STATISTICAL ANALYSIS PLAN

NCT Number: NCT04198363

Study Title: A Randomized Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of Bismuth-Containing Quadruple Therapy With Oral TAK-438 20 mg Compared to Esomeprazole 20 mg Twice Daily in Subjects With Helicobacter Pylori Infection

Study Number: Vonoprazan-3002

SAP Version and Date:

Version 3.0: 31-August-2021

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vonoprazan-3002

A Randomized Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of Bismuth-Containing Quadruple Therapy With Oral TAK-438 20 mg Compared to Esomeprazole 20 mg Twice Daily in Subjects With *Helicobacter Pylori* Infection

PHASE 3

Version**: 3**

Date**:** 24 August 2021

Prepared by:

[redacted] Biostatistics

Based on:

Protocol Version: Amendment 03

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[redacted]

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

[redacted]

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

^{13}C-UBT	^{13}C-urea breath test
γ-GTP	gamma-glutamyl transferase
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CK	creatine kinase
CPK	creatine phosphokinase
ECG	electrocardiogram
FAS	full analysis set
HP	*Helicobacter pylori/ H.pylori*
LDH	lactate dehydrogenase
LLN	lower limit of normal
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
O/E	overencapsulated
PPS	per protocol set
PT	preferred term
PTE	pretreatment adverse event
RBC	red blood cell
SOC	system organ class
TB	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

[redacted]

4.0 OBJECTIVES

4.1 Primary Objective

The primary objective of this study:

- To demonstrate the efficacy of HP eradication with bismuth-containing quadruple therapy with TAK-438 versus esomeprazole in all HP+ subjects.

4.2 Secondary Objectives

Secondary objectives of this study are:

- To demonstrate the efficacy of HP eradication with bismuth-containing quadruple therapy with TAK-438 versus esomeprazole in clarithromycin resistant HP+ subjects.
- To compare the safety of bismuth-containing quadruple therapy with TAK-438 versus esomeprazole in subjects with HP infection.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This is a randomized, double-blind, phase 3 study to compare the efficacy and safety of bismuth-containing quadruple therapy administered with either oral TAK-438 20 mg or esomeprazole 20mg BID in all HP+ subjects.

Treatment Period—Dose and Regimen:

HP+ subjects whose eligibility is confirmed will take O/E TAK-438 20 mg or O/E esomeprazole 20 mg (which are identical in appearance) BID in conjunction with bismuth-containing quadruple therapy for 2 weeks (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg [equivalent to 220 mg bismuth], BID). The randomization ratio of TAK-438 group to esomeprazole group is 1:1.

A bacteriological test will be performed to determine if there are any resistant bacteria to the antibiotics used in the study. Biopsy specimens will be obtained from the central greater curvature of the antrum and upper greater curvature of the gastric body at the start of study (Visit 1). MICs of amoxicillin and clarithromycin against HP will be determined using the strains isolated from these specimens by the 2-fold agar dilution method. Cla >2, Amo >0.5 μg/mL is determined as resistance breakpoint.

Follow-up Period:

The subjects will be followed up at Week 4 post-treatment to provide a post-study ^{13}C-UBT to ascertain HP eradication status and to evaluate safety.

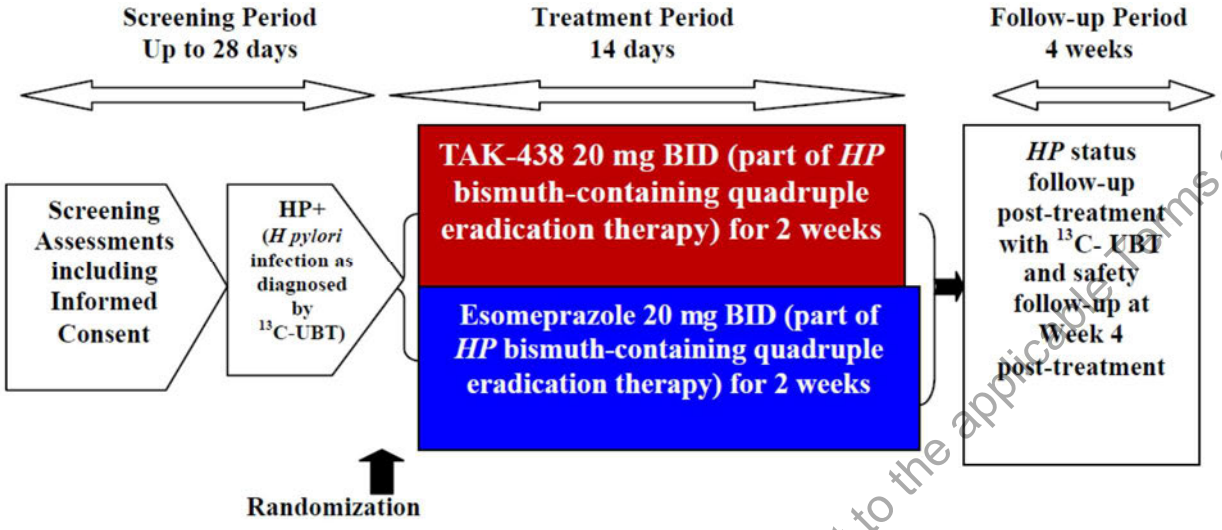

Figure 4.a Schematic of Study Design

5.0 ANALYSIS ENDPOINTS

Primary Endpoint

The primary endpoint for this study is the:

- Proportion of all HP+ subjects with successful HP eradication after the double-blind treatment period, as determined by ^{13}C-UBT at Week 4 post-treatment.

