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

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Phathom Pharmaceuticals, Inc.

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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

09Apr2021

Statistical Analysis Plan

Version *3.0*

Prepared by:

Signature Page

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Approved by:

[redacted]

Senior Director, Biostats & Programming

[redacted]

TABLE OF CONTENTS

Document History – Changes compared to Final version 1.0

Version	Date	Changes
Final version 1.0 Final version 2.0	09-Dec-2019 21-Dec-2020	Final version 1. Updated protocol version to Amendment 2, dated 11May2020, and included revised Schedule of Events in Table 5. 2. Changed the method for type 1 error control in Section 4 and Section 8. Type 1 error will be controlled using a hierarchical testing of endpoints and weighted Bonferroni for regimen comparisons. Figure 2 and Section 8.1.1 were updated to reflect the new method. 3. In Section 4.1, added references for the sample size assumptions and updated the justification for the non-inferiority margins for the comparisons of vonoprazan triple therapy and vonoprazan dual therapy to lansoprazole triple therapy. 4. In Section 5 Subject Disposition, subsections were re-organized and the summary of protocol deviations was clarified. 5. Added Race, Ethnicity, Clinical Conditions, and Subregion as baseline characteristics parameters in Section 6.1 and added subgroup analyses by these parameters in Section 8.1.4. 6. Section 7 Treatments and Medications was updated to clarify the summarization of medications, including that ATC level 4 instead of level 2 coding will be used. 7. Changed the compliance calculation algorithm in Section 7.2.1. 8. Updated the α level in the tipping point analysis in Section 8.1.3.2 based on the method for type 1 error control. 9. Updated the method for multiple imputation in Section 8.1.3.3. 10. Section 8.1.3 was updated to categorize analysis using the PPp Set as a supportive analysis. Moved this analysis to Section 8.1.3.4. Added new supportive analyses in Section 8.1.3.5 and 8.1.3.6. 11. Added the details of SMQs and CQs for Adverse Events of Special Interest in Section 9.1.2. 12. Updated that clinical laboratory results will be summarized for both SI and US conventional units, clarified the criteria for total bilirubin as 2xULN, and added additional criteria for abnormal liver function tests in Section 9.2. 13. Added criteria for abnormal vital signs and for abnormal ECG values in Section 9.3 and 9.5, respectively. 14. Added Section 10 Pharmacokinetics and definition of PK Set in Section 4.4. 15. Added Section 11.2 to describe the handling of impacts from COVID-19 pandemic. Changed the visit analysis window to include out-of-window ^{13}C-UBT due to COVID-19 in Section 4.3.2.

Version	Date	Changes
		16. Added Section 12 to describe changes in the planned analysis 17. Throughout the document, additional edits were made for clarity and formatting with no change to content.
Final Version 3.0	09Apr2021	Modified visit window in Table 3 to allow ^{13}C-UBT results obtained on day 27 post treatment or greater than 56 days post treatment to be included in the MITT analyses for the primary and secondary endpoints. Sensitivity analyses were added in Sections 8.1.3.1 and 8.2 to assess the impact of this change. In Section 5.2, clarified that protocol deviations will be summarized by CTMS activity type and subtype in the summary table. In Section 7.2.2, imputation of missing last dose date will be based on date of first dose instead of date of randomization. In Section 8.1.3.7, the summary of shifts in antibiotic susceptibility will be done for both the MITTp and MITT sets. In Section 8.1.4, clarified that the subgroup analysis for study drug compliance will be based on compliance with the complete regimen. In Section 10, removed PK summary table.

List of Abbreviations

^{13}C-UBT	carbon 13-urea breath test
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
CI	confidence interval
COVID-19	coronavirus disease 2019
CQ	customized queries
CRF	case report form
CYP	cytochrome P450 isoenzymes
ECG	electrocardiogram
FSH	follicle-stimulating hormone
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HP	*Helicobacter pylori*
HP+	*Helicobacter pylori* positive
ICF	informed consent form
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
MITTp	modified intent-to-treat primary
PK	pharmacokinetic
PPI	proton pump inhibitor
PP	per protocol
PPp	per protocol primary
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	standardized MedDRA queries
SOC	system organ class
TEAE	treatment-emergent adverse events
TID	three times daily
ULN	upper limit of normal
WHO	World Health Organization

1. Introduction

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.

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the Protocol Amendment 2, dated 11May2020.

2. Objectives

The primary objective of this study is as follows:

- 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

The secondary objectives of this study are as follows:

- 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

The safety objective of this study is as follows:

To compare the safety of vonoprazan dual and triple therapy regimens versus lansoprazole triple therapy regimen in HP+ subjects

3. Investigational Plan

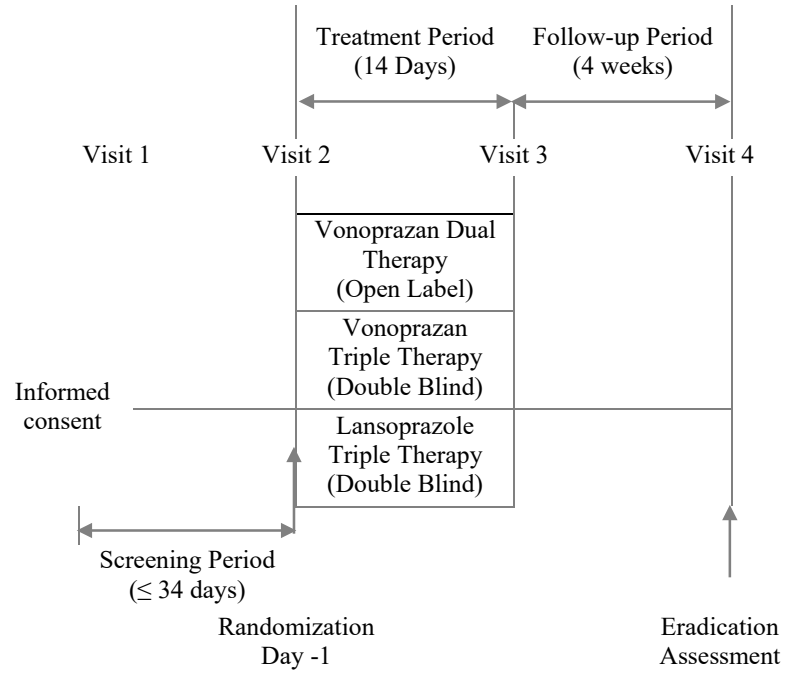
3.1. Overall Study Design and Plan

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 1.

