STATISTICAL ANALYSIS PLAN

NCT Number: NCT04753437

Study Title: A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With Vonoprazan Versus Quadruple Therapy With Esomeprazole

Study Number: Vonoprazan-1001

SAP Version and Date: Version

Version 2.0: 10-November-2021

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Study Title: *A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With Vonoprazan Versus Quadruple Therapy with Esomeprazole*

Phase: 1

Version: 2.0

Date: 08-Nov-2021

Prepared by: [redacted], Statistical & Quantitative Sciences Japan

Based on:

Protocol Version: 2 (Amendment 1)

Protocol Date: 23-June-2021

[redacted]

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

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REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
1.0 (Original version)	12-Apr-2021	[Not Applicable]
2.0	08-Nov-2021	2.0 STUDY DESIGN, 4.0 SAMPLE-SIZE DETERMINATION Updated sample size from 34 to 42 (maximum 46) based on Protocol Amendment 1 from Version 1. 5.2 Pharmacokinetic Analysis Set Clarified with that the additional / detail definition of PK Analysis Set is defined in CPAP. 9.2.3.2 Handling of Vital Signs and 12-Lead ECGs Deleted Time Windows of Vistal Sign related evening dose, because vital sign is not captured at evening dose.

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ABBREVIATIONS

AE	adverse event
Ae_τ	amount of drug excreted in urine during a dosing interval
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AUC_τ	area under the concentration-time curve during a dosing interval
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
C_{max}	maximum observed plasma concentration
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
GGT	γ-glutamyl transferase
HP	*Helicobacter pylori*
LDH	lactate dehydrogenase
LLN	lower limit of normal
MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic(s)
PT	Preferred Term (MedDRA)
PTE	pretreatment event
QTcF	QT interval corrected by Fridericia's method
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class (MedDRA)
TAK-438	Vonoprazan
TAK-438F	freebase of TAK-438
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO Drug	World Health Organization Drug Dictionary

[redacted]

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To evaluate the safety, tolerability, and PK of quadruple therapy with bismuth, clarithromycin, amoxicillin, and vonoprazan versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and esomeprazole.

1.1.2 Secondary Objective

Not Applicable.

1.1.3 Additional Objective

Not Applicable.

1.2 Endpoints

1.2.1 Primary Endpoint

The primary endpoint of the study is:

- *To evaluate plasma PK parameters of bismuth potassium citrate (600 mg) when coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), andvonoprazan (20 mg BID), and when coadministered with clarithromycin (500 mg BID),amoxicillin (1000 mg BID), and esomeprazole (20 mg BID):*
  - *C_{max} at Day 14.*
  - *The area under the plasma concentration-time curve during a dosing interval (area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval [AUC_{τ}]) at Day 14.*
  - *The amount of drug excreted in urine during a dosing interval (Ae_{τ}) at Day 14.*

1.2.2 Secondary Endpoints

1.2.2.1 Key Secondary Endpoint

Not Applicable.

1.2.2.2 Other Secondary Endpoints

The secondary endpoints will be assessed through evaluation of the following parameters:

- *Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).*
- *Percentage of subjects who discontinue due to an adverse event (AE).*

[redacted]

1.2.3 Exploratory Endpoint

Evaluation of plasma drug concentrations at the end of dosing intervals (C_{trough}) of vonoprazan and esomeprazole.

1.2.4 Safety Endpoints

Safety endpoints are as follows:

- *Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once post dose.*
- *Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once post dose.*
- *Percentage of subjects who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once post dose.*

1.2.5 Other Endpoints

Not Applicable.

1.3 Estimand

Not Applicable.

2.0 STUDY DESIGN

A Phase 1, double-blind, parallel group study in healthy subjects with Helicobacter pylori (H pylori–positive) to evaluate the safety, tolerability, and pharmacokinetics (PK) of a quadruple therapy with bismuth, clarithromycin, amoxicillin, and vonoprazan versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and esomeprazole. Approximately 42 (maximum 46 subjects) H pylori–positive healthy subjects aged 18 to 60 years, inclusive, who are considered eligible based on the inclusion and exclusion criteria, will participate in this study. All subjects will be enrolled and randomized to 1 of the 2 treatment groups as indicated in the schematic in Protocol, Section2.0.