Additional Endpoint

The additional endpoint for this study is the:

- Proportion of baseline clarithromycin resistant HP+ subjects with successful HP eradication after the double-blind treatment period, as determined by ^{13}C-UBT at Week 4 post-treatment.

Safety Endpoints

Safety endpoints for this study include:

- AEs.
- Laboratory test values.
- ECG.
- Vital signs.

6.0 DETERMINATION OF SAMPLE SIZE

This study is planned to begin with 425 randomized subjects in total (which ensures approximately 400 evaluable subjects in total) and to possibly increase up to 510 randomized subjects in total, according to a pre-specified sample size adaptation rule.

This sample size provides over 90% power to establish noninferiority using the Farrington and Manning test with a noninferiority margin of 10% (1-sided 2.5% overall significance level), assuming that the true eradication rates are 90% for both TAK-438 and esomeprazole and 1 interim analysis is performed at 50% information fraction with critical value which is obtained from an O'Brien-Fleming type alpha spending function (2.96259 and 1.96860 for interim and final analysis, respectively). And, this provides approximately 80% power to establish superiority using score test, assuming that the true eradication rates are 95% for TAK-438 and 87% for esomeprazole.

[redacted]

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Descriptive statistics: Number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- BMI (kg/m^2): Weight (kg) / height $(m)^2$ (rounded to 1 decimal place)
- Clarithromycin Resistant: A subject will be considered clarithromycin resistant if maximum of the MICs of clarithromycin against HP is >2 μg/mL
- Amoxicillin Resistant: A subject will be considered amoxicillin resistant if maximum of the MICs of amoxicillin against HP is >0.5 μg/mL
- Duration of exposure to study drug (days) : Date of last dose of study drug - date of first dose of study drug + 1
- Study drug compliance (%) (rounded to 1 decimal place).
  - TAK-438/esomeprazole: Number of study drugs taken / 28 * 100
  - Amoxicillin: Number of study drugs taken / 56 * 100
  - Clarithromycin: Number of study drugs taken / 56 * 100
  - Bismuth potassium citrate: Number of study drugs taken / 56 * 100
- TEAE: An adverse event whose date of onset occurs on or after the start of study drug. An event whose type entered into the EDC is Adverse Event will be treated as a TEAE if its start date is missing.
- PTE: Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug
- Relationship of TEAE to study drug: If relationship to study drug is missing, the TEAE is considered to be a drug-related TEAE in analyses
- Intensity of TEAE: If intensity is missing, the TEAE is considered to be a severe TEAE in analyses
- Significant TEAE: Any TEAE (not including serious TEAE) that led to an intervention, including withdrawal of drug treatment, dose increase, dose reduction, dose interruption or significant additional concomitant therapy
- QTcF interval (msec): QT interval (msec) / RR interval $(sec)^{0.33}$ (rounded to the whole number)

[redacted]

7.1.2 Definition of Study Days

The following definitions and calculation formulas will be used.

- Study Day: The day before the first dose of the study drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1.
- Follow-up Day: The day after the last dose of the study drug will be defined as Follow-up Day 1.

7.1.3 Definition of Study Visit Windows

When calculating Study Day relative to a reference date (i.e., date of first dose of study drug [Day 1]) , if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

When calculating Follow-up Day relative to a reference date (i.e., date of last dose of study drug [Follow-up Day 0]), it will be calculated as: date of observation - reference date. Hence, reference day is always Follow-up Day 0.

All evaluable data (i.e., non-missing data) will be handled according to the following rules.

For each visit, observation obtained in the corresponding time interval will be used. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are 2 observations equidistant to the scheduled Study Day, the later observation will be used.

Table 7.a Visit Window of ^{13}C-UBT

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Week 4 Post-Treatment	Follow-up Day: 28		28 - 35

Table 7.b Visit Window of Laboratory Test Values, ECG, and Vital Signs

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 - 1	
End of Treatment	Study Day: 15	2 <=	<15

Table 7.c Visit Window of Weight

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 - 1	
Week 4 Post-Treatment	Follow-up Day: 28		28 - 35

[redacted]

7.1.4 Significance Level and Confidence Coefficient

- Significance level: 2.5% (1-sided test)
- Confidence coefficient: 95% (2-sided)

7.1.5 Conventions for Missing Adverse Event Dates

Not applicable.

