involve the following:

- Indicates a new diagnosis or unexpected worsening of a pre-existing condition. (intermittent events for 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.
- Is caused by a study procedure (eg, a bruise after blood draw); those events should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

- Each event is required to be recorded to represent a single diagnosis, or disorder using standard medical terminology, rather than its individual symptoms. Accompanying signs (including abnormal laboratory values or electrocardiogram [ECG] findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters 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 re-test and/or continued monitoring of an abnormal value are 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 a pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, or X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, “worsening of…”).
- If a subject has a pre-existing episodic condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from baseline (eg. “worsening of…”).

- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent than that which would be expected. Again, investigators should ensure that the AE term recorded 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 starting administration of the study drug, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (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 AE term recorded captures the change in the condition (eg, "worsening of…").
- At each required study visit, all AEs that have occurred since the previous visit or AEs that have changed in severity since the previous visit must be recorded in the AE record of the eCRF.

Changes in severity of AEs /Serious PTEs:

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

Preplanned procedures:

- Preplanned procedures 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 captured appropriately as a PTE or an AE. Complications resulting from any procedure should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where 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:

- Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

6.2.1.6 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the subject's daily activities. The intensity of the AE will be rated 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 an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.2.1.7 Assessment of Causality

The investigator's assessment of an AE's relationship to the study drug is part of the documentation process, but it 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 relationship or association of each AE to study drug(s) will be assessed using the following categories:

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

6.2.1.8 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.

6.2.1.9 Start Date

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

6.2.1.10 Stop Date

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

6.2.1.11 Frequency

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

6.2.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.

- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, or dosing with the study drug was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted/held due to the particular AE.

6.2.1.13 Outcome

- Recovered/Resolved –the subject returned to baseline status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; or the subject died 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 has worsened from when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved."
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to a hospital change or residence change at the end of the subject's participation in the study.

6.2.1.14 Time Period and Frequency for Collecting AE and SAE Information

6.2.1.14.1 Collection and Reporting of Adverse Events

Collection of PTEs (including PTEs that are SAEs) will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug or until screen failure. For subjects who discontinue prior to study

drug administration, PTEs are collected until the subject discontinues study participation. Collection of AEs (including AEs that are SAEs) will commence from the time that the subject is first administered study drug (Day 1). Routine collection will continue until the end of the Follow-Up Period or withdrawal from the study.

At each study visit, 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. Non-serious PTEs, related or unrelated to the study procedure, need not 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.

All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date
3. Severity
4. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs)
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
6. Action concerning study drug (not applicable for PTEs)
7. Outcome of event
8. Seriousness

6.2.1.14.2 Collection and Reporting of Serious Adverse Events

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE eCRF form must be completed and submitted via Medidata Rave immediately or within 24 hours of the investigator first becoming aware of the SAE occurrence, including for those SAEs that are PTEs. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious
- Subject identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

If the Medidata Rave system is not functioning for any reason, a paper SAE case report form must be completed (in English), signed by the investigator and faxed to the contact listed below.

The SAE eCRF form should be transmitted within 24 hours to [redacted]

[redacted]

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

Investigators are not obligated to actively seek information regarding new AEs or SAEs after conclusion of the 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/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 procedure described for SAEs.

6.2.1.14.3 Follow-up of 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, ECGs, laboratory tests, 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.

6.2.1.14.4 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor designee (contract research organization) will be delegated the responsibility for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, investigators and the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs), as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, 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, unless otherwise required by national regulations. The sponsor designee will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products.

6.2.1.15 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor /sponsor designee of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.

The sponsor/sponsor designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor/sponsor designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

If there is an increase in unexpected SAEs or if there is a change in the frequency and character of expected SAEs based on the known safety profile of vonoprazan, further evaluation will be conducted to characterize these events and any impact on benefit/risk. Health Authorities will be consulted to agree upon the appropriate action to be taken regarding the conduct of the study including no change to the protocol, revision of the safety monitoring plan, suspension of enrollment, or discontinuation of the study.

6.3 Safety Monitoring Committee

Not applicable.

6.4 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn, and any sponsor-supplied drug (vonoprazan active, lansoprazole active, amoxicillin active, clarithromycin active) should be immediately discontinued. If the pregnancy occurs during administration of active study drug, eg, after Visit 2 (Randomization) 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 6.2.1.14.2. Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. If the female subject agrees to the primary care physician being 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 (blinded or unblinded, as applicable). All pregnancies in subjects on active study drug including comparator 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.

6.5 Laboratory Analyses

- See Table 6-3 for the list of clinical laboratory tests to be performed and to the SoE (Section 13.1) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Abnormal laboratory findings that are expected with the underlying disease should not be considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with abnormal values considered clinically significant during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Table 6-3, must be conducted in accordance with the Laboratory Manual and the SoE.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the Unscheduled Labs eCRF.

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be provided in the Laboratory Manual.

All study-required laboratory assessments will be performed by a central laboratory.

Table 6-3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices: MCV, MCH • %Reticulocytes • WBC count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils
Clinical chemistry[a]	• Blood urea nitrogen • Creatinine • Total and direct bilirubin • ALT/ SGPT • AST/ SGOT • Alkaline phosphatase • Total protein • Potassium • Sodium • Calcium • Glucose, fasting • GGT
Routine urinalysis	• Specific gravity, appearance, color • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal)
Other screening tests	• FSH if menopause is suspected[b] • Urine drug screen including amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone and phencyclidine[c] • Serum human chorionic gonadotropin (hCG) pregnancy test[d] at Screening Visit 1 • Urine human chorionic gonadotropin (hCG) pregnancy test[d] at randomization and all other study visits • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody; hepatitis C viral load RNA[e] [Qualitative])

Laboratory Assessments	Parameters

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eCRF, electronic case report form; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; RBC, red blood cells, RNA, ribonucleic acid; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; ULN, upper limits of normal; WBC, white blood cell.

a For liver test monitoring see Section 13.3.1. For temporary and permanent discontinuation of study drugs due to abnormal liver function tests see Section 13.3.2 and Section 13.3.3, respectively.

b Follicle-stimulating hormone will be conducted at the investigator's discretion to determine the postmenopausal status of women whose duration of (consecutive) amenorrhea is borderline or open to doubt and where the investigator believes the subject to be menopausal by history.

c The central laboratory will confirm any positive drug screen results.

d As needed for women of childbearing potential. Serum pregnancy test will be performed if the urine pregnancy test is positive at randomization and all other visits.

e Reflex- if Hepatitis C positive

Investigators must document their review of each laboratory safety report.