Figure 1 Study Design



3.2. Study Endpoints

The primary efficacy endpoint of this study is as follows:

- 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

The secondary efficacy endpoints of this study are as follows:

- 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

The safety endpoints of this study are as follows:

- Adverse events (AEs)
- Laboratory test values (hematology, serum chemistry, urinalysis)
- Electrocardiogram (ECG)
- Vital signs

3.3. Treatments

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.

The open-label treatment of this study is:

- Vonoprazan dual therapy: vonoprazan 20 mg BID in conjunction with amoxicillin 1 g TID for 14 days

The double-blinded treatments of this study are:

- Vonoprazan triple therapy: vonoprazan 20 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days
- Lansoprazole triple therapy: lansoprazole 30 mg BID in conjunction with amoxicillin 1 g BID and clarithromycin 500 mg BID for 14 days

3.4. Dose Adjustment/Modifications

No dose adjustments or modifications are allowed for this study.

4. General Statistical Considerations

In general, descriptive statistics will be presented by treatment group and by visit, as applicable. For continuous variables, summary statistics for the raw value and change from baseline at each time-point will include the number of subjects (n), arithmetic mean, standard deviation (SD), median, minimum and maximum.

Categorical variables will be summarized using subject counts and percentages. Percentages will be calculated using the total subjects per treatment unless otherwise specified.

The efficacy analyses will be conducted on the Modified Intent-to-Treat Set and Per Protocol Set using the planned treatment. See Section 4.4 for the Modified Intent-to-Treat Set and Per Protocol Set definitions.

The safety analyses will be conducted on the Safety Set using the actual treatment the subject received. See Section 4.4 for the Safety Set definition.

The type 1 error will be controlled at a level of $\alpha = 0.05$ using a hierarchical testing of endpoints and weighted Bonferroni for regimen comparisons (Bretz 2011). An initial assigned significance level of $\alpha = 0.04$ will be used for analysis of vonoprazan triple therapy and an initial assigned significance level of $\alpha = 0.01$ will be used for analysis of vonoprazan dual therapy. More details are addressed in Section 8. Statistical tests for noninferiority and superiority will be one-sided and will be conducted at the assigned $\alpha/2$ significance level. P-values will be reported to 4 decimal places, with p-values less than 0.0001 reported as "<0.0001".

SAS® version 9.4 or higher will be used to perform all statistical analyses or procedures.

4.1. Sample Size

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 (Savoldi et al 2018), 325 subjects per treatment group (975 total) will be enrolled. *H pylori* resistance to amoxicillin is expected to be low with rates less than 2% reported among isolates in the US (Meyer et al 2002) and Europe (Megraud 2012). Thus, the amoxicillin resistance rate has not be considered in the sample size estimates for the primary endpoint.

Based on historical eradication rates, a fixed noninferiority margin of -10% is justified for the comparisons of vonoprazan triple therapy and vonoprazan dual therapy to lansoprazole triple therapy. These historical eradication rates are from studies in which the clarithromycin and amoxicillin resistance rate was low (approximately 5% or less) and are therefore relevant to establishing the noninferiority margins for the primary endpoint in this study.

A fixed noninferiority margin of -10% for the comparison of the two triple therapy regimens is justified based on historical eradication rates from the original lansoprazole 14-day therapy development (Table 1; PREVACID 2018) and the original omeprazole 10-day therapy development (Table 2; PRILOSEC 2016) where the respective triple therapy regimens were compared to the clarithromycin/amoxicillin regimen. Due to the limited data for the

clarithromycin/amoxicillin eradication rate from the lansoprazole 14-day therapy studies, the justification has been supplemented with data from the omeprazole 10-day therapy studies.

Table 1 Historical 14-day *H pylori* Eradication Rates

Amoxicillin/Clarithromycin		Lansoprazole Triple Therapy	
Study M95-392	64% (51/80)	Study M95-392	83% (58/70)
		Study M93-131	85% (47/55)
		Study M95-399	82% (103/126)
Pooled	**64% (51/80)**	**Pooled**	**83% (208/251)**
Difference (95% CI)		**19% (7.6%, 30.6%)**	

Table 2 Historical 10-day *H pylori* Eradication Rates

Amoxicillin/Clarithromycin		Omeprazole Triple Therapy	
Prilosec Study 1	37% (31/84)	Prilosec Study 1	69% (55/80)
Prilosec Study 2	36% (30/83)	Prilosec Study 2	73% (56/77)
Prilosec Study 3	32% (32/99)	Prilosec Study 3	83% (70/84)
Pooled	**35% (93/266)**	**Pooled**	**75% (181/241)**
Difference (95% CI)		**40% (32.2%, 48.1%)**	

From Table 1, the difference in eradication rates between lansoprazole triple therapy and amoxicillin/clarithromycin was 19%. In Table 2, the difference in eradication rates between omeprazole triple therapy and amoxicillin/clarithromycin was 40%. Considering only the 14-day regimen data, a -10% noninferiority margin maintains approximately 50% of the treatment effect of the PPI triple therapy, when using the observed difference between the two treatments. When also considering the more robust amoxicillin/clarithromycin data set from the 10-day regimen, a -10% noninferiority margin maintains 67% of the treatment effect of the PPI triple therapy, when using the more conservative lower bound of the 2-sided 95% confidence interval as the true difference between the two treatments.

A fixed noninferiority margin of -10% is also justified for the comparison of vonoprazan dual therapy to lansoprazole triple therapy. An eradication rate for amoxicillin 3 g of 0% was observed in a double-blind, multicenter study evaluating lansoprazole and amoxicillin dual therapy for 14 days (Harford et al 1996). 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).

4.2. Randomization and Blinding

Subjects will be randomized to receive vonoprazan dual therapy, vonoprazan triple therapy, or lansoprazole triple therapy for 14 days using a 1:1:1 allocation ratio.

The vonoprazan dual therapy is open-label, and the other two treatment groups are double-blinded to both investigators and subjects. Biostatistics and Programming will treat this study as a double-blinded study. [redacted] Biostatistics and Programming will remain blinded to the actual randomization and material schedules until database lock. However, due to the dose regimen of the vonoprazan open-label dual therapy, subjects who enter this arm can be identified from the data collected on the eCRF. To maintain study blind, including vonoprazan open-label dual therapy, for the Sponsor throughout the study, data or summaries that contain potentially unblinded information (i.e. Drug and Antibiotic Accountability CRF page) will not be delivered to the Sponsor until final database lock after the study blind has been broken.