7.1.6 Conventions for Missing Concomitant Medication Dates

Not applicable.

7.2 Analysis Sets

- FAS:
  All subjects who were randomized and received at least 1 dose of study drug. Analyses based on the FAS will be performed according to the randomization assignment.
- PPS:
  All FAS subjects who did not have any of the major protocol deviations listed below, and whose primary endpoint was evaluable
  - Subjects who did not meet inclusion criteria #4
  - Subjects who met exclusion criteria #5, #6, #7, or #10
  - Subjects with any of the study medication compliances of less than 70%
  - Subjects who have been unblinded by the investigator prior to database lock
  - Subjects who have violated the rules specified in section 7.3 of the protocol

  Analyses based on the PPS will be performed according to the actual treatment received.
- Safety analysis set:
  All subjects who received at least 1 dose of study drug. Analyses based on the safety analysis set will be performed according to the actual treatment received.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date First Subject Signed Informed Consent Form

[redacted]

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:

All Subjects Who Were Not Randomized

Analysis Variables:

Age (years) [Min<= - <65, 65<= - <75, 75<= - <=Max]

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status

[Eligible for Randomization, Not Eligible for Randomization]

Primary Reason for Subject Not Being Eligible

[Adverse Event, Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal by Subject, Study Terminated by Sponsor, Screen Failure, Other]

Analytical Methods:

(1) Eligibility for Randomization

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

[redacted]

7.3.4 Number of Subjects Randomized by Site and Treatment Group

Analysis Set:

Randomized Set

Analysis Variables:

Randomization Status

[Randomized]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Randomized by Site and Treatment Group

Frequency distribution will be provided for each stratum by treatment group and overall.

7.3.5 Disposition of Subjects

Analysis Set:

Randomized Set

Analysis Variables:

Study Drug Administration Status

[Randomized but Not Treated]

Reason for Not Being Treated

[Adverse Event, Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Other]

Study Drug Completion Status

[Completed Study Drug, Prematurely Discontinued Study Drug]

Reason for Discontinuation of Study Drug

[Adverse Event, Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Other]

Completion Status of the Follow-up Period

[Completed Follow-up Period, Prematurely Discontinued Follow-up Period]

Reason for Discontinuation of the Follow-up Period

[Adverse Event, Protocol Deviation, Lost to Follow-up, Voluntary Withdrawal by Subject, Study Terminated by Sponsor, Pregnancy, Lack of Efficacy, Other]

[redacted]

Analytical Methods:

(1) Disposition of Subjects

Frequency distributions will be provided for each treatment group and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

(2) Flow Diagram of Subject Disposition

A flow diagram which shows, for each treatment group, the number of subjects who were randomized, received assigned treatment, discontinued study drug with reasons, and discontinued follow-up period with reasons will be presented.

7.3.6 Protocol Deviations and Analysis Sets

7.3.6.1 Protocol Deviations

Analysis Set:

Randomized Set

Analysis Variables:

Significant Protocol Deviation

[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Other]

Analytical Methods:

(1) Protocol Deviations

Frequency distribution will be provided by treatment group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.6.2 Analysis Sets

Analysis Set:

Randomized Set

Analysis Variables:

Analysis Sets

Full Analysis Set [Included]

Per Protocol Set [Included]

Safety Analysis Set [Included]

Analytical Methods:

(1) Analysis Sets

Frequency distributions will be provided by treatment group and overall.

7.4 Demographic and Other Baseline Characteristics

Analysis Set:

FAS

Analysis Variables:

Age (years) [Min<= - <65, 65<= - <75, 75<= - <=Max]

Gender [Male, Female]

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]

Height (cm) [Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]

Weight (kg) at Baseline

[Min<= - <50.0, 50.0<= - <60.0, 60.0<= - <70.0, 70.0<= - <80.0, 80.0<= - <=Max]

BMI (kg/m^2) at Baseline

[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]

Smoking Classification

[Never Smoked, Current Smoker, Ex-Smoker]

Alcohol Consumption

[Everyday, Couple of Days Per Week, Couple of Days Per Month, Never, Former Drinker]

Caffeine Consumption [Yes, No]

Clarithromycin Resistant [Yes, No]

Amoxicillin Resistant [Yes, No]

Analytical Methods:

(1) Summary of Demographics and Baseline Characteristics

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

[redacted]

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term

(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided for each treatment group and overall. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medication History

Concomitant Medications

Analytical Methods:

(1) Medication History by Preferred Medication Name

(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided for each treatment group and overall. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

[redacted]

7.7 Study Drug Exposure and Compliance

Analysis Set:

Safety Analysis Set

Analysis Variables:

Duration of Exposure to Study Drug (days)

[Min<= - <10, 10<= - <12, 12<= - <=14, 14< - <=Max]