6.6 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.7 Vital Signs

Vital signs will include body temperature (oral, tympanic or temporal measurement), sitting blood pressure (resting more than 5 minutes), and pulse (beats per minute). When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

6.8 Electrocardiograms

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart

rate, RR interval, PR interval, QT interval and QRS interval. A copy of the ECG trace should be kept with the subject's notes. For ECG results printed on thermal paper, nonthermal paper copies should be made to avoid degradation of trace over time.

6.9 Pharmacogenetics

Collection for genotyping is optional. Subjects willing to participate must sign the informed consent form. During the study, a blood sample will be collected for CYP2C19 genotype testing to determine the subject's metabolizer status, unless prohibited by local regulations. The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation in the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the clinical efficacy of lansoprazole.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

6.10 Pharmacogenomics

Gastric mucosal biopsy specimens that were not used for culture (and subsequent antimicrobial susceptibility testing; Section 6.1.2.1) or histopathology evaluation (Section 6.1.2.2) may be available from the central laboratory and may be used for possible future genomic analysis of HP in the specimens.

6.11 Pharmacokinetics

During the study, blood samples will be collected for pharmacokinetic analysis of drug concentrations, unless prohibited by local regulations. The sample collection day will be per the SoE (Section 13.1). Details for collection, sample processing, shipment, and destruction of these samples can be found in the Laboratory Manual.

7 Statistical and Analytical Plan

This section briefly describes the statistical and analytical methods to be used for the study. A statistical analysis plan (SAP) will provide details of the statistical methods and definitions for the analysis of efficacy and safety data. To preserve the integrity of the statistical analysis and study conclusions, the SAP will be finalized before database lock.

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, in subjects who do not have a clarithromycin or amoxicillin resistant strain of HP at baseline.

7.2 Secondary Efficacy Endpoint

The secondary efficacy endpoints are the proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, among subjects who had a clarithromycin resistant strain of HP at baseline and the proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug among all subjects.

7.3 Sample Size Calculations

Assuming a true eradication rate for the primary endpoint of 90% for lansoprazole triple therapy and 90% for both vonoprazan triple therapy and vonoprazan dual therapy, a sample size of 260 subjects per treatment group provides >90% power to achieve noninferiority with a noninferiority margin of 10% using the Farrington Manning test (Farrington and Manning 1990). Assuming 20% of subjects will have a clarithromycin resistant strain of HP at baseline, 325 subjects per treatment group (975 total) will be enrolled.

A fixed noninferiority margin of -10% is justified based on the following historical eradication rates. These historical eradication rates are from studies in which the clarithromycin resistance rate was low (approximately 5%) and are therefore relevant to establishing the noninferiority margin for the primary endpoint in this study.

- A pooled estimate of the eradication rate for lansoprazole triple therapy of 83%, based on the eradication rates with lansoprazole triple therapy from three studies (M93-131, M95-392, and M95-399) as reported in the US full prescribing information for Prevacid (PREVACID 2018).

- A pooled estimate of the eradication rate for a regimen of amoxicillin 2 g and clarithromycin 1 g of 42%, based on eradication rates with amoxicillin and clarithromycin reported in Study M95-392 and in three studies included in the US full prescribing information for Prilosec (PRILOSEC 2016).

- An eradication rate for amoxicillin 3 g of 0% from a double-blind, multicenter study evaluating lansoprazole and amoxicillin dual therapy (Harford et al 1996).

For the comparison of the two triple therapies, the difference in the HP eradication rate for triple therapy with lansoprazole (83%) versus treatment with a combination of amoxicillin and clarithromycin (42%) is 41%; the lower limit of the 2-sided 95% CI for the difference is 34%. Using the conservative assumption of the lower bound as the true treatment effect of lansoprazole triple therapy, a -10% noninferiority margin assures that the vonoprazan triple therapy regimen retains at least 70% of the treatment effect of lansoprazole triple therapy.

For the comparison of vonoprazan dual therapy to lansoprazole triple therapy, the difference in the HP eradication rate for triple therapy with lansoprazole (83%) versus treatment with amoxicillin alone (0%) is 83%; the lower limit of the 2-sided 95% CI for the difference is 75%. Using the conservative assumption of the lower bound as the true treatment effect of lansoprazole triple therapy, a -10% noninferiority margin assures that the vonoprazan dual therapy regimen retains at least 87% of the treatment effect of the active control (lansoprazole triple therapy).

7.4 Analysis Sets

In this study, 3 analysis sets are defined: modified intent-to-treat (MITT) analysis set, the per protocol (PP) analysis set, and the safety analysis set. The primary and secondary endpoints will be summarized using the MITT and PP sets, respectively. The MITT set will be considered the primary population for efficacy analysis.

The MITT analysis set includes the randomized subjects with HP infection documented by ^{13}C-UBT and biopsy at baseline. The MITT analysis set will be analyzed according to the treatment group into which each subject was randomized. Subjects who do not have a post-baseline ^{13}C-UBT will be considered treatment failures, ie, "not eradicated."

The PP analysis set includes the randomized subjects with all of the following:

- The subject is included in the MITT analysis set
- Visit 4 occurs between 28 and 56 days after the end of treatment with documented diagnostic testing by ^{13}C-UBT, unless the subject has documented persistence of HP infection at any time after the end of treatment
- At least 75% of each study drug was taken, unless caused by treatment failure
- An antimicrobial known to be effective against HP was not taken within 7 days of Day 1, during treatment, or between completion of treatment and the test-of-cure visit, unless given for treatment failure
- A proton pump inhibitor or high dose (as per below) H_2-receptor antagonist was not taken within 14 days of Day 1, during treatment, or between completion of treatment and the test-of-cure visit, unless given for treatment failure

Subjects can use no more than standard doses of H_2-receptor antagonists, as indicated below, and still be included in the per-protocol population:

- Ranitidine less than or equal to 300 mg/day
- Cimetidine less than or equal to 800 mg/day
- Famotidine less than or equal to 40 mg/day
- Nizatidine less than or equal to 300 mg/day

The PP analysis set will be analyzed with each subject included in the treatment group according to the treatment group into which each subject was randomized.