4.3. Assessment Windows

4.3.1. Study Day

The date of first dosing day is defined as Day 1 for this study. When study day is used for display or in comparisons the following algorithm will be used:

- study day = date of assessment - Day 1 +1,
  if date of assessment ≥ Day 1.
- study day = date of assessment - Day 1,
  if date of assessment < Day 1.

Note that the date of randomization is defined as Day -1. There is no Day 0 for study day.

4.3.2. Visit Window for Analysis

Visit windows will be defined for by-visit summary and analysis purposes. Summary data (such as AEs and concomitant medications) that are not reported by visit will not use visit windows. Both scheduled and unscheduled assessments will be considered as valid assessments for analysis. Visit labels will be assigned to each post-baseline record based on the windows for study day relative to the date of first dose. If an assessment on Day -1 is missing, the closest visit with non-missing assessment on or before the date of first dose will be used as baseline. All by-visit summary and analysis will be based on the analysis visit windows in Table 3.

Table 3 Analysis Visit Windows

Nominal Visit (recorded on eCRF)	Analysis Visit	Target Study Day of Visit	Analysis Visit Window
Visit 1	Screening	-35 to -2	NA
Visit 2	Baseline	-1	NA
Visit 3	Week 2	15	12 to 22 days
Visit 4	4-Week Post-Treatment	56	≥ 41 days for efficacy (≥ 27 days post treatment); 23 to 70 days for safety

Unscheduled and early termination assessments will also be assigned to analysis visits based on the analysis visit window. When data is summarized by assigned analysis visit based on study day, visits will be referenced in summary tables by analysis visits only. Listings will present both nominal visits as recorded on the eCRF, and the analysis visits. After all the records have been assigned to an analysis visit window based on study day, if there are multiple valid records for an assessment within an assigned analysis visit, only one of their records will be used for summary statistics and analyses. The record to be used is determined using the following hierarchy (in descending order):

Safety assessments, including laboratory tests, ECG and vital signs:

- the record closest to the target visit day
- The latest visit in the analysis visit window

^{13}C-UBT assessments:

- The latest visit in the analysis visit window

4.4. Analysis Set

4.4.1. Screened Set

All subjects who signed the informed consent form (ICF) before entering the study. Screen failures are defined as subjects who were not randomized into the study.

4.4.2. Randomized Set

All subjects randomly assigned to receive study drug regardless of whether or not they received a dose of study drug during the study.

4.4.3. Modified Intent-to-Treat (MITT) Set

The MITT Set will be defined as all subjects randomized into the study who have HP infection documented by ^{13}C-UBT and biopsy (i.e. culture or histology) at baseline. All analyses using the MITT set will group subjects according to the randomized treatment.

4.4.4. Modified Intent-to-Treat primary (MITTp) Set

The MITTp Set will be defined as the subset of subjects in the MITT Set who did not have a clarithromycin or amoxicillin resistant strain of HP at baseline.

This analysis set will be used for the primary analysis. All analyses using the MITTp set will group subjects according to the randomized treatment.

4.4.5. Per Protocol (PP) Set and Per Protocol primary (PPp) Set

The PP Set and PPp Set will consist of all MITT and MITTp subjects, respectively, with all of the following:

- Test-of-cure visit (4-Week Post-Treatment) 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 (i.e. treatment failure)
- 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 during the 7 days prior to 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 during the 14 days prior to Day 1, during treatment, or between completion of treatment and the test-of-cure visit, unless given for treatment failure

Subjects can use 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

4.4.6. Safety Set

The safety set will be defined as all subjects who received at least 1 dose of study drug. All analyses using the safety set will group subjects according to the treatment actually received.

4.4.7. Pharmacokinetic (PK) Set

The PK Set will consist of all subjects who have received at least one dose of study drug and who have at least 1 evaluable post-dose PK concentration value.

4.5 Missing Data Handling for ^{13}C-UBT Assessments

For the analyses of endpoints assessed by ^{13}C-UBT, subjects who do not have post-baseline ^{13}C-UBT will be considered treatment failures, i.e., "not eradicated" for the primary analysis.

5. Subject Disposition

5.1. Disposition

5.1.1. Screened and Screen Failure Subjects

The number of screened and screen failure subjects will be presented for overall subjects included in the Screened Set.

The following will be summarized for the Screened Set:

- The total number of screened subjects.
- The number and percentage of screen failures.
- The number and percentage of each primary reason for screen failures.

Subjects who fail to fulfill all inclusion/exclusion criteria will be listed for the Screened Set.

5.1.2. Randomized Subjects

The number of subjects included in each analysis set will be presented by treatment group and overall for all randomized subjects.

The following will be summarized for the Randomized Set:

- The number of randomized subjects.
- The number and percentage of subjects in the MITT Sets (MITT and MITTp), PP Sets (PP and PPp) and Safety Set.
- The number and percentage with each reason for exclusion from the MITT Set and the PP Set.
- The number and percentage of subjects who completed the treatment period.
- The number and percentage of subjects who discontinued from the treatment period.
- The number and percentage of subjects who completed the participation of the entire study.
- The number and percentage of subjects who completed or discontinued from the follow-up period.

Reasons for discontinuation from the study drug will be summarized. Reasons for discontinuation from the study participation will also be summarized. Percentages will be based on the number of Randomized Set.

The screening disposition for screen failures will be listed using the Screened Set. Subject disposition data for the treatment period will be listed for the Randomized Set. Disposition data for the treatment period will be listed separately for subjects who discontinued from the study for the Randomized Set.

5.2. Protocol Deviations

Protocol deviations will be recorded within the [redacted] Clinical Trial Management System (CTMS) and will undergo a blinded review prior to database lock and unblinding. Significant protocol deviations are defined as the subset of deviations which are considered to affect primary efficacy and safety assessments, the safety or mental integrity of a subject, or the scientific value of the trial.

The number and percentage of subjects with subject-specific significant protocol deviations will be summarized by CTMS activity type, subtype, treatment group and overall for the Randomized Set. Individual subject protocol deviations, both significant and non-significant, will be presented in a by-treatment, by-subject data listing using the Randomized Set.

6. Demographics and Baseline Characteristics

6.1. Demographics and Baseline Characteristics

Demographic variables collected at Screening, such as age, sex, race, ethnicity, height (cm), weight (kg), and body mass index (BMI) will be summarized. Continuous variables, including age (years), BMI, weight, height, will be summarized using descriptive statistics for each treatment group and overall. The following categorical variables will be summarized by

reporting the number and percentage of subjects in each category for each treatment group and overall using the MITT Set, MITTp Set, PP Set, PPp Set, and Safety Set.