Study Drug Compliance (%)

TAK-438 or Esomeprazole

[Min<= - <70.0, 70.0<= - <85.0, 85.0<= - <=Max]

Amoxicillin

[Min<= - <70.0, 70.0<= - <85.0, 85.0<= - <=Max]

Clarithromycin

[Min<= - <70.0, 70.0<= - <85.0, 85.0<= - <=Max]

Bismuth Potassium Citrate

[Min<= - <70.0, 70.0<= - <85.0, 85.0<= - <=Max]

Analytical Methods:

(1) Study Drug Exposure and Compliance

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.8 Efficacy Analysis

The FAS will be the main analysis set used. The PPS will be used for an analysis performed secondarily on the primary endpoint in order to examine the robustness of the results.

7.8.1 Primary Endpoint

Analysis Set:

FAS

PPS

Analysis Variables:

Proportion of all HP+ subjects with successful HP eradication after the double-blind treatment period, as determined by ^{13}C-UBT at Week 4 post-treatment

Analytical Methods:

[redacted]

(1) Primary Analysis

The following analyses will be conducted using the FAS. Subjects whose HP eradication status determined by ^{13}C-UBT at Week 4 post-treatment is missing will be excluded from the analyses.

Frequency distributions of HP eradication status (Success/Failure) at Week 4 post-treatment as well as the proportion of subjects with successful HP eradication and its 2-sided 95% exact CI will be provided for each treatment group. The proportion difference between treatment groups and its 2-sided 95% Wald CI will also be provided.

Noninferiority of TAK-438 to esomeprazole will be evaluated using Farrington and Manning test with a noninferiority margin of 10%, and superiority of TAK-438 to esomeprazole will be evaluated using a score test if and only if the noninferiority test achieves statistical significance at either of the interim analysis or the final analysis. If the test for noninferiority is statistically significant at the interim analysis, no further analysis for noninferiority will be performed for statistical testing purposes.

The hypotheses to be evaluated in the noninferiority test are:

$$H_0: p_{TAK\text{-}438} \leq p_{esomeprazole} - \delta$$

$$H_A: p_{TAK\text{-}438} > p_{esomeprazole} - \delta,$$

and the hypotheses to be evaluated in the superiority test are:

$$H_0: p_{TAK\text{-}438} \leq p_{esomeprazole}$$

$$H_A: p_{TAK\text{-}438} > p_{esomeprazole},$$

where $p_{TAK\text{-}438}$ and $p_{esomeprazole}$ are the proportion of subjects with successful HP eradication at Week 4 post-treatment for TAK-438 and esomeprazole groups, respectively, and δ is the noninferiority margin (10%).

There are 2 analyses planned in this study: 1 interim analysis and the final analysis. At the interim analysis, sample size re-estimation will also be performed based on the conditional powers for noninferiority and superiority tests. Inflation of type 1 error rate associated with multiple testing (noninferiority/superiority, interim analysis/final analysis) will be controlled using the closed testing procedure and O'Brien-Fleming type alpha spending function. Inflation of type 1 error rate associated with the sample size re-estimation will be controlled using Cui-Hung-Wang test [1] at the final analysis based on the stage-wise test statistics by Farrington and Manning test for noninferiority and score test for superiority. The actual critical values for the interim analysis and the final analysis, and the actual weights for Cui-Hung-Wang test will be determined based on the observed information fraction in the first stage and the initial sample size for the primary analysis of 400.

(2) Secondary Analysis

[redacted]

The same analyses as those in the primary analysis will be conducted using the PPS.

(3) Other Analysis

In order to evaluate the impact of subjects whose HP eradication status determined by ^{13}C-UBT at Week 4 post-treatment is missing, the following two types of analyses will be conducted including:

1) All subjects in the FAS whose HP eradication status determined by ^{13}C-UBT post-baseline is available (i.e. without applying visit window of ^{13}C-UBT in Table 7.a., and excluding subjects whose HP eradication status post-baseline is missing).

2) All subjects in the FAS, where i) HP eradication status determined by ^{13}C-UBT post-baseline will be used for subjects whose HP eradication status is available post-baseline, and ii) HP eradication status will be treated as Failure for subjects whose HP eradication status post-baseline is missing.

For both of the analyses 1) and 2) above, frequency distributions of HP eradication status (Success/Failure) at Week 4 post-treatment as well as the proportion of subjects with successful HP eradication and its 2-sided 95% exact CI will be provided for each treatment group. The proportion difference between treatment groups and its 2-sided 95% Wald CI will also be provided.

7.8.2 Secondary Endpoint

Not applicable.

7.8.3 Additional Efficacy Endpoint

Analysis Set:

FAS

Analysis Variables:

Proportion of baseline clarithromycin resistant HP+ subjects with successful HP eradication after the double-blind treatment period, as determined by ^{13}C-UBT at Week 4 post-treatment

Analytical Methods:

The following analyses will be conducted for subjects in the FAS who are clarithromycin resistant at baseline and whose HP eradication status determined by ^{13}C-UBT at Week 4 post-treatment is non-missing.