The treatment phase will consist of quadruple therapy twice daily (BID) with bismuth potassium citrate (600 mg [equivalent to 220 mg bismuth]), BID clarithromycin (500 mg), amoxicillin (1000 mg), and vonoprazan (20 mg) (Group B) or quadruple therapy BID with bismuth potassium citrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and esomeprazole (20 mg) (Group A) administered from Days 1 to 14. Subjects will be discharged on Day 15 after all procedures have been performed. The subjects who complete study treatment are to be followed-up at Week 4 post-treatment to provide a ^{13}C urea breath test (^{13}C UBT) for H pylori.

[redacted]

Study Schematic

<table>
<tr><th colspan="2">Pretreatment</th><th colspan="4">Treatment Period</th><th colspan="2">Follow-Up</th></tr>
<tr><th>Screening</th><th>Check-in Baseline</th><th colspan="3"><----------Confinement----------></th><th>Check-out</th><th>Follow-up call</th><th>Follow-up visit</th></tr>
<tr><th>Days -28 to -2</th><th>Day -1</th><th>Days 1-11</th><th>Days 12-13</th><th>Day 14</th><th>Day 15</th><th>Day 17 (+2 days)</th><th>Day 42 (+ 6 days)</th></tr>
<tr><td rowspan="4">^{13}C UBT for <i>H pylori</i></td><td rowspan="4"></td><td colspan="3">Group A: clarithromycin [a] + amoxycillin [b] + bismuth [c] + esomeprazole [d]</td><td rowspan="4"></td><td rowspan="4"></td><td rowspan="4">^{13}C UBT for H pylori</td></tr>
<tr><td colspan="3">Group B: clarithromycin [a] + amoxycillin [b] + bismuth [c] + vonoprazan [e]</td></tr>
<tr><td></td><td colspan="2">Vonoprazan PK or esomeprazole PK in plasma [f]</td></tr>
<tr><td colspan="2"></td><td>Bismuth PK in plasma and urine [g]</td></tr>
</table>

^{13}C: carbon 13 isotope; BID: twice daily; PK: pharmacokinetic(s); UBT: urea breath test.

[a] Clarithromycin 500 mg BID.

[b] Amoxycillin 1000 mg BID.

[c] Bismuth potassium citrate 600 mg BID.

[d] Esomeprazole 20 mg BID.

[e] Vonoprazan: 20 mg BID.

[f] Blood samples for vonoprazan and esomeprazole PK on Days 12-14 are to be taken predose (morning and evening).

[g] Blood samples for bismuth PK are to be taken on Day 14 predose (0 hours), 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours after the morning dose. Urine samples for bismuth PK are to be taken on Day 14 at 0 to 12 hours after the morning dose.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not Applicable.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

The study will randomize approximately 42 subjects(maximum 46 subjects, if drop-out rate from PK Analysis Set increases to more than 25%) to provide at least 80% power of showing no significant difference in plasma bismuth C_{max} and AUC_{τ} between vonoprazan and esomeprazole quadruple therapy.

5.0 ANALYSIS SETS

5.1 Safety Analysis Set

The safety analysis set will consist of subjects who received at least 1 dose of the study drug.

5.2 Pharmacokinetic Analysis Set

The PK analysis set will consist of subjects who received the study drug, completed the minimum protocol specified procedures with no significant protocol deviations, and were evaluable for the PK.

Subjects who received the study drug (bismuth/vonoprazan/esomeprazole/clarithromycin/amoxicillin) and have at least 1 measurable plasma drug concentration, after start of dosing without protocol violations or events with potential to affect the PK concentrations and who have completed minimum protocol procedures will be evaluated. The detail definition of the minimum protocol specified procedures with the potential to affect the PK concentrations will be described in the clinical pharmacology analysis plan (CPAP).

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Definitions

The following definitions and calculation formulas will be used.

- TEAE: An AE whose date of onset occurs on or after the start of study drug.
- PTE: An AE whose date of onset occurs before the start of study drug.
- Significant TEAE: any AEs (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment or significant additional concomitant therapy.
- Study Day: The day before the first dose of the study medication will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. Other study days are defined relative to Study Day 1, eg, the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2.

As for complex data handling conventions and definition of visit windows, refer to Appendix section 9.2.

6.2 Disposition of Subjects

6.2.1 Study Information

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: Date First Subject Signed Informed Consent Form
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.