- Age group at Screening (<45, ≥45 - <65, ≥65 - <75, ≥75)
- Age group 2 at Screening (≥18 - ≤64, ≥65 - ≤84, ≥85)
- Sex (Male, Female)
- Race
- Ethnicity
- BMI category (<25, ≥25 - <30, ≥30)
- Minimum Inhibitory Concentration (MIC) Against *H pylori* (µg/mL) value (<=0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, >=128, Not Applicable)
  - Amoxicillin
  - Clarithromycin
  - Metronidazole
- MIC Against *H pylori* (µg/mL) category
  - Amoxicillin (≤0.125, >0.125, Not Applicable)
  - Clarithromycin (<1, ≥1, Not Applicable)
  - Metronidazole (≤8, >8, Not Applicable)
- Region (United States, Europe)
- Subregion (US-West, US-Southwest, US-Southeast, US-North, Europe-Bulgaria, Europe-Czech Republic, Europe-United Kingdom, Europe-Hungary, Europe-Poland)
  Classification of the US study sites to subregion will be done according to the following:
  - West: California, Colorado, Nevada, Utah, Washington
  - Southwest: Arizona, Oklahoma, Texas
  - Southeast: Alabama, Arkansas, Florida, Georgia, Louisiana, North Carolina, South Carolina, Tennessee, Virginia
  - North: Connecticut, Illinois, Indiana, Iowa, Maryland, Michigan, Missouri, Nebraska, New York, Ohio, Pennsylvania, South Dakota, Wisconsin
- MIC Against *H pylori* (µg/mL) category by region
- MIC Against *H pylori* (µg/mL) category by subregion
- CYP2C19 status (extensive metabolizer, poor metabolizer)
- Smoking status (never smoked, current smoker, ex-smoker)
- Alcohol use (drink every day, drink a couple of days per week, drink a couple of days per month, never drink)
- Clinical conditions (Dyspepsia 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)

The concordance of the tests for HP infection at baseline (^{13}C-UBT, culture, and histology) will be summarized for the Randomized Set. The following categories will be summarized by reporting the number and percentage of subjects with positive results for HP infection in each category for each treatment group and overall.

- ^{13}C-UBT only
- ^{13}C-UBT and culture

- ^{13}C-UBT and histology
- ^{13}C-UBT, either culture or histology
- ^{13}C-UBT, culture and histology

Demographic and baseline characteristics data will be listed by treatment and subject using the Randomized Set.

6.2. Medical History

6.2.1. General Medical History

Medical history will be coded using Version 22 of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with medical history coded to each MedDRA SOC and PT will be summarized by treatment group and overall using the Safety Set.

Medical history will be listed by treatment and subject using the Safety Set.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Any prior and concomitant medication used during the study will be recorded and coded using WHODRUG Version B3-March 2019. Summaries of all medications by drug class (ATC Level 4 coding) and preferred term will be provided separately for prior medications and concomitant medications for each treatment group and overall. All summaries will be performed using the Safety Set.

Prior medications are those with the start and stop dates prior to the first dose of the study drug. Concomitant medications are those with start dates prior to the first dose and continuing after the first dose of the study drug, or with start dates on or after the first dose of the study drug.

The prior medications will be summarized by treatment group and overall. Concomitant medications with start dates on or before the last dose of study drug will be summarized by treatment group and overall. Concomitant medications with start dates after the last dose of study drug will be summarized separately by treatment group and overall.

All prior medications and concomitant medications will be listed.

In instances where a medication start date is incomplete, it will be conservatively imputed to determine whether or not the medication was prior or concomitant. If the start date is missing, then it will be assumed to be concomitant. Imputation details for missing concomitant medication start and end date are presented in Appendix section 12.2.

All prior and concomitant medications will be listed by treatment and subject for the Safety Set.

7.2. Study Treatments

7.2.1. Treatment Compliance

Treatment compliance will be calculated separately for each study drug. For vonoprazan 20 mg, lansoprazole 30 mg, and clarithromycin, compliance will be calculated as:

Compliance (%) = (total actual capsules taken / total expected capsules) × 100, where

total expected capsules = 14 × 2 and

total actual capsules taken = total number of capsules dispensed – total number of capsules returned

For amoxicillin, compliance will be calculated as:

Compliance (%) = (total actual capsules taken / total expected capsules) × 100, where

total expected capsules = 14 × 2 × $n^{(*)}$ and

total actual capsules taken = total number of capsules dispensed – total number of capsules returned

(*) n = 2 if regimen is BID, n = 3 if regimen is TID.

In addition, an overall compliance of the complete regimen will be calculated as:

Compliance (%) = (total actual capsules taken / total expected capsules) × 100, where

total expected capsules is the sum of all expected capsules from all study drug and

total actual capsules taken is the sum of all actual capsules taken from all study drug

If a kit is not returned, the compliance of the lost kit will be imputed as 100%. Compliance rate will be summarized for each treatment group and overall.

Overall compliance information will be used to categorize subjects as being either compliant or not. A subject is considered compliant if the overall study drug compliance is greater than or equal to 75% and less than or equal to 120%.

Treatment compliance for the treatment period will be summarized for the Safety Set. Summary statistics for treatment compliance percentages will be summarized for each treatment group and overall. Individual subject compliance information will be listed by treatment and subject using the Safety Set.

7.2.2. Extent of Exposure

Descriptive summary statistics including the number of subjects, mean, standard deviation, median, minimum, and maximum for the duration of study drug exposure (days) will be presented by treatment group and overall.

Treatment duration of exposure will be categorized and summarized as follows: ≥1 to ≤10 days, >10 to ≤14 days, >14 days.

Treatment exposure will be calculated as the number of days from first to last dose date:

Exposure = Date of last dose – Date of first dose + 1

The date of last dose is recorded on the End of Treatment (EOT) page on the eCRF. The date of first dose is recorded on the Drug and Antibiotic Accountability page on the eCRF. If the date of first dose is missing, it will be imputed using the date of randomization + 1. If the date of last dose is missing, it will be imputed as the date of first dose + 13. All summaries for the treatment period will be performed using the Safety Set.

All data for treatment exposure during the treatment period will be listed by treatment and subject using the Safety Set.