Frequency distributions of HP eradication status (Success/Failure) at Week 4 post-treatment as well as the proportion of subjects with successful HP eradication and its 2-sided 95% exact CI will be provided for each treatment group. The proportion difference between treatment groups and its 2-sided 95% Wald CI will also be provided.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Adjustments for covariates are currently not planned in this study.

7.8.4.2 Handling of Dropouts or Missing Data

Missing test results will not be used for hypothesis testings and estimations unless otherwise specified.

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values greater than or equal to the upper limit of quantification will be treated as the upper limit value when calculating the descriptive statistics.

7.8.4.3 Multicenter Studies

Evaluation of treatment-by-center interaction is currently not planned in this study.

7.8.4.4 Multiple Comparison/Multiplicity

Two types of statistical tests are planned for the primary endpoint: noninferiority and superiority, at the interim analysis and the final analysis. Inflation of type 1 error rate associated with this multiple testing will be controlled using the closed testing procedure and O'Brien-Fleming type alpha spending function. More specifically, the superiority test of TAK-438 to esomeprazole will be performed if and only if the noninferiority test of TAK-438 to esomeprazole achieves statistical significance, and the critical values for the interim and the final analyses will be calculated based on the O'Brien-Fleming type alpha spending function. Also, inflation of type 1 error rate associated with the sample size re-estimation will be controlled using Cui-Hung-Wang test [1] at the final analysis.

7.8.4.5 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary endpoint using the FAS, a secondary analysis will also be performed using the PPS to examine the robustness of the results.

7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

For the primary endpoint, noninferiority of TAK-438 to esomeprazole will be evaluated with a noninferiority margin of 10% using Farrington and Manning test as described in 7.8.1 (1) Primary Analysis.

In phase 3 studies of PPI-based triple therapy (PPI, amoxicillin and clarithromycin) in HP+ subjects, the proportions of subjects with successful HP eradication were 86.4-89.2% [2], 78.8-83.0% [3], and 85.7-91.4% [4] for lansoprazole, omeprazole, and rabeprazole, respectively, showing the variation in the results greater than 10% (78.8-91.4%).

On the other hand, very low percentage of HP eradication were observed for lansoprazole or amoxicillin monotherapy. The proportions of subjects with successful HP eradication for

[redacted]

lansoprazole monotherapy were 0.0% and 4.4% for subjects with gastric ulcer and duodenal ulcer, respectively, in the phase 3 study comparing lansoprazole monotherapy and lansoprazole-based triple therapy (lansoprazole, amoxicillin and clarithromycin) [2]. The proportions of subjects with successful HP eradication were both 0% for lansoprazole or amoxicillin monotherapy in a study evaluating lansoprazole and amoxicillin dual therapy [5].

Furthermore, host factors, such as drug metabolism, as well as factors such as drug resistance may have some effects on HP eradication result.

For these reasons, the noninferiority margin of 10% is considered appropriate and used in the primary analysis of this study although limited data are available for the efficacy of PPI-based bismuth-containing quadruple therapy (PPI, amoxicillin, clarithromycin and bismuth potassium citrate).

7.8.4.7 Examination of Subgroups

Analysis Set:

FAS

Analysis Variables:

Proportion of all HP+ subjects with successful HP eradication after the double-blind treatment period, as determined by ^{13}C-UBT at Week 4 post-treatment

Subgroups:

Age (years)	[Min<= - <65, 65<= - <=Max]
Gender	[Male, Female]
Clarithromycin Resistant	[Yes, No]
Amoxicillin Resistant	[Yes, No]

Analytical Methods:

(1) Subgroup analysis of proportion of subjects with successful HP eradication at Week 4 post-treatment

For each subgroup, the following analyses will be conducted. Subjects whose HP eradication status determined by ^{13}C-UBT at Week 4 post-treatment is missing will be excluded from the analyses.

Frequency distributions of HP eradication status (Success/Failure) at Week 4 post-treatment as well as the proportion of subjects with successful HP eradication and its 2-sided 95% exact CI will be provided for each treatment group. The proportion difference between treatment groups and its 2-sided 95% Wald CI will also be provided.

[redacted]

7.9 Safety Analysis

7.9.1 Adverse Events

7.9.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Relationship to Study Drug	[Related, Not Related]
Intensity	[Mild, Moderate, Severe]

Analytical Methods:

The following summaries will be provided for each treatment group.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
2) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

[redacted]

Number of subjects

- Summaries for 2) and 6)

  A subject with occurrences of TEAE in both categories (i.e., Related and Not Related) will be counted once in the Related category.

