Title: A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With TAK-438 Versus Quadruple Therapy With Lansoprazole.

NCT Number: NCT02892409

SAP Approve Date: 15MAY2017

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438_115

A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With TAK-438 Versus Quadruple Therapy With Lansoprazole.

PHASE 1

Version: 2.0

Date: 15MAY2017

Prepared by:

PPD

1.0 APPROVAL SIGNATURES

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

Study Title: A Phase 1, Double-Blind, Parallel Group Study to Evaluate the Safety and Pharmacokinetics of Quadruple Therapy (Bismuth, Clarithromycin, and Amoxicillin) With TAK-438 Versus Quadruple Therapy With Lansoprazole.

TDC Approvals:

PPD Date

PPD Date

PPD Date

PPD Date

PPD Date

2.0 TABLE OF CONTENTS

3.0 LIST OF 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
AUC_∞	area under the plasma concentration-time curve from time 0 to infinity
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
CAL	clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and lansoprazole (30 mg BID)
CAT	clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and TAK-438 (20 mg BID)
CL/F	apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
CRF	case report form
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
$f_{e,\tau}$	Fraction of administered dose of drug excreted in urine during a dosing interval. Molecular weight adjustment needed for metabolites.
GGT	γ-glutamyl transferase
HP	*Helicobacter pylori*
LDH	lactate dehydrogenase
LLN	lower limit of normal
λ_z	terminal disposition phase rate constant
MAV	markedly abnormal values
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamics
PK	pharmacokinetics
PTE	pretreatment event
QTcF	QT interval corrected by Fridericia's method
SAP	statistical analysis plan
TAK-438F	freebase of TAK-438
TEAE	treatment-emergent adverse event
$t_{1/2z}$	terminal disposition phase half-life

t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration
WHO Drug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1. PRIMARY OBJECTIVES

The primary objective is to evaluate the safety, tolerability, and PK of quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and TAK-438 (20 mg) versus quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and lansoprazole (30 mg).

4.2. SECONDARY OBJECTIVES

Not applicable

4.3. ADDITIONAL OBJECTIVES

Not applicable

4.4. STUDY DESIGN

This is a phase 1, double-blind, parallel group study in HP positive subjects to evaluate the safety, tolerability, and PK of quadruple therapy with bismuth, clarithromycin, amoxicillin, and TAK-438 versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and lansoprazole.

Thirty HP positive male or female subjects aged 19 to 60 years, inclusive, considered eligible based on the inclusion and exclusion criteria, will participate in this study. All subjects will be enrolled and will be randomized to 1 of 2 treatment groups as indicated in Figure 1. One site in Asia will be selected to conduct this study.

The treatment phase consists of quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and TAK-438 (20 mg) or quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and lansoprazole (30 mg) for 14 days (Days 1 to 14). Subjects will be discharged on Day 15 after final PK blood samples are collected and all procedures performed.

Screening for potential subjects will occur between Days -28 and -2 prior to confinement at the phase 1 unit. Eligibility will be reconfirmed on Day -1. Having fasted for a minimum of 8 hours, oral doses of tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and TAK-438 (20 mg) or tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and lansoprazole (30 mg) will be administered BID from Days 1 to 14. The last dose will be on the evening of Day 14. Blood sampling for TAK-438 and lansoprazole PK measurements will be taken on Days 12 to 14 (predose evening and morning) and for bismuth PK measurements on Day 14 (pre–morning dose to 12 hours post–morning dose). Urine sampling for bismuth PK measurements will be taken on Day 14 (pre–morning dose to 12 hours post–morning dose). The subject will be confined to the phase 1 unit from Day -1 (Check-in) through to Day 15 (Check-out), and will be required to contact the study site once again for a follow-up call on Day 17 and a clinic visit on Day 42 for a HP breath test.

A schematic of the study design is included as Figure 1.