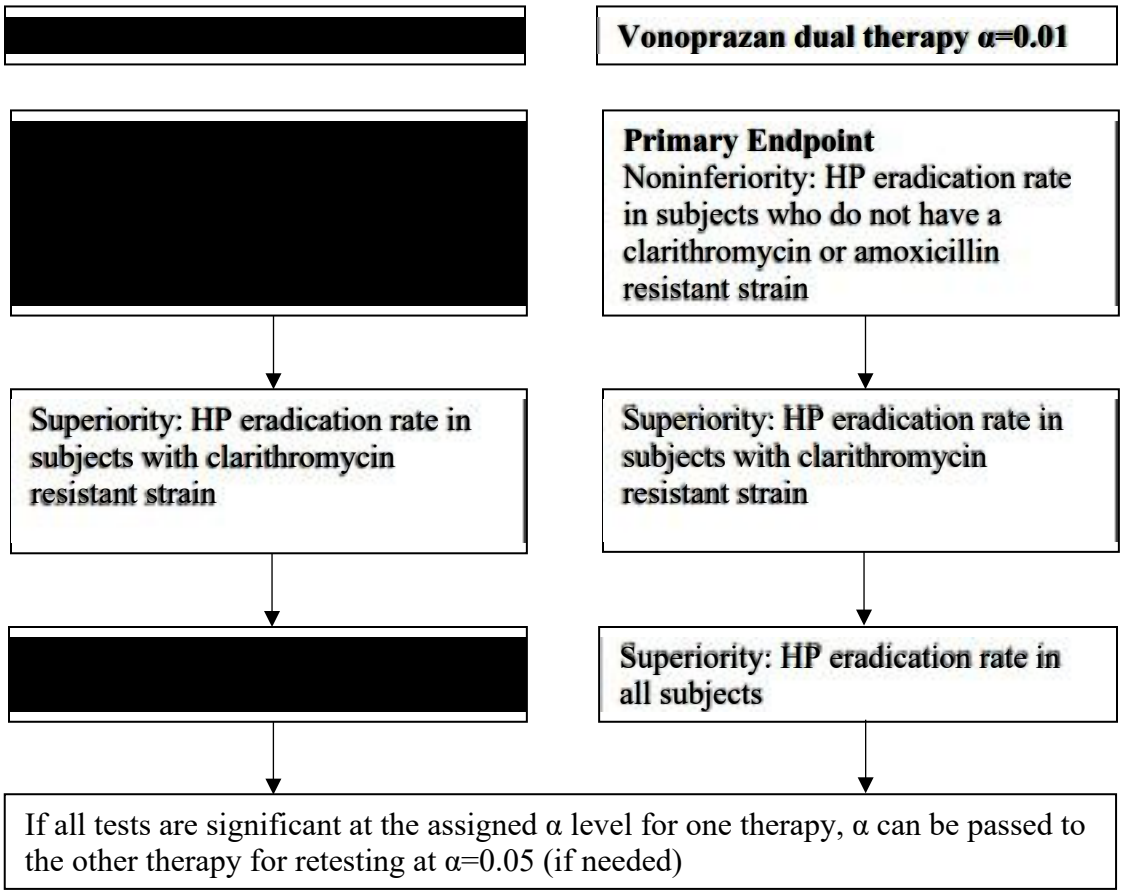
8. Efficacy Analysis

The type 1 error will be controlled at an overall level of $\alpha = 0.05$ using hierarchical testing of the primary and secondary endpoints and weighted Bonferroni for the regimen comparisons (Bretz 2011), as shown in the testing hierarchy in Figure 2. An α level of 0.04 will be initially assigned to the vonoprazan triple therapy, and an α level of 0.01 will be initially assigned to the vonoprazan dual therapy. For each therapy, the 1-sided p-value must be less than the assigned $\alpha/2$ to be significant. If non-inferiority is declared from the primary efficacy analysis of a therapy, testing for that therapy will continue to the next endpoint following the testing hierarchy. If all endpoints are significant for a therapy, the α can be passed to the other therapy, if needed. Therefore, endpoints for the other therapy can be retested at the 0.05 level in hierarchical order until a 1-sided p-value is > 0.025.

Only p-values that are significant according to this sequential order are inferential and statistically significant. All other p-values are descriptive.

Additional comparisons will be made between the two vonoprazan therapies (dual therapy vs. triple therapy) for each primary and secondary efficacy endpoint as a reference with no adjustment for multiple comparisons.

Figure 2 Testing Hierarchy



8.1. 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, i.e., the MITTp Set.

8.1.1. Primary Analysis

The frequency and the percentage of subjects with successful HP eradication will be summarized for 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% for the difference in HP eradication rates between treatments. The noninferiority test will be 1-sided with an overall significance level of $\alpha/2$ for each pair of treatments. The point estimate and 2-sided $(1-\alpha)\%$ 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 as an exploratory analysis.

If a subject's ^{13}C-UBT test is positive at 4-Week Post-Treatment, an endoscopy and antibiotic susceptibility testing will be performed. HP culture and antibiotic susceptibility results at post-treatment assessments will be listed.

8.1.2. Assumption Testing

Given the large sample sizes for each treatment group, the test statistic for the Farrington and Manning test is expected to be normally distributed. Testing for normality with Farrington and Manning test might be added as an ad hoc analysis at the end of the study.

8.1.3. Sensitivity and Supportive Analyses

The following sensitivity and supportive analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint.

8.1.3.1. Sensitivity Analysis to Assess the Impact of Early and Late Test-of-Cure Visits

To assess the impact of early and late test-of-cure visits on the robustness of the primary analysis, a sensitivity analysis will be performed for non-inferiority in which subjects with test-of-cure visits outside the window of 28 to 56 days post treatment will be considered treatment failures, i.e. "not eradicated".

8.1.3.2. Sensitivity Analysis on Use of Prohibited Medications

To explore how use of the prohibited medications of antimicrobials known to be effective against HP, proton pump inhibitors or high dose H_2-receptor antagonists affects the robustness of the primary analysis, a sensitivity analysis will be performed for non-inferiority considering subjects as non-responders after use of these prohibited medications. Use of these prohibited medications will be defined consistent with the definition of the PP Set in Section 4.4.5. This sensitivity analysis will be performed using the MITTp Set.

8.1.3.3. Tipping Point Analysis

A tipping point analysis will also be performed as a sensitivity analysis. The tipping point analysis begins with most conservative imputation for missing data (e.g., most heavily slanted against the active treatment non-inferior to active control).