- Summary for 3)

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2) , 3) , and 6)

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.9.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Intensity [Mild, Moderate, Severe]

Analytical Methods:

The following summaries will be provided using frequency distribution for each treatment group.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

[redacted]

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(8) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(9) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(10) Drug-Related Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(11) Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(12) Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(13) Most Frequent Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

Most frequent TEAEs refer to PTs whose percentages are at least 2% in any one of the treatment groups.

Most frequent non-serious TEAEs refer to PTs whose percentages are at least 5% in any one of the treatment groups. If there are no PTs that meet this criterion, the threshold will be lowered to 2%. The number of subjects who experienced any one of the most frequent non-serious TEAEs will also be displayed in this summary.

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT.

[redacted]

- Summary tables for (5) and (6)

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity.

7.9.1.3 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

7.9.2 Clinical Laboratory Evaluations

7.9.2.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Erythrocytes (RBC), Leukocytes (WBC), Hemoglobin, Hematocrit, Platelets, Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes

Serum Chemistry

ALT, ALP, AST, γ-GTP, TB, Direct Bilirubin, LDH, CK (CPK), Albumin, Total Protein, Creatinine, BUN, Urate, Total Cholesterol, Triglycerides (Fasting), Glucose (Fasting), Potassium, Sodium, Magnesium, Calcium, Phosphate, Chloride

[redacted]

Visit:

Baseline, End of Treatment

Analytical Methods:

For each variable, summaries (1) and (2) will be provided by treatment group.

For applicable variables, summaries (3) and (4) will be provided by treatment group.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Summary of Shifts of Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Parameters

Overall frequency distributions of MAV after baseline will be provided. If a laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(4) Number and Percentage of Subjects with Elevated Liver Enzyme Laboratory Parameters

Overall frequency distributions of elevated hepatic parameters after baseline will be provided. Further details are given in Appendix.

7.9.2.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

Protein

Glucose

Visit:

Baseline, End of Treatment

Analytical Methods:

For each variable, summary (1) will be provided by treatment group.

[redacted]

(1) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

7.9.3 Vital Signs and Weight

Analysis Set:

Safety Analysis Set

Analysis Variables:

Body Temperature

Systolic Blood Pressure

Diastolic Blood Pressure

Respiration Rate

Pulse Rate

Weight

Visit:

Body Temperature, Systolic Blood Pressure, Diastolic Blood Pressure, Respiration Rate, Pulse Rate:

Baseline, End of Treatment

Weight:

Baseline, Week 4 Post-Treatment

Analytical Methods:

For each variable, summary (1) will be provided by treatment group.

For applicable variables, summary (2) will be provided by treatment group.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters

Overall frequency distributions of MAV after baseline will be provided. If a vital sign parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

[redacted]

7.9.4 12-Lead ECGs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Heart Rate

RR Interval

PR Interval

QRS Interval

QT Interval

QTcF Interval

Interpretation

[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]

Visit:

Baseline, End of Treatment

Analytical Methods:

For each variable other than 12-lead ECG interpretations, summary (1) will be provided by treatment group.

For applicable variables, summary (2) will be provided by treatment group.

For 12-lead ECG interpretation, summary (3) will be provided by treatment group.

(1) Summary of ECG Parameters and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters

Overall frequency distributions of MAV after baseline will be provided. If an ECG parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(3) Summary of Shift of 12-lead ECG Interpretation

Shift table showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

[redacted]

7.9.5 Other Observations Related to Safety

Not applicable.

7.10 Interim Analysis

A single interim analysis will be conducted after approximately 200 evaluable subjects in total have been assessed for the primary endpoint. Statistical analyses for the primary endpoint at the interim analysis include noninferiority test by Farrington and Manning test and superiority test by score test, and calculation of conditional powers for noninferiority test and superiority test for the purpose of sample size re-estimation. The decisions taken after the interim analysis are early stopping for efficacy (noninferiority only or both noninferiority and superiority), study continuation without sample size increase, or study continuation with sample size increase.

Type 1 error rate will be controlled by O'Brien-Fleming type alpha spending function and Cui-Hung-Wang test (for final analysis only). The actual critical values for the interim analysis and the final analysis, and the actual weights for Cui-Hung-Wang test will be determined based on the observed information fraction in the first stage and initial sample size for the primary analysis of 400.

If the test for noninferiority is statistically significant at the interim analysis, no further analysis for noninferiority will be performed for statistical testing purposes.

7.11 Changes in the Statistical Analysis Plan

The analyses in the statistical analysis plan do not differ from the analyses specified in the protocol.

[redacted]

8.0 REFERENCES

[1] Cui, L., Hung, HMJ. and Wang, S-J. (1999). Modification of sample size in group sequential clinical trials. *Biometrics* **55**, 853-7.

[2] Asaka, M., Sugiyama, T., Kato, M., Satoh, K., Kuwayama, H., Fukuda, Y., ... & Kobayashi, S. (2001). A multicenter, double-blind study on triple therapy with lansoprazole, amoxicillin and clarithromycin for eradication of *Helicobacter pylori* in Japanese peptic ulcer patients. Helicobacter, **6**(3), 254-261.