Figure 1. Schematic of Study Design

<table>
<tr><td colspan="2">Pretreatment</td><td colspan="4">Treatment Period</td><td colspan="2">Follow up</td></tr>
<tr><td>Screening</td><td>Check-in Baseline</td><td colspan="3">Confinement</td><td>Check-out</td><td>Follow-up call</td><td>Follow-up visit</td></tr>
<tr><td>Days -28 to -2</td><td>Day -1</td><td colspan="2">Day 1-11</td><td>Day 12-13</td><td>Day 14</td><td>Day 15</td><td>Day 17 (+2 days)</td><td>Day 42 (+6 days)</td></tr>
<tr><td rowspan="4"></td><td rowspan="4"></td><td colspan="3">Group A: CA + bismuth + lansoprazole dosing</td><td rowspan="4"></td><td rowspan="4"></td><td rowspan="4">HP breath test</td></tr>
<tr><td colspan="3">Group B: CA + bismuth + TAK-438 dosing</td></tr>
<tr><td colspan="2"></td><td colspan="2">TAK-438 PK or lansoprazole PK in plasma</td></tr>
<tr><td colspan="2"></td><td></td><td>Bismuth PK in plasma and urine</td></tr>
</table>

Bismuth: tripotassium bismuth dicitrate (600 mg BID, equivalent to bismuth 220 mg BID); CA: clarithromycin (500 mg BID), amoxicillin (1000 mg BID); TAK-438: 20 mg BID; lansoprazole: 30 mg BID.
Blood PK samples for Bismuth: 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 morning dose.
Urine PK samples for Bismuth: Day 14 at 0 to 12 hours post–morning dose.
Blood PK samples for TAK-438 and lansoprazole: Day 12-14 predose (morning and evening)
Analyte: bismuth, TAK-438F, and lansoprazole.
Comparison of Group A and Group B: C_{max} and AUC_{τ}.

5.0 ANALYSIS ENDPOINTS

- Percentage of subjects who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of subjects who discontinue due to an adverse event (AE).
- Percentage of subjects who meet the markedly abnormal criteria for safety laboratory tests at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for vital sign measurements at least once postdose.
- Percentage of subjects who meet the markedly abnormal criteria for safety electrocardiogram (ECG) parameters at least once postdose.
- Plasma PK parameters of tripotassium bismuth dicitrate (600 mg) when coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and TAK-438 (20 mg BID) (CAT), and coadministered with clarithromycin (500 mg BID), amoxicillin (1000 mg BID), and lansoprazole (30 mg BID) (CAL):
  - C_{max} at Day 14.
  - The area under the plasma concentration-time curve during a dosing interval (AUC_{τ}) at Day 14.
  - The amount of drug excreted in urine during a dosing interval (Ae_{τ}) at Day 14.

6.0 DETERMINATION OF SAMPLE SIZE

A sample size of 30 (15 subjects per group) will be used in this exploratory study. Although this planned sample size is not primarily based on statistical considerations, it will allow precise estimation of the relative treatment effect of TAK-438 versus lansoprazole on bismuth exposure as follows:

Estimated Ratio TAK-438/Lansoprazole	CV	Expected 90% CI	Expected 95% CI
1.5	0.40	1.15, 1.96	1.09, 2.07
1.5	0.50	1.07, 2.10	1.00, 2.25
1.5	0.60	1.00, 2.24	0.92, 2.44
2.0	0.40	1.53, 2.62	1.45, 2.76
2.0	0.50	1.43, 2.80	1.33, 3.00
2.0	0.60	1.34, 2.99	1.23, 3.25

CV=coefficient of variation.

These calculations allow for up to 2 dropouts per group and are based on estimates of CV of 0.40 to 0.60 for PK parameters (area under the plasma concentration-time curve from time 0 to infinity [AUC_{∞}] and C_{max})

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 GENERAL PRINCIPLES

7.1.1 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.
- Descriptive statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- 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, e.g., the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2.
- 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/ lansoprazole and bismuth or 2)clarithromycin and amoxicillin.
- QTcF interval (msec): QT interval (msec) / (RR interval (msec)/1000)$^{0.33}$ (rounded to the nearest whole number)
- Baseline and Screening values: The last evaluable observation (i.e., 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.