6.2.2 Screen Failures

Analysis Set: All Subjects Who Were Not Randomized

Analysis Variables:

Age (years)	[Min<= - <30, 30<= - <50, 50<= - <=Max]
Gender	[Male, Female]
Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported]

Analytical Methods: **(1) Screen Failures**
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

6.2.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status	[Yes, No]
Primary Reason for Subject Not Being Eligible	[Pretreatment Event/Adverse Event, Did Not Meet Inclusion Criteria or Did Meet Exclusion Criteria, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Other]

Analytical Methods: **(1) Eligibility for Randomization**
Frequency distributions will be provided. When calculating the percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

[redacted]

6.2.4 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variables:	TAK-438/Esomeprazole Study Drug Administration Status	[No]
	Reason for Not Being Treated	[Pretreatment Event/Adverse Event, Liver Function Test Abnormalities, Lost to Follow-Up, Pregnancy, Significant Protocol Deviation, Study Termination, Voluntary Withdrawal, Other]
	TAK-438/Esomeprazole Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of TAK-438/Esomeprazole Study Drug	[Pretreatment Event/Adverse Event, Liver Function Test Abnormalities, Lost to Follow-Up, Pregnancy, Significant Protocol Deviation, Study Termination, Voluntary Withdrawal, Other]

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 of study drug, the total number of subjects who prematurely discontinued the study drug will be used as the denominator.

(2) Flow Chart of Subject Distribution

Flow chart will be provided.

6.2.5 Protocol Deviations and Analysis Sets

Protocol Deviations

Analysis Set:	Randomized Set	
Analysis Variables:	Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]

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.

[redacted]

Analysis Sets

Analysis Set:	Randomized Set	
Analysis Variables:	Analysis Sets	
	PK Analysis Set	[Included]
	Safety Analysis Set	[Included]
Analytical Methods:	**(1) Analysis Sets**	
	Frequency distributions will be provided by treatment group and overall.	

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Analysis Set:	PK Analysis Set	
	Safety Analysis Set	
Analysis Variables:	Age (years)	[Min<= - <30, 30<= - <50, 50<= - <=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) (Baseline)	[Min<= - <50.0, 50.0<= - <60.0, 60.0<= - <70.0, 70.0<= - <80.0, 80.0<= - <=Max]
	BMI (kg/m^2) (Baseline)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	Smoking Classification	[Never, Former, Current]
	Consumption of Alcohol	[Never, Former, Current]
	Consumption of Caffeine	[Never, Former, Current]
	CYP2C19 Genotype	[*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3]
Analytical Methods:	**(1) Summary of Demographics and Other Baseline Characteristics**	
	Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.	

6.3.2 Medical History and Concurrent Medical Conditions

Medical history is defined as significant conditions or diseases that stopped at or prior to the time of informed consent. Concurrent medical conditions are defined as significant conditions ongoing or present at the time of informed consent.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0) coding system.

There will be no analysis of medical history and concurrent medical conditions.

6.4 Medication History and Concomitant Medications

Medication history information includes any medication relevant to eligibility criteria stopped prior to signing of informed consent. Concomitant medications are recorded on the eCRF and include any medications, other than the study drug, taken at any time between informed consent and on or prior to the last dose of study drug.

Medication history and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO Drug) version Global B3 March 2021.

There will be no analysis of medication history and concomitant medications.

6.5 Study Drug Exposure and Compliance

TAK-438/Esomeprazole and Bismuth Exposure and Compliance

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Duration of Exposure to Study Drug (days)	
	Study Drug Compliance (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=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.	

Clarithromycin and Amoxicillin Exposure and Compliance

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Duration of Exposure to Study Drug (days)	
	Study Drug Compliance (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=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.	

6.6 Efficacy Analysis

Not applicable.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

The contents of PK analysis will be described in the clinical pharmacology analysis plan (CPAP).

[redacted]

6.8 Other Analyses

H Pylori Urea Breath Test

Analysis Set:	Safety Analysis Set	
Analysis Variable:	H Pylori Urea Breath Test	[Positive, Negative]
Visit	Screening and Day 42	
Analytical Methods:	**(1) Summary of H Pylori Urea Breath Test**	
	Frequency distributions will be provided by treatment group and overall.	