[3] Kuwayama, H., Luk, G., Yoshida, S., Nakamura, T., Kubo, M., Uemura, N., ... & Nakazawa, S. (2005). Efficacy of a low-dose omeprazole-based triple-therapy regimen for *Helicobacter pylori* eradication independent of cytochrome P450 genotype. Clinical drug investigation, **25**(5), 293-305.

[4] Kuwayama, H., Asaka, M., Sugiyama, T., Fukuda, Y., Aoyama, N., Hirai, Y., ... & Japan Rabeprazole Study Group. (2007). Rabeprazole-based eradication therapy for *Helicobacter pylori*: a large-scale study in Japan. Alimentary pharmacology & therapeutics, **25**(9), 1105-1113.

[5] Harford, W., Lanza, F., Arora, A., Graham, D., Haber, M., Weissfeld, A., ... & Siepman, N. (1996). Double-blind, multicenter evaluation of lansoprazole and amoxicillin dual therapy for the cure of *Helicobacter pylori* infection. Helicobacter, **1**(4), 243-250.

[redacted]

9.0 APPENDIX

9.1 Criteria for Markedly Abnormal Values

1) Hematology, Serum Chemistry, Vital Signs, and 12-lead ECG

For each parameter, all evaluable data (i.e., non-missing data) obtained after baseline and up to Follow-up Day 35 will be classified as a MAV or not. The criteria in the table below will be used.

Table 9.a MAV Criteria for Hematology

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Erythrocytes (RBC)	<0.8×LLN	>1.2×ULN
Leukocytes (WBC)	<0.5×LLN	>1.5×ULN
Hemoglobin	<0.8×LLN	>1.2×ULN
Hematocrit	<0.8×LLN	>1.2×ULN
Platelets ($\times 10^9$/L)	<75	>600
Neutrophils	<0.5×LLN	>1.5×ULN
Eosinophils	-	>2×ULN
Basophils	-	>3×ULN
Monocytes	-	>2×ULN
Lymphocytes	<0.5×LLN	>1.5×ULN

Table 9.b MAV Criteria for Serum Chemistry

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
ALT	-	>3×ULN
ALP	-	>3×ULN
AST	-	>3×ULN
γ-GTP	-	>3×ULN
TB (μmol/L)	-	>34.2
Direct Bilirubin	-	>2×ULN
CK (CPK)	-	>5×ULN
Albumin (g/L)	<25	-
Total Protein	<0.8×LLN	>1.2×ULN
Creatinine (μmol/L)	-	>177
BUN (mmol/L)	-	>10.7
Total Cholesterol (mmol/L)	-	>7.72
Triglycerides (Fasting)	-	>2.5×ULN
Glucose (Fasting) (mmol/L)	<2.8	>19.4

[redacted]

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Potassium (mmol/L)	<3.0	>6.0
Sodium (mmol/L)	<130	>150
Magnesium (mmol/L)	<0.5	>1.2
Calcium (mmol/L)	<1.75	>2.88
Chloride (mmol/L)	<75	>126

Table 9.c MAV Criteria for Vital Signs

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Body Temperature (°C)	<35.6	>37.7
Systolic Blood Pressure (mmHg)	<85	>180
Diastolic Blood Pressure (mmHg)	<50	>110
Pulse Rate (bpm)	<50	>120

Table 9.d MAV Criteria for 12-lead ECG

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Heart Rate (bpm)	<50	>120
QT Interval (msec)	<=50	>=460
QTcF Interval (msec)	<=50	• Observed value >= 500, or • Observed value >= 450 and change from baseline >= 30

For each parameter and subject, classifications will be made according to the conditions i) to iii) provided below. The lower and the upper criteria will be considered separately.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that doesn't meet the MAV criteria will be considered as a subject without MAV.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV for that parameter.

[redacted]

9.2 Criteria for Elevated Liver Enzyme

All evaluable data (i.e., non-missing data) obtained after baseline and up to Follow-up Day 35 will be used to determine whether each criteria for elevated liver enzyme in the table below is met or not. If there is more than one parameter that need to be considered for a criteria, parameter measurements taken on the same day will be used.