The safety analysis set will include all subjects who received at least one dose of study drug and will be summarized by treatment group according to the test treatment each subject received in the trial.

7.5 Description of Subgroups to be Analyzed

Subgroup analyses for the primary endpoint will be conducted for demographic and other relevant clinical variables, including age, sex, body mass index, smoking status, alcohol use, clinical condition, study drug compliance, CYP2C19 status, region, and baseline susceptibility to amoxicillin, clarithromycin, and metronidazole.

7.6 Statistical Analysis Methodology

Statistical analysis will be performed using SAS software Version 9.4 or later. Continuous variables will be summarized using the mean, the standard deviation, median, minimum value, and maximum value. Categorical variables will be summarized using frequency counts and percentages.

7.6.1 Efficacy Analyses

The primary endpoint (proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug in subjects who do not have a clarithromycin or amoxicillin resistant strain of HP at baseline) will be calculated as a percentage of subjects in each treatment group.

The noninferiority of vonoprazan triple therapy to lansoprazole triple therapy, and vonoprazan dual therapy to lansoprazole triple therapy, will be evaluated with a Farrington and Manning test with a noninferiority margin of 10 percentage points for the difference in HP eradication rates between treatments. The point estimate and 2-sided 95% CI of the difference in HP eradication rates between each of the pairs of treatments will be calculated via the Miettinen and Nurminen method. For each noninferiority comparison that yields statistical significance, superiority will then be assessed via the Farrington and Manning test of the null hypothesis difference ≤ 0 versus the alternative hypothesis difference > 0.

The secondary endpoints will be evaluated in a similar manner as the primary endpoint for superiority of vonoprazan triple therapy to lansoprazole triple therapy and of vonoprazan dual therapy to lansoprazole triple therapy.

In these analyses, subjects who do not have a post-baseline ^{13}C-UBT will be considered treatment failures, ie, “not eradicated.”

Methodology for control of Type I error among the among multiple comparisons will be addressed in the statistical analysis plan.

7.6.2 Safety Analyses

Safety analysis will be performed using the safety analysis set.

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A treatment-emergent adverse event (TEAE) will be defined as an AE occurring after receiving the first dose of study medication.

The number and proportion of subjects with TEAEs will be summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT) overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related AEs overall and by severity.

For tabulations of TEAE frequency, if a subject has more than 1 episode of the same event, the subject will be counted only once for that event. If a subject has more than 1 TEAE that is coded to the same PT, the subject will be counted only once for that PT. If a subject has more than 1 TEAE within a SOC, the subject will be counted only once for that SOC. In the tabulation of TEAE frequency by intensity, a subject will be counted only once using the highest severity for each PT and SOC.

Change from baseline in laboratory test values and in vital signs will be summarized by treatment group. The number and proportion of subjects with markedly abnormal values for laboratory tests and vital signs will be summarized. No statistical testing or inferential statistics will be generated.

7.6.3 Other Analyses

Demographics and other baseline characteristics will be summarized overall and by treatment group using the MITT, per protocol, and safety analysis sets.

7.6.4 Interim Analyses

No interim analysis is planned.

8 Data Quality Assurance

This study will be conducted according to the International Council for Harmonisation (ICH) E6 R2 risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH guidance on quality and risk management.

8.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the subjects treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include diary cards, laboratory reports, ECG strips, etc.

Investigative site personnel will enter subject data into electronic data capture system. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures to ensure the integrity of the data, eg, removing errors and inconsistencies in the data. Adverse event terms will be coded using MedDRA, and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG).

After database lock, each study site will receive a CDROM containing all of their site specific eCRF data as entered into Medidata Rave for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. [redacted] will maintain a duplicate CDROM copy for their records. In all cases, subject initials will not be collected or transmitted to the sponsor.

9 Ethics

9.1 Independent Ethics Committee or Institutional Review Board

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

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

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to subjects.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, the protocol, and all applicable regulations.

9.3 Subject Information and Consent

A written informed consent in compliance with the respective applicable regulatory authority regulations shall be obtained from each subject before entering the study or performing any unusual or nonroutine procedure that involves risk to the subject. An informed consent template may be provided by the sponsor to investigative sites. 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/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC 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 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 consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject.

10 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but 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/IEC but will not result in protocol amendments.

10.1 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 US Food and Drug Administration (FDA), or the IRB/IEC.

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.

10.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 Code of Federal Regulations (CFR) 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 subject's disease.

10.3 Investigator Documentation

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

- IRB/IEC approval.
- 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 for US sites and equivalent form for non-US sites.
- Curriculum vitae for the investigator and each sub-investigator listed on Form FDA 1572 or equivalent form for non-US sites.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 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.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject.
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

10.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6. The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

10.5 Adherence to Protocol

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

10.6 Adverse Events and Study Report Requirements

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

10.7 Investigator's Final Report

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

10.8 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 at least 2 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 investigator/institution as to when these documents no longer need to be retained.

10.9 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 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 prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

11 Study Management

11.1 Monitoring

11.1.1 External Data Monitoring Committee

Not applicable.

11.1.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation 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 letter 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 personnel.

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 GCP and current standard operating procedures.

11.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC 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, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

11.2 Management of Protocol Amendments and Deviations

11.2.1 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 its

designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before subjects can be enrolled into an amended protocol.

11.2.2 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 of, the protocol to eliminate an immediate hazard to study subjects without prior IRB/IEC 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/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the subject or investigator that results in a significant, additional risk to the subject. Significant deviations can include nonadherence to inclusion or exclusion criteria, or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the subject being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

11.3 Study Termination

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

The end of the study is defined as the date on which the last subject completes the last visit (includes Follow-up Visit).

11.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the 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 the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The study results will be posted on publicly available clinical trial registers.