6.9 Safety Analysis

6.9.1 Adverse Events

6.9.2 Overview of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variables:	TEAE	
Categories:	Relationship to Study Drug	
	Relationship to TAK-438/ Esomeprazole	[Related, Not Related]
	Relationship to Bismuth	[Related, Not Related]
	Relationship to Clarithromycin	[Related, Not Related]
	Relationship to Amoxicillin	[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 [TAK-438/Esomeprazole, Bismuth, Clarithromycin, Amoxicillin] (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 TAK-438/Esomeprazole Study Drug Discontinuation (number of events, number and percentage of subjects)
5) Relationship of Treatment-Emergent Adverse Events Leading to TAK-438/Esomeprazole Study Drug Discontinuation (number of events, number and percentage of subjects)
6) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
7) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug [TAK-438/Esomeprazole, Bismuth, Clarithromycin, Amoxicillin] (number of events, number and percentage of subjects)
8) Serious Treatment-Emergent Adverse Events Leading to TAK-438/Esomeprazole Study Drug Discontinuation (number of events, number and percentage of subjects)

9) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and percentage of subjects)

10) Significant Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

11) Relationship of Significant Treatment-Emergent Adverse Events to Study Drug [TAK-438/Esomeprazole, Bismuth, Clarithromycin, Amoxicillin] (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2), 7) and 11)
  A subject with occurrences of TEAE in both categories (ie, 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), 7) and 11)
  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.

6.9.3 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.

Drug-related TEAEs will be summarized for TAK-438/Esomeprazole, Bismuth, Clarithromycin and Amoxicillin, respectively.

(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 [TAK-438/Esomeprazole, Bismuth, Clarithromycin, Amoxicillin]

(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 [TAK-438/Esomeprazole, Bismuth, Clarithromycin, Amoxicillin]

(7) Treatment-Emergent Adverse Events Leading to TAK-438/Esomeprazole Study Drug Discontinuation by System Organ Class and Preferred Term

[redacted]

(8) Drug-Related Treatment-Emergent Adverse Events Leading to TAK-438/Esomeprazole Study Drug Discontinuation by System Organ Class and Preferred Term

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

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

(11) Drug-Related Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term [TAK-438/Esomeprazole, Bismuth, Clarithromycin, Amoxicillin]

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. Percentages will be based on the number of subjects in the safety analysis set.
- 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. Percentages will be based on the number of subjects in the safety analysis set.

6.9.4 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.

6.9.5 Adverse Events of Special Interest

Not applicable.

Additionally, as for Significant TEAE, refer to section 6.1.

[redacted]

6.9.6 Other Safety Analysis

6.9.6.1 Clinical Laboratory Evaluations

Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variables: Hematology

RBCs ($\times 10^{12}$/L)	WBCs ($\times 10^{9}$/L)	Hemoglobin (g/L)
Hematocrit (%)	Platelets ($\times 10^{9}$/L)	
White Blood Cell Fractions (Neutrophils (%), Eosinophils (%), Basophils (%), Monocytes (%), Lymphocytes (%))		
PT/INR	aPTT (sec)	Reticulocyte count ($\times 10^{12}$/L)
Serum Chemistry		
ALT (U/L)	Alkaline phosphatase (U/L)	AST (U/L)
GGT (U/L)	Total Bilirubin (µmol/L)	Direct Bilirubin (µmol/L)
Creatine kinase (U/L)	Creatine kinase MB (ng/mL)	Albumin (g/L)
Total Protein (g/L)	Serum creatinine (µmol/L)	LDH (U/L)
Uric Acid (µmol/L)	HDL Cholesterol (mmol/L)	LDL Cholesterol (mmol/L)
Triglycerides (mmol/L)	Glucose (mmol/L)	Potassium (mmol/L)
Sodium (mmol/L)	Magnesium (mmol/L)	Calcium (mmol/L)
Chloride (mmol/L)	Amylase (U/L)	Blood urea nitrogen (mmol/L)

Visit: Baseline, Day 5, 8, 12, 13, 14, 15

Analytical Methods: The following summaries will be provided for each treatment group.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided for each visit.

(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 Test results
Overall frequency distributions of MAV during treatment phase will be provided. If a laboratory test result has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

[redacted]

Urinalysis

Analysis Set:	Safety Analysis Set	
Analysis Variables:	pH	[Min<= - <5.0, 5.0<= - <=8.5, 8.5< - <=Max]
	Specific gravity	[Min<= - <1.005, 1.005<= - <=1.030, 1.030< - <=Max]
	Protein	[Negative, Positive]
	Glucose	[Negative, Positive]
	Nitrites	[Negative, Positive]
	Bilirubin	[Negative, Positive]
	Hemoglobin	[Negative, Positive]
	Ketones	[Negative, Positive]
	Leucocytes	[Negative, Positive]
	Urobilinogen	[Negative, Positive]
Visit:	Baseline, Day 5, 8, 12, 13, 14, 15	

Analytical Methods: The following summaries will be provided for each treatment group.