Implementation of the tipping point approach will involve the following steps for each vonoprazan therapy vs. lansoprazole therapy:

1. The missing data for lansoprazole subjects is assumed to be responders. Missing data for vonoprazan subjects is assumed to be non-responders.
2. The data set is analyzed using the Farrington and Manning method to see if the p-value is ≤ the assigned α/2 level of this regimen; and if so, the tipping point analysis will be stopped at this point.
3. Repeat step #1 switching an imputed responder for one lansoprazole subject to an imputed non-responder.
4. Repeat step #2 to obtain the p-value to see if the p-value is ≤ the assigned α/2 level of this regimen.

Repeat steps #3 and #4 increasing the number of imputed lansoprazole non-responders one at a time until the p-value is ≤ the assigned α/2 level of this regimen or all missing data has been switched from an imputed responder to a non-responder for all lansoprazole subjects with an imputed result. The number of non-responders that achieves this p-value will be considered the "tipping point."

8.1.3.4. Multiple Imputation Analysis

A multiple imputation analysis under missing at random (MAR) followed by calculation of difference in HP eradication with 95% CI will also be performed as a sensitivity analysis for the primary endpoint. The missing pattern of this endpoint will be monotone as it is being collected only once post-baseline. Considering that the endpoint being imputed is binary, the logistic regression method will be used. The following steps will be followed:

1. Impute missing primary endpoint using the LOGISTIC option on the MONOTONE statement in PROC MI.
2. Analyze each imputed dataset using the same method as the primary analysis.
3. Repeat the process K (K=50) times.
4. Combine results using PROC MIANALYZE.

8.1.3.5. Supportive Analysis Using PPp Set

The primary analysis will be repeated using PPp Set.

8.1.3.6. Supportive Analysis with Different Amoxicillin Resistance Breakpoint

An analysis will also be performed to assess the sensitivity of the primary endpoint results to the choice of resistance breakpoint for amoxicillin. In the primary analysis of the primary endpoint, HP strains are considered resistant to amoxicillin if the MIC is >0.125 μg/mL. In this sensitivity analysis, HP strains will be considered resistant to amoxicillin if the MIC is > 0.25 μg/mL. This analysis will be based on the MITT Set and exclude subjects with a HP strain with an amoxicillin MIC > 0.25 μg/mL or a clarithromycin MIC ≥1 μg/mL.

8.1.3.7. Shift Summary on Antibiotics Assessment

Shift tables for the change in antibiotic susceptibility assessment from baseline to 4-Week Post-Treatment will be presented by treatment group for the MITTp Set and the MITT Set for amoxicillin, clarithromycin and metronidazole separately. The baseline assessment values include susceptible, intermediate and resistant. The 4-Week Post-Treatment assessment values include HP eradicated, susceptible, intermediate, resistant, and no MIC.

8.1.4. Subgroup Analysis

The primary efficacy endpoint will be analyzed separately for the following subgroups using the same method as the primary, except MIC against *H pylori* (μg/mL) value. Only summary statistics will be reported for subgroup analysis by MIC against *H pylori* (μg/mL) value.

- Age group at Screening (<45, ≥45 - <65, ≥65 - <75, ≥75)
- Sex (Male, Female)
- Race
- Ethnicity
- BMI category (<25, ≥25 - <30, ≥30)
- MIC Against *H pylori* (μg/mL) value (<=0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, >=128, Not Applicable)
  - Amoxicillin
  - Clarithromycin
  - Metronidazole
- MIC Against *H pylori* (μg/mL) category
  - Amoxicillin (≤0.125, >0.125)
  - Clarithromycin (<1, ≥1)
  - Metronidazole (≤8, >8)
- Region (United States, Europe)
- Subregion (US-West, US-Southwest, US-Southeast, US-North, Europe-Bulgaria, Europe-Czech Republic, Europe-United Kingdom, Europe-Hungary, Europe-Poland)
  Classification of the US study sites to subregion will be done according to the following:
  - West: California, Colorado, Nevada, Utah, Washington
  - Southwest: Arizona, Oklahoma, Texas

  - Southeast: Alabama, Arkansas, Florida, Georgia, Louisiana, North Carolina, South Carolina, Tennessee, Virginia
  - North: Connecticut, Illinois, Indiana, Iowa, Maryland, Michigan, Missouri, Nebraska, New York, Ohio, Pennsylvania, South Dakota, Wisconsin
- MIC Against *H pylori* (µg/mL) category by region
- MIC Against *H pylori* (µg/mL) category by subregion
- CYP2C19 status (extensive metabolizer, poor metabolizer)
- Smoking status (never smoked, current smoker, ex-smoker)
- Alcohol use (drink every day, drink a couple of days per week, drink a couple of days per month, never drink)
- Clinical conditions (Dyspepsia 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)
- Study drug compliance of the complete regimen (<75%, ≥75% - 100%, ≥100% - 120%, ≥120%)

The subgroup analyses will be performed using the MITTp Set. If the number of subjects within a subgroup in a treatment group is not sufficient to run a Farrington and Manning test, subgroups might be combined to perform the test. Alternatively, only summary statistics might be reported for such subgroups.

8.2. Secondary Efficacy Endpoint

The secondary endpoints are

- 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. This analysis will be performed using the subset of subjects that are in MITT Set that 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. This analysis will be performed using the MITT Set.

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 addition, the analysis of both secondary endpoints will be repeated using the PP set.

To assess the impact of early and late test-of-cure visits on the robustness of the analysis, a sensitivity analysis will be performed for both secondary endpoints in which subjects with test-

of-cure visits outside the window of 28 to 56 days post treatment will be considered treatment failures, i.e. “not eradicated”.

The secondary efficacy endpoint in subjects with a clarithromycin resistant strain will be analyzed separately, using the MITT Set, for the following subgroups. MIC against *H pylori* (µg/mL) category will be analyzed using the same method as the primary. MIC against *H pylori* (µg/mL) value will be reported only using summary statistics.

- MIC Against *H pylori* (µg/mL) value
  - Amoxicillin
  - Metronidazole
- MIC Against *H pylori* (µg/mL) category
  - Amoxicillin (≤0.125, >0.125)
  - Metronidazole (<8, >8)

The secondary efficacy endpoint in all subjects will be analyzed separately, using the MITT Set, for the following subgroups. MIC against *H pylori* (µg/mL) category will be analyzed using the same method as the primary. MIC against *H pylori* (µg/mL) value will be reported only using summary statistics.