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13 Appendices

13.1 Appendix 1: Schedule of Events

Table 13-1 Schedule of Events

	Screening Period	Treatment Period				Follow-Up Period		Early Termination
Timing		**Day -1 [a]**	**Week 0 Day 1**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**4-Week Post-Treatment**	
Visit Windows (Days):	**-35 to -2**	**-**	**-**	**6 to 10**	**15 to 18**	**26 to 32**	**42 to 70**	
Visit Number:	**1**	**2**	**NA**	**Phone call [b]**	**3**	**Phone call [c]**	**4**	**-**
Informed consent	X[d]							
Inclusion/exclusion criteria	X	X						
Demographics and medical history	X							
Smoking status and alcohol use	X							
Medication history	X							
Physical examination [e]	X	X			X		X	X
Vital signs	X	X			X		X	X
Weight and height	X							
Concomitant medications	X	X		X [b]	X	X [c]	X	X
Concurrent medical conditions	X							
^{13}C-UBT for HP infection status	X [f]						X [g]	X [h]
Hepatitis B & C + HIV	X							
Urine drug screen	X							
Clinical laboratory test including hematology, serum chemistry, urinalysis	X				X			X
FSH [i]	X							

	Screening Period	Treatment Period				Follow-Up Period		Early Termination
Timing		**Day -1 [a]**	**Week 0 Day 1**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**4-Week Post-Treatment**	
Visit Windows (Days):	**-35 to -2**	**-**	**-**	**6 to 10**	**15 to 18**	**26 to 32**	**42 to 70**	
Visit Number:	**1**	**2**	**NA**	**Phone call [b]**	**3**	**Phone call [c]**	**4**	**-**
Pregnancy test (serum hCG) [j,]	X							
Pregnancy test (urine hCG) [j]		X [k]			X [k]		X [k]	X [k]
Guidance on avoidance of pregnancy	X	X			X			X
CYP2C19 genotyping test					X [l]			
ECG	X				X			X
Endoscopy	X						X [g]	
Gastric mucosa biopsy for antibiotic susceptibility test [m, n]	X [o]						X [g]	
Gastric mucosa biopsy for presence of HP [n, p]	X							
Randomization		X [a]						
Dispense study drug		X						
First day of study drug administration			X					
Study drug return/ accountability/review treatment compliance [q]				X [b]	X			X
Pharmacokinetics [r]					X			
AE/pre-treatment event assessment	X	X		X [b]	X	X [c]	X	X

	Screening Period	Treatment Period				Follow-Up Period		Early Termination
Timing		**Day -1 [a]**	**Week 0 Day 1**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**4-Week Post-Treatment**	
Visit Windows (Days):	**-35 to -2**	**-**	**-**	**6 to 10**	**15 to 18**	**26 to 32**	**42 to 70**	
Visit Number:	**1**	**2**	**NA**	**Phone call [b]**	**3**	**Phone call [c]**	**4**	**-**

Abbreviations: AE, adverse events; CYP2C19, cytochrome P450 2C19; ECG, electrocardiogram; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; HP, Helicobacter pylori; NA, not applicable; PPI, proton pump inhibitor; UBT, urea breath test.

a The date of randomization is defined as Day -1.

b Subjects will receive a phone call for Week 1, Day 8 that will include a compliance reminder, and an assessment of concomitant medications and any AEs.

c Subjects will receive a phone call for Week 4, Day 29 that will include an assessment of concomitant medications and any AEs.

d Subjects may be pre-screened for HP infection using a fingerstick test performed not more than 30 days prior to screening. The subjects will sign a pre-screening ICF for optional fingerstick test of HP status.

e Full physical examination is performed at baseline; a brief physical examination is performed at all other visits.

f If the subject takes PPI prior to ^{13}C-UBT test, it may show false negative, for those cases retest can be allowed 2 weeks after the PPI discontinuation when appropriate in investigator's judgment.

g If subject's ^{13}C-UBT test is positive at 4 weeks post-treatment, an endoscopy and antibiotic susceptibility testing should be performed within 4 weeks of a positive ^{13}C-UBT test result. The subject can then be treated as per standard of care.

h Should be performed between 4-weeks and 8-weeks after last dose of study medication.

i If menopause is suspected.

j Only female subjects of childbearing potential.

k If the urine hCG is positive, serum hCG to be performed.

l Collection for genotyping is optional. Subjects willing to participate must sign the informed consent form.

m Gastric mucosa is to be sampled: one from the greater curve of the antrum and one from the lesser curve of the gastric body. This sample to be taken prior to the histopathology sample for HP.

n Gastric mucosal biopsy specimens that were not used for culture (and subsequent antimicrobial susceptibility testing) or histopathology evaluation may be available from the central laboratory and may be used for possible future genomic analysis of HP in the specimens.

o If the subject fails screening, susceptibility test is not to be performed with the collected sample.

	Screening Period	Treatment Period				Follow-Up Period		Early Termination
Timing		**Day -1 [a]**	**Week 0 Day 1**	**Week 1 Day 8**	**Week 2 Day 15**	**Week 4 Day 29**	**4-Week Post-Treatment**	
Visit Windows (Days):	**-35 to -2**	**-**	**-**	**6 to 10**	**15 to 18**	**26 to 32**	**42 to 70**	
Visit Number:	**1**	**2**	**NA**	**Phone call [b]**	**3**	**Phone call [c]**	**4**	**-**

p Gastric mucosa is to be sampled: one each from the greater and lesser curve of the gastric body, and one each from the greater and lesser curve of the antrum and sent to a central laboratory at the start of study to document HP infection.

q As subjects will self-administer study drug(s) at home, compliance with study drug will be assessed at each visit. For on-site visits, compliance will be assessed by direct questioning and counting returned tablets/capsules during the site visits. For phone visits, a compliance reminder will be provided to the subjects; compliance will be assessed by direct questioning. Subject treatment compliance assessment results will be documented in the source documents and eCRF.

r For pharmacokinetic analysis of drug concentrations, blood samples will be collected at the Week 2 Visit, unless prohibited by local regulations. Date and time of blood sample, as well as date and time of last study drug(s) dose will be collected in source documents and eCRF.