7.1.2 Handling of Plasma Bismuth Concentrations at Day 14

For each time, all evaluable observation (i.e., 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.

Time	Scheduled Time From Morning Dose* at Day 14 (min)	Time Interval (min)
		Sampling Time From Morning Dose* at Day 14
Pre–morning dose (0 hours)	0	-10 – 0
0.25 hours post–morning dose	15	10 - 20

0.5 hours post–morning dose	30	25 - 35
0.75 hours post–morning dose	45	40 - 50
1.0 hour post–morning dose	60	55 - 65
1.5 hours post–morning dose	90	85 - 95
2.0 hours post–morning dose	120	115 - 125
3.0 hours post–morning dose	180	175 - 185
4.0 hours post–morning dose	240	235 - 245
5.0 hours post–morning dose	300	295 - 305
6.0 hours post–morning dose	360	355 - 365
8.0 hours post–morning dose	480	470 - 490
10.0 hours post–morning dose	600	590 - 610
12.0 hours post–morning dose	720	710 - 730

* Start Time of Bismuth, TAK-438, Lansoprazole at morning

Concentrations below the lower limit of quantification will be treated as zero in the analysis of concentration-time data.

7.1.3 Handling of Plasma TAK-438F/ Lansoprazole Concentrations

For each visit, all evaluable observation (i.e., 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 time to the scheduled time will be used. If there are two observations equidistant to the scheduled time, the later observation will be used.

Visit	Time	Scheduled Time From Dose* (min)		Time Interval (min) Sampling Time From Dose*
Day 12	Pre-morning dose	Morning	0	-10 – 0
Day 12	Pre-evening dose	Evening	0	-10 – 0
Day 13	Pre-morning dose	Morning	0	-10 – 0
Day 13	Pre-evening dose	Evening	0	-10 – 0
Day 14	Pre-morning dose	Morning	0	-10 – 0
Day 14	Pre-evening dose	Evening	0	-10 – 0

* Start Time of Bismuth, TAK-438, Lansoprazole

Concentrations below the lower quantifiable concentration will be treated as zero in the analysis of concentration-time data.

7.1.4 Handling of Laboratory Test

For each visit, all evaluable observation (i.e., 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.

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

Visit	Scheduled Study Day (days)	Time Interval (days)
		Study Day
Day 15	Study Day: 15	15

Values below the lower limit of quantification will be handled as zero.

7.1.5 Handling of Vital Signs

For each visit, all evaluable observation (i.e., 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 time to the scheduled time will be used. If there are two observations equidistant to the scheduled time, the later observation will be used.

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 1	Pre–evening dose	Study Day: 1	Evening 0	Time: -60 – 0
Day 2 to 14	Pre-morning dose	Study Day: 2 to 14	Morning 0	Time: -60 – 0
	Pre-evening dose	Study Day: 2 to 14	Evening 0	Time: -60 – 0
Day 15		Study Day: 15		Study Day: Post-dose – 15

* Start Time of Bismuth, TAK-438, Lansoprazole

7.1.6 Handling of 12-Lead ECGs

For each visit, all evaluable observation (i.e., 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 time to the scheduled time will be used. If there are two observations equidistant to the scheduled time, the later observation will be used.

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

Visit	Time	Scheduled Study Day (days)	Scheduled Time From Dose* (min)		Time Interval (min) / Study Day (days) Assessment Time From Dose*
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, Lansoprazole

7.1.7 Handling of HP Breath Test

For each visit, all evaluable observation (i.e., 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.