- MIC Against *H pylori* (µg/mL) value
  - Amoxicillin
  - Clarithromycin
  - Metronidazole
- MIC Against *H pylori* (µg/mL) category
  - Amoxicillin (≤0.125, >0.125)
  - Clarithromycin (<1, ≥1)
  - Metronidazole (≤8, >8)

9. Safety Analysis

Safety will be assessed by summarizing the incidence of AEs and changes in clinical laboratory tests, vital signs and ECG. For all safety analyses, baseline will be the last available assessment prior to the first dose of study drug.

All safety analyses will be conducted for each treatment group and overall using the Safety Set.

9.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA version used for reporting the study will be documented in the summary table footnotes. 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. A subject with multiple adverse events within a primary SOC or preferred term is only counted once towards the total for that SOC and/or preferred term. For the AE severity and relationship summaries, if a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity or relationship will be presented. If a subject reported more than one adverse event within the same primary system organ class, then the subject will be counted only once with the greatest severity or relationship at the system organ class level. For table summaries, if severity is missing then 'severe' is assumed. If relationship is missing, relationship to study drug is assumed to be 'related'.

An overall summary of the number of subjects and the number of events with TEAEs in each treatment group will be presented, including TEAEs, serious TEAEs, study drug related TEAEs, study drug related serious TEAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to death.

The number and percentage of subjects with TEAEs will be summarized in the following ways:

- by primary system organ class, preferred term, and treatment group
- by primary system organ class, preferred term, maximum severity, and treatment group
- by primary system organ class, preferred term, relationship to study drug, and treatment group
- by primary system organ class, preferred term, day of onset, and treatment group

The number and percentage of subjects with TEAEs related to study drug will be summarized in the following ways:

- by primary system organ class, preferred term, and treatment group
- by primary system organ class, preferred term, maximum severity, and treatment group
- by primary system organ class, preferred term, day of onset, and treatment group

Summaries of TEAEs by day of onset will use the following categories: Day 1 to 14, Day 15 to 28, Day 28 and above.

The most common TEAEs (≥5% of subjects in any treatment group) and TEAEs related to study drug (≥2% of subjects in any treatment group) will be presented by preferred term in descending frequency starting from the most common event. The most common non-serious AEs (>5% of subjects in any treatment group) will be presented by primary system organ class, preferred term and treatment group.

The number and proportion of subjects as well as the number of events (except for deaths) with the following types of events will be summarized by primary system organ class, preferred term

and treatment group:

- Adverse events leading to treatment discontinuation
- Serious Adverse Events (SAEs)
- Deaths
- Adverse events of special interest

All adverse events will be included in a listing using the Screened Set. The following select adverse events will be displayed in separate listings using the Safety Set:

- Adverse events leading to treatment discontinuation
- SAEs
- Deaths
- Adverse events of special interest

9.1.2. Adverse Events of Special Interests (AESI)

The number and percentage of subjects with TEAEs and SAEs that are in one of the AESI categories presented in Table 4 will be summarized by AESI category, primary system organ class and preferred term for each treatment group and overall. The search criteria that will be used to identify AESIs are specified in the table.

Table 4 Adverse Events of Special Interest – Search Criteria

Adverse Event of Special Interest	Search Criteria
Clostridium difficile enteric infection	Pseudomembranous colitis SMQ (Narrow)
Bone Fracture	Bone Fracture Custom Query (PTs defined below) Acetabulum fracture Ankle fracture Atypical femur fracture Atypical fracture Avulsion fracture Bone fissure Bone fragmentation Chance fracture Clavicle fracture Comminuted fracture Complicated fracture Compression fracture Craniofacial fracture Epiphyseal fracture Facial bones fracture Femoral neck fracture Femur fracture Fibula fracture Foot fracture Forearm fracture Fracture Fracture blisters Fracture displacement Fracture malunion Fracture nonunion Fracture of clavicle due to birth trauma Fractured coccyx Fractured ischium Fractured sacrum Fractured skull depressed Lumbar vertebral fracture Metaphyseal corner fracture Multiple fractures Open fracture Osteoporotic fracture Patella fracture Pathological fracture Pelvic fracture Pubis fracture Radius fracture Rib fracture Sacroiliac fracture Scapula fracture Skull fracture Skull fractured base Spinal compression fracture Spinal fracture Spinal fusion fracture Sternal fracture Stress fracture Subchondral insufficiency fracture Thoracic vertebral fracture Tibia fracture Torus fracture Traumatic fracture Ulna fracture Upper limb fracture Wrist fracture
Severe cutaneous adverse reactions	Severe cutaneous adverse reactions SMQ (Narrow)
Hepatotoxicity	• Drug related hepatic disorders - comprehensive search (SMQ) (Narrow) • Cholestasis and jaundice of hepatic origin (SMQ) (Broad) • Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions SMQ (Broad) • Hepatitis, non-infectious (SMQ) (Broad) • Liver related investigations, signs and symptoms (SMQ) (Narrow)
Gastric cancer	Gastric Neoplasms Malignant MedDRA High Level Term
Hypersensitivity	Hypersensitivity SMQ (narrow)
QT prolongation	• Torsade de pointes/QT prolongation (SMQ) (Broad) • Seizure MedDRA Preferred Term

MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SMQ: Standardized MedDRA Queries.

9.2. Clinical Laboratory Evaluations

Descriptive statistics for clinical laboratory values ((hematology, chemistry and urinalysis laboratory tests; in SI units and in US conventional units) will be presented by treatment group and overall. Changes from baseline will also be presented for quantitative variables by treatment group and overall. For categorical variables (ie, normal or abnormal findings, or qualitative clinical laboratory tests), shift tables for the change from baseline to each post-baseline time point will be presented by treatment group and overall.

Abnormal liver function tests are defined as liver test values that meet at least one of the criteria listed below. The number and percentage of subjects with at least one post-baseline abnormal liver function test and with the test value higher than baseline, if available, will be presented by treatment group and overall. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

- ALT > 3xULN
- ALT > 5xULN
- ALT > 10xULN
- ALT > 3xULN and Total Bilirubin > 2xULN

- AST > 3xULN
- AST > 5xULN
- AST > 10xULN
- AST > 3xULN and Total Bilirubin > 2xULN

- Total Bilirubin > 2xULN

- AST > 3xULN or ALT > 3xULN
- AST > 5xULN or ALT > 5xULN
- AST > 10xULN or ALT > 10xULN
- (AST > 3xULN or ALT > 3xULN) and Total Bilirubin > 2xULN

- AST > 3xULN and ALT > 3xULN
- AST > 5xULN and ALT > 5xULN
- AST > 10xULN and ALT > 10xULN
- AST > 3xULN and ALT > 3xULN and Total Bilirubin > 2xULN

- Alkaline phosphatase > 1.5xULN
- ALT > 3xULN and Alkaline phosphatase > 1.5xULN
- AST > 3xULN and Alkaline phosphatase > 1.5xULN

- Alkaline phosphatase > 3xULN
- ALT > 3xULN and Alkaline phosphatase > 3xULN

- AST > 3xULN and Alkaline phosphatase > 3xULN

9.3. Vital Sign

Descriptive statistics for vital signs, including body temperature, systolic blood pressure, diastolic blood pressure and pulse rate, will be presented by treatment group and overall. Changes from baseline will also be presented by treatment group and overall.