13.2 Appendix 2: Contraceptive Guidance

Contraception Guidance:

From signing of informed consent through Day -2, female subjects of childbearing potential* who are sexually active with a non-sterilized male partner** must use adequate contraception. Starting on Day -1, throughout the duration of the study, and for 4 weeks after the last dose of study drug, female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use 2 forms of adequate contraception. In addition, they must be advised not to donate ova during this period.

> *Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy, or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study drug is implemented).
>
> **Sterilized males should be at least 1-year post vasectomy and should have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

Birth Control: Birth control methods considered acceptable for this study include:

Barrier methods (each time the subject has intercourse)[1]:

- Male condom PLUS spermicide
- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide

[1] Barrier methods are only applicable in countries where spermicide is available

Intrauterine devices (IUDs):

- Copper T
- Progesterone T PLUS condom or spermicide

Hormonal Contraceptives:

- Implants
- Hormone shot/injection
- Combined pill
- Minipill
- Patch
- Vaginal ring PLUS male condom and spermicide

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (see Section 13.1, Schedule of Events). Female subjects must have a negative urine hCG pregnancy test on Day 1 prior to study drug dispensation.

13.3 Appendix 3: Liver Safety Monitoring and Withdrawal Criteria

13.3.1 Liver Function Test Monitoring

Liver function will be carefully monitored throughout the study. Additional monitoring may be necessary and is recommended for subjects with abnormal LFTs.

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 (GGT), and international normalized ratio (INR) should be repeated within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was 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, GGT, and INR) should be repeated within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

If subjects with either a 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, GGT, and INR) should be repeated within a maximum of 48 hours after the abnormality was found.

13.3.2 Considerations for Temporary Discontinuation of Study Drug

If the ALT or AST levels remain elevated >3 × ULN in subjects with normal baseline ALT or AST levels and a 2-fold increase above baseline OR if the ALT or AST levels remain elevated >5 × ULN in subjects with elevated baseline ALT or AST levels on 2 consecutive occasions, the investigator must contact the medical monitor to discuss additional testing, recommended monitoring, possible temporary discontinuation of study medication, and possible alternative etiologies.

13.3.3 Permanent Discontinuation of Study Drug

If any of the following circumstances occur as mentioned in Table 13-2 at any time during treatment, the study medication should be permanently discontinued:

Table 13-2 Abnormal Liver Function Criteria For Permanent Discontinuation of Study Drug

Subject Baseline Aminotransferases	Criteria for Discontinuation of Study Medication
Normal or Elevated ALT or AST (all subjects)	ALT or AST >8 × ULN
Normal ALT and AST	ALT or AST >5 × ULN and persists for more than 2 weeks
	ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value in conjunction with elevated total bilirubin >2 × ULN **or** INR >1.5
	ALT or AST >3 × ULN **AND** a 2-fold increase above baseline value with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
Elevated ALT or AST	ALT or AST >5 × ULN **AND** persists for more than 2 weeks
	ALT or AST >5× ULN **AND** elevated total bilirubin >2 ULN or INR >1.5
	ALT or AST >5 × ULN **AND** appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio ULN, upper limit of normal

In each of these instances, appropriate clinical follow-up should be instituted (including repeat laboratory tests) until a satisfactory conclusion (ie, until the AE resolves, the laboratory value returns to baseline, or the condition becomes stable).

If a subject meets the liver safety criteria and must be discontinued from study medication, the subject will continue to be followed per the protocol schedule until the study is completed. If the subject refuses to return for the study visits, telephone visits may be conducted; however, this is not preferred nor recommended. The reason for discontinuation of study medication should be listed as an LFT abnormality.

If any of the above circumstances occur at any time during the study, the abnormality should be documented as an SAE, and a Liver Function Test Increase Form completed and sent to:

[redacted]

The Investigator must complete the AE/SAE eCRF page. If the event meets serious criteria, the SAE eCRF page must be completed and an SAE Fax Notification form must be sent to the sponsor or sponsor's designee within 1 working day of the repeat laboratory test.

13.3.4 Re-initiation of Study Drug

If the study medication is discontinued due to any of the scenarios provided above, the study medication must not be re-initiated without consultation with the medical monitor.

13.4 Appendix 4: Protocol Amendments

Changes to the protocol text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the study protocol are shown in **bold** and deletions are shown in ~~strike-through~~ text. Corrections of obvious typing errors or omissions are not highlighted.

13.4.1 Protocol Amendment 1

Protocol Synopsis

Objectives (Primary Objective):

To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects ~~excluding subjects~~ who ~~had~~ **do not have** a clarithromycin **or amoxicillin** resistant strain of HP at baseline

Pharmacokinetic or Pharmacodynamic Assessments:

In order to determine the subject's metabolizer status, ~~a~~ **an optional** blood sample will be obtained for CYP2C19 genotype testing, unless prohibited by local regulations.

Study Drug, Dosage, and Route of Administration

All study drugs will be administered orally **starting on Day 1 (the day after randomization)**.

Statistical Methods:

The primary endpoint (proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, ~~excluding~~ **in** subjects who ~~had~~ **do not have** a clarithromycin **or amoxicillin** resistant strain of HP at baseline) will be calculated as a percentage of subjects in each treatment group.

Table 2-1 Study Objectives and Endpoints

Objectives	Endpoints
Primary • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects ~~excluding subjects~~ who ~~had~~ **do not have** a clarithromycin **or amoxicillin** resistant strain of HP at baseline	• Proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug ~~excluding~~ **in** subjects who ~~had~~ **do not have** a clarithromycin **or amoxicillin** resistant strain of HP at baseline
Secondary • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in subjects infected with a clarithromycin resistant strain of HP • To compare the efficacy of HP eradication with vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in all subjects	• Proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT at 4 weeks after the last dose of study drug, among subjects who had a clarithromycin resistant strain of HP at baseline • Proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug among all subjects
Safety • To compare the safety of vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects	• Adverse events (AEs) • Laboratory test values (hematology, serum chemistry, urinalysis) • Electrocardiogram (ECG) • Vital signs

Study Design (Section 3.1)

The study will include 3 main periods:

Screening Period (Day -35 to Day -2): Subjects ~~and/or subject's legally acceptable representative(s)~~ will provide informed consent and the subject will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will enter the study.