(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.

6.9.6.2 Vital Signs

Analysis Set:	Safety Analysis Set
Analysis Variables:	Body Temperature (C)
	Systolic Blood Pressure (mmHg)
	Diastolic Blood Pressure (mmHg)
	Respiratory Rate (bpm)
	Pulse (bpm)
Visit:	Baseline, Day 1 to 15 at Predose

Analytical Methods: For each variable, following summary will be provided by treatment group.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters
Overall frequency distributions of MAV during treatment phase 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.

6.9.6.3 12-Lead ECGs

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Heart Rate (bpm)	
	RR Interval (msec)	
	PR Interval (msec)	
	QT Interval (msec)	
	QTcF Interval (msec)	
	QRS Interval (msec)	
	12-Lead ECG Interpretation	["Within Normal Limits", "Abnormal, Not Clinically Significant", "Abnormal, Clinically Significant", "Not Evaluable"]
Visit:	Baseline, Day 3, Day 7 at Pre–morning dose, Day 14 at Pre–morning dose, 1, 2, 4 hour Post-morning dose, Day 15	
Analytical Methods:	For each variable other than 12-lead ECG interpretations, summary (1) will be provided by treatment group.	
	For 12-lead ECG interpretations, summary (3) will be provided by treatment group.	

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
Overall frequency distributions of MAV during treatment phase 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 Shifts of ECG Parameters
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

6.10 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

Not applicable.

6.11 Interim Analyses

Not applicable.

6.12 Data Monitoring Committee/Internal Review Committee

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Changes made from the previous version of the SAP that have a **material impact to the planned statistical analysis methods** are described below. In addition, there were textual changes purely to improve the flow, organization and clarity. As these represent cosmetic changes with no impact to the planned statistical analyses, they are not included in the table below.

SAP Section	Impacted Text (shown in bold)	Change	Rationale for Change
(Not applicable)			

The other changes from Statistical Analysis Plan version 1 are as follows:

- 5.2 Clarified with the additional / detail definition of PK Analysis Set is in CPAP
  - Old text: The definition of PK analysis set will be described in the clinical pharmacology analysis plan (CPAP).
  - Revised text: The detail definition of PK analysis set that completed the minimum protocol specified procedures with no significant protocol deviations that is potentially to affect the PK concentration will be described in the clinical pharmacology analysis plan (CPAP).
- 9.2.3.2 Deleted Time Windows of Vistal Sign related evening dose, because vital sign is not captured at evening dose.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

- Descriptive statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Duration of exposure to study medication (days): date of last dose of study medication - date of first dose of study medication + 1
- Study drug compliance (%): (number of times "Dose Start Time" was collected) / (2* Duration of exposure to study medication) *100 (rounded to 1 decimal place). Study drug compliance will be calculated each group of study drugs, 1) TAK438/Esomeprazole and Bismuth or 2) Clarithromycin and Amoxicillin.

[redacted]

- QTcF interval (msec): QT interval (msec) / (RR interval (msec) / 1000) $^{0.33}$ (rounded to the nearest whole number)
- As for laboratory test values, below the lower limit of quantification will be handled as zero.

9.2.1.1 Criteria for Markedly Abnormal Values

Hematology, Serum Chemistry, Vital Signs, and 12-lead ECG (except Upper MAV Criteria of QTcF Interval)

For each parameter, all evaluable data (ie, non-missing data) obtained up to Day 15 will be classified as a MAV or not. The criteria in the table below will be used.

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.

Hematology

Parameter	MAV Criteria	
	Lower Criteria	**Upper Criteria**
RBCs ($\times 10^{12}$/L)	<0.8×LLN	>1.2×ULN
WBCs ($\times 10^{9}$/L)	<0.5×LLN	>1.5×ULN
Hemoglobin (g/L)	<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
aPTT (sec)		>1.5×ULN
PT/INR		>1.5

[redacted]