Abnormal vital sign values are defined as vital sign values that meet one of the criteria listed below. The number and percentage of subjects with at least one post-baseline abnormal vital sign value and with the value higher than the baseline value, if available, will be presented by treatment group and overall. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

- Systolic blood pressure (mmHg):
  - <50
  - >180
- Diastolic blood pressure (mmHg):
  - <50
  - >100
- Heart rate (bpm):
  - <50
  - >120

9.4. Physical Examination

All data collected from the physical examinations assessments must be available in the source documents but will not be added to the analysis database.

9.5. Electrocardiogram

Descriptive statistics for ECG parameters, including heart rate, RR interval, PR interval, QT interval, QTc Fridericia (QTcF), and QRS interval, will be presented by treatment group and overall. All ECG assessment values and interpretations will be listed for all subjects in the Safety Set.

Changes from baseline will also be presented for quantitative variables by treatment group and overall.

For ECG interpretations (within normal limits, abnormal but not clinically significant, or abnormal and clinically significant), shift tables for the change from baseline to each post-baseline time point will be presented by treatment group and overall.

Abnormal QTcF values are defined as ECG values that meet at least one of the criteria listed below, the number and percentage of subjects with at least one of the post-baseline abnormal values and with post-baseline value higher than baseline value, if available, will be presented by treatment group and overall. A supportive listing of subjects with such post-baseline elevations will be provided including the subject ID, baseline, and post-baseline values.

- Absolute QTcF interval prolongation:
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500

- Change from baseline in QTcF interval:
  - QTc interval increases from baseline >30
  - QTc interval increases from baseline >60
  - QTc interval > 450 with increase from baseline >30

10. Pharmacokinetics

A data listing with plasma concentration data will be provided based on the PK Set.

11. Interim Analysis/Other Analyses

11.1. Interim Analysis

No interim analysis is planned.

11.2. Coronavirus Pandemic

Shortly after this study began enrolling subjects, the SARS-COV-2 virus, which causes COVID-19 was declared a global pandemic by the World Health Organization. In accordance with guidance issued by regulatory agencies, study data collection has been amended for subjects to capture visits missed/delayed due to COVID-19 related reasons, and assessment completed via alternative method due to COVID-19 related reasons.

COVID-19 impacts on individual subjects collected on COVID-19 CRF pages will be listed for the Randomized Set. Protocol deviations related to COVID-19 will be marked in the protocol deviation listing for the Randomized Set. Delayed or missed ^{13}C-UBT due to COVID-19 will be identified in the ^{13}C-UBT listing for the Randomized Set.

The anticipated impact of COVID-19 is widely regarded as unknown. If the impact of COVID-19 on the conduct of this study is observed to be significant, further summaries and listings of the impact will be explored.

12. Changes in the Planned Analysis

The following change to the analysis specified in Protocol Amendment 2, dated 11May2020 has been made.

In the first amendment to the SAP, to account for the COVID-19 impact, subjects with out-of-window ^{13}C-UBT results that are late (>56 days post treatment) due to COVID-19 were planned to be included in the 4-Week Post-Treatment visit in the efficacy analyses.

Beyond those that were directly cited as related to COVID-19, there were many cases of indirect effects of COVID-19 on the visit schedules. To maximize obtaining ^{13}C-UBT results, some sites needed to use discretion and flexibility for subject visits including those subjects that needed to return to the site for a repeat ^{13}C-UBT that was initially indeterminate.

Based on the complex operational conditions that were faced during this study, the visit window was modified to allow late (>56 days post treatment) ^{13}C-UBT results as well as those obtained one day early (day 27 posttreatment) to be included in the MITT analyses for the primary and secondary endpoints.

Sensitivity analyses were added to assess the impact of this change.

13. References

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14. Appendices

14.1. Schedule of Events

Table 5 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, k]	X							
Pregnancy test (urine hCG) [j, k]		X			X		X	X
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

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.

	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**	**-**

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.

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.

14.2. Imputation Rules for Missing Date Information

14.2.1. Rules for Concomitant Medication Start Date Imputation

The following rules will be applied to impute the missing numerical fields. If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Missing day and month

- If the year of the incomplete start date is the same as the year of the date of the first dose of study drug, then the day and month of the date of the first dose of study drug will be assigned to the missing fields.
- If the year of the incomplete start date is before the year of the date of the first dose of study drug, then 31 December will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the date of the first dose of study drug, then the day of the date of the first dose of study drug will be assigned to the missing day.
- If either the year is before the year of the date of the first dose of study drug or if both years are the same but the month is before the month of the date of the first dose of study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the date of the first dose of study drug or if both years are the same but the month is after the month of the date of the first dose of study drug, then the first day of the month will be assigned to the missing day.

14.2.2. Rules for Concomitant Medication End Date Imputation

The following rules will be applied to impute the missing numerical fields. If the date of the last dose of study drug is missing, then replace it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the same as the year as of the date of the last dose of study drug, then the day and month of the date of the last dose of study drug will be assigned to the missing fields.
- If the year of the incomplete stop date is before the year of the date of the last dose of study drug, then 31 December will be assigned to the missing fields.
- If the year of the incomplete stop date is after the year of the date of the last dose of study drug, then 01 January will be assigned to the missing fields.

Missing month only

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the date of the last dose of study drug, then the day of the date of the last dose of study drug will be assigned to the missing day.
- If either the year is before the year of the date of the last dose of study drug or if both years are the same but the month is before the month of the date of the last dose of study drug, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last dose of study drug or if both years are the same but the month is after the month of the date of the last dose of study drug, then the first day of the month will be assigned to the missing day.

14.2.3. Rules for AE Start Date Imputation

For AEs, incomplete (i.e., partially missing) start dates will be imputed and will follow the same rules as in Section 14.2.1. Incomplete stop dates will not be imputed.