Inclusion Criteria (Section 4.1.1)

2. In the opinion of the investigator or sub-investigators, the subject is capable of understanding and complying with protocol requirements.

3. ~~The subject or, when applicable, the subject's legally acceptable representative~~ **The subject** signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures. The subject ~~(or legally acceptable representative, if applicable)~~ is informed of the full nature and purpose of the study, including possible risks and side-effects. The subject has the ability to cooperate with the investigator. Ample time and opportunity should be given to read and understand verbal and/or written instructions.

5. A female subject of childbearing potential who is or may be routinely sexually active with a nonsterilized male partner agrees to routinely use adequate **double barrier** contraception from the signing of informed consent until **Day -2 and 2 forms of adequate contraception from Day -1 until** 4 weeks after the last dose of study drug as detailed in Appendix 2 (Section 13.2) of this protocol.

Screen Failures (Section 4.1.4)

If a suspected erroneous laboratory result is obtained at screening, retesting of that laboratory parameter will be allowed at investigator discretion with medical monitor approval.

Rescreening of subjects is permitted if approved by the Medical Monitor. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

Reasons for Withdrawal/Discontinuation (Section 4.2.1)

5. Voluntary withdrawal: The subject ~~(or subject's legally acceptable representative)~~ wishes to withdraw from the study. The reason for the withdrawal, if provided, should be recorded in the eCRF.

Handling of Withdrawals (Section 4.2.2)

Subjects who discontinue study drug or active participation in the study will no longer receive study drug. When a subject withdraws from the study drug or active participation in the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the eCRF. Whenever possible, all subjects who discontinue study drug or withdraw from the study prematurely will undergo all ~~end of study~~ **early termination** assessments. Subjects who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

Treatments Administered (Section 5.2)

Subjects randomly assigned to lansoprazole triple therapy will receive lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days.

All study drugs will be administered orally starting on Day 1 **(the day after randomization, Table 13-1)**.

Study drug administration will be as presented in Table 5-1.

Subjects should instructed as follows:

- **Starting on Day 1,** ~~T~~to take study drug(s) 30 minutes before breakfast, lunch and dinner (for subjects enrolled in the dual-therapy arm) or breakfast and dinner (for subjects enrolled in the triple-therapy arm) at about the same time as he/she usually does with approximately 240 mL (8 oz) water.

Treatment Compliance (Section 5.7)

Noncompliance is defined as (taking less than ~~80~~ **75**% or more than 120% of study drug during any evaluation period [visit to visit]). Subjects exhibiting poor compliance as assessed by tablet/capsule counts should be counseled on the importance of good compliance to the study dosing regimen.

Table 5-2 Excluded Medications and Treatments

Excluded Medications and Treatments	Beginning of Exclusion	End of Exclusion
Other investigational drugs or drugs administered due to participation in another clinical trial	30 days prior to start of Screening Period	4-week Post-Treatment Visit
Medications (excluding PPIs and antibiotics) that may interfere with ^{13}C-UBT (ecabet, sodium hydrate)[a]	14 days prior to Screening ^{13}C-UBT	4-week Post-Treatment Visit
Antibiotics, Bismuth	30 days prior to screening ^{13}C-UBT	4-week Post-Treatment Visit
Antiprotozoals	30 days prior to Day 1	4-week Post-Treatment Visit
H_2 receptor antagonists	14 days prior to Screening ^{13}C-UBT	4-week Post-Treatment Visit
PPIs	14 days prior to Screening ^{13}C-UBT	4-week Post-Treatment Visit
Medications contraindicated with clarithromycin: colchicine, pimozide, ergot derivatives, tadalafil, terfenadine, astemizole, cisapride, simvastatin, lovastatin, atorvastatin, etc. Note: other statins such as fluvastatin, pravastatin, and rosuvastatin may be allowed but used with caution	30 days prior to Day 1	End of treatment
Strong inhibitors or inducers of CYP2C19 (eg, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampicin, ritonavir)	14 days prior to Day 1	End of treatment
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	14 days prior to Day 1	End of treatment
CYP3A4 substrates with a narrow therapeutic index	**14 days prior to Day 1**	**End of treatment**
Surgical procedures that could affect gastric acid secretion (eg, any form of partial gastrectomy, vagotomy)	30 days prior to Day 1	4-week Post-Treatment Visit
Other agents affecting digestive organs including muscarinic antagonists (eg, hyoscyamine), prokinetics, oral anticholinergic agents, prostaglandins, bismuth, sucralfate	30 days prior to Day 1	4-week Post-Treatment Visit
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with vonoprazan)	5 days prior to Day 1	4-week Post-Treatment Visit

[a] Prohibited period is 14 days prior to any ^{13}C-UBT or as otherwise stated in **the** package insert for the ^{13}C-urea breath testing kit package to be used. **The exclusion period is not applicable to proton pump inhibitors and antibiotics; they have a separate exclusion period.**

Biopsy for Culture and Antibiotic Susceptibility Test (Section 6.1.2.1)

Minimum inhibitory concentrations of amoxicillin, clarithromycin, and metronidazole against HP will be determined using the strains isolated from these specimens by the 2-fold agar dilution method.

Clarithromycin ≥ 1 μg/mL, amoxicillin > 0.~~03~~ **125** μg/mL and metronidazole ≥ **>** 8 μg/mL are determined as resistance breakpoints.

Regulatory Reporting Requirements for SAEs (Section 6.2.1.15)

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

If there is an increase in unexpected SAEs or if there is a change in the frequency and character of expected SAEs based on the known safety profile of vonoprazan, further evaluation will be conducted to characterize these events and any impact on benefit/risk. Health Authorities will be consulted to agree upon the appropriate action to be taken regarding the conduct of the study including no change to the protocol, revision of the safety monitoring plan, suspension of enrollment, or discontinuation of the study.

Pharmacogenetics (Section 6.9)

Collection for genotyping~~:~~ ~~every subject~~ **is optional. Subjects willing to participate** must sign the informed consent ~~in order to participate~~ ~~in this study~~ **form**. During the study, a blood sample will be collected for CYP2C19 genotype testing to determine the subject's metabolizer status, unless prohibited by local regulations. The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation in the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the clinical efficacy of lansoprazole.