Serum Chemistry

Parameter	MAV Criteria	
	Lower Criteria	**Upper Criteria**
ALT (U/L)	-	>3×ULN
Alkaline phosphatase (U/L)	-	>3×ULN
AST (U/L)	-	>3×ULN
GGT (U/L)	-	>3×ULN
Total Bilirubin (µmol/L)	-	>34.2
Creatine kinase (U/L)	-	>5×ULN
Albumin (g/L)	<25	-
Total Protein (g/L)	<0.8×LLN	>1.2×ULN
Blood urea nitrogen (mmol/L)	-	>10.7
Uric acid (mmol/L)	-	>0.773
Triglycerides (mmol/L)	-	>2.5×ULN
Glucose (mmol/L)	<2.8	>19.4
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
Amylase (U/L)	-	>2×ULN
Serum creatinine (µmol/L)	-	>177

*For Uric acid, there is unit discrepancy between measurement as "Uric Acid (**µ**mol/L)" and MAV criteria as "Uric acid (**m**mol/L)"

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 (bpm)	<50	>120

[redacted]

12-Lead ECG

Parameter	MAV Criteria	
	Lower Criteria	**Upper Criteria**
Heart Rate (bpm)	<50	>120
QT Interval (msec)	<=50	>=460
QTcF Interval (msec)	<=50	-

9.2.1.2 12-lead ECG (Upper MAV Criteria of QTcF Interval)

All evaluable data (ie, non-missing data) obtained up to Day 15 will be classified as a MAV or not. The criteria in the table below will be used. Note that the observed value and the change from baseline used for classification should be measurements taken on the same day.

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

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 meets any of the following will be considered as a subject without MAV.

- Observed value is less than 450 msec and not missing.
- Change from baseline is less than 30 msec and not missing, and observed value is less than 500 msec and not missing.

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

Parameter	MAV Criteria	
	Lower Criteria	**Upper Criteria**
QTcF Interval (msec)	-	If either of the following conditions is met: • observed value >=500 • change from baseline >= 30 and observed value >=450

9.2.2 Definition of Baseline

Baseline and Screening values: The last evaluable observation (ie, non-missing) before the first dose of study medication. If no evaluable observation is obtained before the first dose, the baseline value will be missing.

[redacted]

9.2.3 Definition of Visit Windows

9.2.3.1 Handling of HP Breath Test and Laboratory Test

For each visit, all evaluable observation (ie, non-missing) 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 sampling day to the scheduled study day will be used. If there are two observations equidistant to the scheduled study day, the later observation will be used.

HP Breath Test

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Screening	-2	-28 – -2
Day 42	42	Post dose – 48

Laboratory Test

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Baseline	Study Day: -1	-28 – -1
Day 5	Study Day: 5	1 – 6
Day 8	Study Day: 8	7 – 9
Day 12	Study Day: 12	10 – 12
Day 13	Study Day: 13	13
Day 14	Study Day: 14	14
Day 15	Study Day: 15	15

9.2.3.2 Handling of Vital Signs and 12-Lead ECGs

For each visit, all evaluable observation (ie, non-missing) obtained in the corresponding time interval will be used. If more than one observation lies within the same time window, the observation with the closest sampling time to the scheduled time will be used. If there are two observations equidistant to the scheduled time, the later observation will be used.

Vital Signs

Visit	Time	Scheduled Study Day (days)	Scheduled Time from Dose* (min)		Time Interval (min) / Study Day (days) Assessment Time from Dose*
Baseline	Pre-morning dose	Study Day: 1	Morning	0	Study Day: -28 – 1
Day 2 to 14	Pre-morning dose	Study Day: 2 to 14	Morning	0	Time: -60 – 0
Day 15		Study Day: 15			Study Day: Post dose – 15

* Start Time of bismuth, TAK-438, Esomeprazole

12-Lead ECGs

Visit	Time	Scheduled Study Day (days)	Scheduled Time from Dose* (min)		Time Interval (min) / Study Day (days) Assessment Time from Dose*
Baseline	Pre-morning dose	Study Day: 1	Morning	0	Study Day: -28 – 1
Day 3	Pre-morning dose	Study Day: 3	Morning	0	Time: -60 – 0
Day 7	Pre-morning dose	Study Day: 7	Morning	0	Time: -60 – 0
Day 14	Pre-morning dose	Study Day: 14	Morning	0	Time: -60 – 0
	1 hour post-morning dose		Morning	60	Time: 0< – 90
	2 hours post-morning dose		Morning	120	Time: 90< – 180
	4 hours post-morning dose		Morning	240	Time: 180< – 300
Day 15		Study Day: 15			Study Day: Post dose – 15

* Start Time of bismuth, TAK-438, Esomeprazole

9.3 Analysis Software

SAS 9.4

[redacted]

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	10-Nov-2021 00:17 UTC