Table 9.e Criteria for Elevated Liver Enzyme

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
ALT > 3xULN	ALT is greater than 3 times the ULN	ALT is non-missing and less than or equal to 3 times the ULN
ALT > 5xULN	ALT is greater than 5 times the ULN	ALT is non-missing and less than or equal to 5 times the ULN
ALT > 8xULN	ALT is greater than 8 times the ULN	ALT is non-missing and less than or equal to 8 times the ULN
ALT > 3xULN with TB > 2xULN	ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
AST > 3xULN	AST is greater than 3 times the ULN	AST is non-missing and less than or equal to 3 times the ULN
AST > 5xULN	AST is greater than 5 times the ULN	AST is non-missing and less than or equal to 5 times the ULN
AST > 8xULN	AST is greater than 8 times the ULN	AST is non-missing and less than or equal to 8 times the ULN
AST > 3xULN with TB > 2xULN	AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
ALT or AST > 3xULN	Either ALT or AST is greater than 3 times the ULN	Both ALT and AST are non-missing and less than or equal to 3 times the ULN
ALT or AST > 5xULN	Either ALT or AST is greater than 5 times the ULN	Both ALT and AST are non-missing and less than or equal to 5 times the ULN
ALT or AST > 8xULN	Either ALT or AST is greater than 8 times the ULN	Both ALT and AST are non-missing and less than or equal to 8 times the ULN
ALT or AST > 3xULN with TB > 2xULN	Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - Both ALT and AST are non-missing and less than or equal to 3 times the ULN. - Total bilirubin is non-missing and less than or equal to twice the ULN.
ALT and AST > 3xULN	Both ALT and AST are greater than 3 times the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

[redacted]

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
ALT and AST > 5xULN	Both ALT and AST are greater than 5 times the ULN	Either ALT is non-missing and less than or equal to 5 times the ULN, or AST is non-missing and less than or equal to 5 times the ULN
ALT and AST > 8xULN	Both ALT and AST are greater than 8 times the ULN	Either ALT is non-missing and less than or equal to 8 times the ULN, or AST is non-missing and less than or equal to 8 times the ULN
ALT and AST > 3xULN with TB > 2xULN	Both ALT and AST are greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - ALT is non-missing and less than or equal to 3 times the ULN - AST is non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALP > 3xULN	ALP is greater than 3 times the ULN	ALP is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN with ALT > 3xULN	Both ALP and ALT are greater than 3 time the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or ALT is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN with AST > 3xULN	Both ALP and AST are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

For each criteria and subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject who met criteria (a) at least once after baseline will be considered to have met the criteria for elevated liver enzyme.

ii) If condition i) is not met but if criteria (b) is met at least once after baseline, then the subject will be considered to have not met the criteria for elevated liver enzyme.

iii) If neither i) nor ii) is met, then the subject will be excluded from the analysis for the criteria for elevated liver enzyme.

[redacted]

9.3 Statistical Analysis Plan Version 3 Summary of Changes

The changes from Statistical Analysis Plan version 2 are as follows:

- 7.1.1 Definition of TEAE was revised to address adverse events whose start date is completely or partially missing.
  - Old text: An adverse event whose date of onset occurs on or after the start of study drug
  - Revised text: An adverse event whose date of onset occurs on or after the start of study drug. An event whose type entered into the EDC is Adverse Event will be treated as a TEAE if its start date is missing.
- 7.8.1 (3) Other Analysis was added to evaluate the impact of subjects whose HP eradication status determined by 13C-UBT at Week 4 post-treatment is missing.
- 7.8.4.6 Active-Control Studies Intended to Show Equivalence or Non-Inferiority was revised to describe the rationale for the noninferiority margin used in the study.
  - Old text: For the primary endpoint, noninferiority of TAK-438 to esomeprazole will be evaluated with a noninferiority margin of 10% using Farrington and Manning test as described in 7.8.1 (1) Primary Analysis.
  - Revised text: For the primary endpoint, noninferiority of TAK-438 to esomeprazole will be evaluated with a noninferiority margin of 10% using Farrington and Manning test as described in 7.8.1 (1) Primary Analysis.

    In phase 3 studies of PPI-based triple therapy (PPI, amoxicillin and clarithromycin) in HP+ subjects, the proportions of subjects with successful HP eradication were 86.4-89.2% [2], 78.8-83.0% [3], and 85.7-91.4% [4] for lansoprazole, omeprazole, and rabeprazole, respectively, showing the variation in the results greater than 10% (78.8-91.4%).

    On the other hand, very low percentage of HP eradication were observed for lansoprazole or amoxicillin monotherapy. The proportions of subjects with successful HP eradication for lansoprazole monotherapy were 0.0% and 4.4% for subjects with gastric ulcer and duodenal ulcer, respectively, in the phase 3 study comparing lansoprazole monotherapy and lansoprazole-based triple therapy (lansoprazole, amoxicillin and clarithromycin) [2]. The proportions of subjects with successful HP eradication were both 0% for lansoprazole or amoxicillin monotherapy in a study evaluating lansoprazole and amoxicillin dual therapy [5].

    Furthermore, host factors, such as drug metabolism, as well as factors such as drug resistance may have some effects on HP eradication result.

    For these reasons, the noninferiority margin of 10% is considered appropriate and used in the primary analysis of this study although limited data are available for the efficacy of PPI-based bismuth containing quadruple therapy (PPI, amoxicillin, clarithromycin and bismuth potassium citrate).

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	31-Aug-2021 14:10 UTC