Primary Efficacy Endpoint (Section 7.1)

The primary efficacy endpoint is the proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug, ~~excluding~~ **in** subjects who ~~had~~ **do not have** a clarithromycin **or amoxicillin** resistant strain of HP at baseline.

Analysis Sets (Section 7.4)

The MITT analysis set includes the randomized subjects with ~~all of the following~~:

- HP infection ~~is~~ documented by ^{13}C-UBT and biopsy at baseline
- ~~At least one dose of study drug is taken~~

The PP analysis set includes the randomized subjects with all of the following:

- The subject is included in the MITT analysis set
- Visit 4 occurs between 28 and 56 days after the end of treatment with documented diagnostic testing by ^{13}C-UBT, unless the subject has documented persistence of HP infection at any time after the end of treatment
- At least 75% of each study drug was taken ~~and/or less than 20% of consecutive doses of each study drug were missed~~, unless caused by treatment failure
- An antimicrobial known to be effective against HP was not taken within 7 days of Day 1, during treatment, or between completion of treatment and the test-of-cure visit, unless given for treatment failure
- A proton pump inhibitor or high dose (as per below) H_2-receptor antagonist was not taken within 14 days of Day 1, during treatment, or between completion of treatment and the test-of-cure visit, unless given for treatment failure

Description of Subgroups to be Analyzed (Section 7.5)

Subgroup analyses for the primary endpoint will be conducted for demographic and other relevant clinical variables, including age, sex, body mass index, **smoking status, alcohol use, clinical condition,** study drug compliance, CYP2C19 status, region, and baseline susceptibility to amoxicillin, clarithromycin, and metronidazole.

Efficacy Analyses (Section 7.6.1)

The primary endpoint (proportion of subjects with successful HP eradication after the Treatment Period, as determined by ^{13}C-UBT, at 4 weeks after the last dose of study drug ~~excluding~~ **in** subjects who ~~had~~ **do not have** a clarithromycin **or amoxicillin** resistant strain of HP at baseline) will be calculated as a percentage of subjects in each treatment group.

The secondary endpoints will be evaluated in a similar manner as the primary endpoint for superiority of vonoprazan triple therapy to lansoprazole triple therapy and of vonoprazan dual therapy to lansoprazole triple therapy.

In these analyses, subjects who do not have a post-baseline ^{13}C-UBT will be considered treatment failures, ie, "not eradicated."

Methodology for control of Type I error among the among multiple comparisons will be addressed in the statistical analysis plan.

Independent Ethics Committee or Institutional Review Board (Section 9.1)

Federal regulations, national regulations, and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human subjects in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject ~~or the subject's legally acceptable representative(s)~~ must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH

harmonised tripartite guideline E6: Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

Subject Information and Consent (Section 9.3)

Before recruitment and enrollment, each prospective subject ~~or his or her legally acceptable representative(s)~~ will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the subject ~~or legally acceptable representative(s)~~ understands the implications of participating in the study, the subject ~~or legally acceptable representative(s)~~ will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the subject ~~or legally acceptable representative(s)~~.

Confidentiality (Section 10.1)

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 ~~(or the subject's legally acceptable representative(s)),~~ except as necessary for monitoring and auditing by the sponsor, its designee, the US Food and Drug Administration (FDA), or the IRB/IEC.

Investigator Documentation (Section 10.3)

- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the subject ~~or legally acceptable representative(s)~~.
- Laboratory certifications and normal ranges for any local laboratories used by the site, in accordance with 42 CFR 493.

Table 13-1 Schedule of Events

- The days for the 4-week post-treatment period were changed from 43 to 71 to 42 to 70
- Smoking status and alcohol use were added as screening assessments
- Assessments of weight and height are removed from Visit 4 and the Early Termination visit
- 'x' is removed for first day of study drug administration at Visit 3
- Footnote (j) is added for the ^{13}C-UBT test: **Should be performed between 4 weeks and 8 weeks after last dose of study medication.**
- Footnote (k) is added for the CYP2C19 genotyping test: **Collection for genotyping is optional. Subjects willing to participate must sign the informed consent form.**

Appendix 2: Contraceptive Guidance (Section 13.2)

From signing of informed consent **through Day -2**, ~~throughout the duration of the study, and for 4 weeks after the last dose of study drug,~~ female subjects of childbearing potential* who are sexually active with a non-sterilized male partner** must use adequate contraception. **Starting on Day -1, throughout the duration of the study, and for 4 weeks after the last dose of study drug, female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use 2 forms of adequate contraception.** In addition, they must be advised not to donate ova during this period.

Appendix 3: Liver Safety Monitoring and Withdrawal Criteria (Section 13.3)

If a subject meets the liver safety criteria and must be discontinued from study medication, the subject will continue to be followed per the protocol schedule until the study is completed. If the subject refuses to return for the study visits, telephone visits may be

conducted; however, this is not preferred nor recommended. The reason for discontinuation of study medication should be listed as an ~~AE~~ **LFT abnormality**.

13.4.2 Protocol Amendment 2

Pharmacokinetic or Pharmacodynamic Assessment (Synopsis)

For pharmacokinetic analysis of drug concentration, blood samples will be collected at the Week 2 Visit, unless prohibited by local regulations.

In order to determine the subject's metabolizer status, an optional blood sample will be obtained for CYP2C19 genotype testing, unless prohibited by local regulations.

Study Design (Section 3.1)

1. Screening Period (Day -35 to Day -2): Subjects will provide informed consent and the subject will undergo screening assessments to determine study eligibility, and baseline assessments will be performed. If all eligibility criteria are met, the subject will enter the study.

   Subjects may have already been pre-screened for HP using a fingerstick test performed not more than 30 days prior to screening. The subjects will sign a pre-screening ICF for optional fingerstick test of HP status.

   An endoscopy will be performed to collect gastric mucosal biopsy specimens (one each from the greater and lesser curve of the gastric body, and one each from the greater and lesser curve of the antrum) at the start of the study for histopathology **(Section 6.1.2.2)** to document HP infection. Two additional gastric mucosal biopsy specimens will be collected (one from the greater curve of the antrum and one from the lesser curve of the gastric body) for culture and susceptibility testing **(Section 6.1.2.1)** to determine resistance to bacteria to clarithromycin, amoxicillin and metronidazole antibiotics which are commonly used in the treatment of HP infection. After randomization, as part of the overall analysis, MICs of amoxicillin, clarithromycin, and metronidazole against HP will be determined using the strains isolated from these specimens by the 2-fold agar dilution method. Results from the gastric mucosal biopsy specimens (histology and culture) will be available post-randomization. **Any remaining gastric mucosal biopsy samples may be used for future pharmacogenomic evaluation of HP (Section 6.10).**

2. Treatment Period (2-week treatment period): HP+ subjects whose eligibility is confirmed by ^{13}C-urea breath test (^{13}C-UBT) during the Screening Period will be randomly assigned in a 1:1:1 ratio to receive vonoprazan 20 mg BID in conjunction with amoxicillin 1 g TID (vonoprazan dual therapy arm) for 14 days, vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID (vonoprazan triple therapy arm) for 14 days, or lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID (lansoprazole triple therapy arm/control arm) for 14 days.

   Subjects will receive a phone call at Week 1 to remind subjects about compliance and other assessments described in the SoE (Section 13.1).

   Subjects will return at Week 2 for laboratory tests and other assessments described in the ~~schedule of activities (SoA)~~ SoE (Section 13.1).

Exclusion Criteria (Section 4.1.2)

11. The subject has a history of alcohol abuse, illegal drug use, or drug addiction within the 12 months prior to screening, or who regularly consume >21 units of alcohol (1 unit = 12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine) per week based on self-report. Subjects must have a negative urine drug screen **for cannabinoids/tetrahydrocannabinol and non-prescribed medications** at screening**.**

Treatment Compliance (Section 5.7)

As subjects will self-administer study drug(s) at home, compliance with study drug will be assessed at each visit. **For on-site visits, ~~C~~**compliance will be assessed by direct questioning and counting returned tablets/capsules during the site visits**.** ~~which~~ **For phone visits, a compliance reminder** will be ~~documented in the source documents and eCRF.~~**provided to the subjects; compliance will be assessed by direct questioning.** Subject treatment compliance assessment results ~~should~~**will** be recorded in the **source documents and** eCRF.

Study Assessments and Procedures (Section 6)

- Before performing any study procedures, all potential subjects will sign and date an ICF. Subjects will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the subject. The investigator or designee will also sign and date the ICF.

- **An optional pre-screening ICF may be used to evaluate a subject for HP infection using a fingerstick assessment.**

Collection and Reporting of Adverse Events (Section 6.2.1.14.1)

Collection of PTEs **(including PTEs that are SAEs)** will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation. Collection of AEs **(including AEs that are SAEs)** 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.

Collection and Reporting of Serious Adverse Events (Section 6.2.1.14.2)

An SAE eCRF form must be completed and submitted via Medidata Rave immediately or within 24 hours of **the investigator** first ~~onset or notification~~ **becoming aware** of the ~~event~~ **SAE occurrence, including for those SAEs that are PTEs**. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious

Electrocardiograms (Section 6.8)

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, **RR interval,** PR interval, QT interval and QRS interval. A copy of the ECG trace should be kept with the subject's notes. For ECG results printed on thermal paper, nonthermal paper copies should be made to avoid degradation of trace over time.

Pharmacogenomics (Section 6.10)

Gastric mucosal biopsy specimens that were not used for culture (and subsequent antimicrobial susceptibility testing; Section 6.1.2.1) or histopathology evaluation (Section 6.1.2.2) may be available from the central laboratory and may be used for possible future genomic analysis of HP in the specimens.

Pharmacokinetics (Section 6.11)

During the study, blood sample will be collected for pharmacokinetic analysis of drug concentrations, unless prohibited by local regulations. The sample collection day will be per the SoE (Section 13.1). Details for collection, sample processing, shipment, and destruction of these samples can be found in the Laboratory Manual.

Table 13-1 Schedule of Events

- New footnote added for informed consent criteria during screening period: **Subjects may be pre-screened for HP infection using a fingerstick test performed not more than 30 days prior to screening. The subjects will sign a pre-screening ICF for optional fingerstick test of HP status.**

- New phone call visit added on Week 1, Day 8. New footnote added for Day 8 assessments: **Subjects will receive a phone call for Week 1, Day 8 that will include a compliance reminder, and an assessment of concomitant medications and any AEs.**

- New footnote added for phone call visit on Day 29 assessments: **Subjects will receive a phone call for Week 4, Day 29 that will include an assessment of concomitant medications and any AEs.**

- New footnote for physical examination: **Full physical examination is performed at baseline; a brief physical examination is performed at all other visits.**

- Adjusted footnote for ^{13}C-UBT: If subject's ^{13}C-UBT test is positive at 4 weeks post-treatment, an endoscopy and antibiotic susceptibility testing ~~will~~**should** be performed **within 4 weeks of a positive ^{13}C-UBT test result**. The subject can then be treated as per standard of care.

- New footnote added to gastric mucosa biopsy assessments: **Gastric mucosal biopsy specimens that were not used for culture (and subsequent antimicrobial susceptibility testing) or histopathology evaluation may be available from the central laboratory and may be used for possible future genomic analysis of HP.**

- New footnote added to study drug return/ accountability/review treatment compliance assessment: **As subjects will self-administer study drug(s) at home, compliance with study drug will be assessed at each visit. For on-site visits, compliance will be assessed by direct questioning and counting returned tablets/capsules during the site visits. For phone visits, a compliance reminder will be provided to the subjects; compliance will be assessed by direct questioning. Subject treatment compliance assessment results will be documented in the source documents and eCRF.**

- Added assessment of 1 PK sample collected at Day 15 and new footnote: **For pharmacokinetic analysis of drug concentrations, blood samples will be collected at the Week 2 Visit, unless prohibited by local regulations. Date and time of blood sample, as well as date and time of last study drug(s) dose will be collected in source documents and eCRF.**