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

7.2 ANALYSIS SETS

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

The PK analysis set will consist of subjects who received the study drug, who have sufficient plasma/urine concentration data to calculate at least 1 pharmacokinetic parameter, and completed the minimum protocol specified procedures with no significant protocol deviations listed below:

- Subjects who did not meet inclusion criteria #3, #4 or #5
- Subjects who met exclusion criteria #1, #4, #6, #7, #8, #10, #11, #13, #14, #15, #16, #17, #21, or #22
- Subjects who have violated the rules specified in section 7.3 (excluded medications and dietary products) of the protocol up to end of Day 14
- Subjects with study medication compliance of less than 100%

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
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<= - <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]

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 [Yes, No]
Primary Reason for Subject Not Being Eligible [Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal,

Study Termination,
Did Not Meet Entrance Criteria,
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.

7.3.4 Disposition of Subjects

Analysis Set: Randomized Set

Analysis Variables:

Study Drug Administration Status	[No]
Reason for Not Being Treated	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Other]
Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
Reason for Discontinuation of Study Drug	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, 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.

7.3.5 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.

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.

7.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

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	[The Subject Has Never Smoked, The Subject Is a Current Smoker, The Subject Is an Ex-smoker]
Consumption of Alcohol	[Drink Every day, Drink a Couple of Days Per Week, Drink a Couple of Days Per Month, Never Drink]
Consumption of Caffeine	[Yes, No]
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.

7.5 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 19.0 or higher) coding system.

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

7.6 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 2016Q1 or higher.

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

7.7 STUDY DRUG EXPOSURE AND COMPLIANCE

TAK-438/ Lansoprazole 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.	

7.8 EFFICACY ANALYSIS

Not applicable.

7.9 PHARMACOKINETIC ANALYSIS

Plasma Bismuth Concentration

Analysis Set: PK Analysis Set

Analysis Variable: Plasma Bismuth Concentrations

Time Point: Pre–morning dose (0 hours) and 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 hours post–morning dose during Day 14

Analytical Methods: Following analysis will be provided by treatment group.

(1) Summary of Plasma Concentrations by Time Point
Descriptive statistics for observed values will be provided for each time point. In addition, geometric mean, and %CV will be provided

(2) Concentration-time Profiles of Bismuth for Individual Subjects
Observed values will be plotted using individual case plot.

(3) Mean Concentration-time Profiles with Standard Deviations
Mean of plasma concentration will be plotted by time point using linear scale and natural log scale.

Plasma TAK-438F/ Lansoprazole Concentration

Analysis Set: PK Analysis Set

Analysis Variable: Plasma TAK-438F Concentrations

Plasma Lansoprazole Concentrations

Visit and Time Point: Day 12 Pre–morning dose, Day 12 Pre–evening dose, Day 13 Pre–morning dose, Day 13 Pre–evening dose, Day 14 Pre–morning dose and Day 14 Pre–evening dose

Analytical Methods: **(1) Summary of Plasma Concentrations by Time Point**
Descriptive statistics for observed values will be provided for each visit and time point. In addition, geometric mean, and %CV will be provided.

Plasma PK Parameters of Bismuth

Analysis Set: PK Analysis Set

Analysis Variable: Plasma PK Parameters of Bismuth

C_{max}	AUC_{τ}	CL/F
λ_z	$t_{1/2z}$	t_{max}
V_z/F		

Visit: Day 14

Analytical Methods: For all variables, Summary (1) will be provided by treatment group.
For C_{max} and AUC_{τ}, Summary (2) will be provided.

(1) Summary of Plasma PK Parameters

Descriptive statistics for PK parameters will be provided. In addition, geometric mean and %CV will be computed for C_{max} and AUC_{τ}.

(2) Analysis of Variance with Natural log-transformed AUC_{τ} and C_{max}

Two-sided confidence intervals (90% and 95% confidence level) of the ratio between administration conditions (bismuth with CAL and bismuth with CAT) will be calculated using an analysis of variance with natural log-transformed AUC_{τ} and C_{max} of bismuth.

Urine PK parameters of Bismuth

Analysis Set: PK Analysis Set

Analysis Variable: Urine PK parameters of Bismuth

Ae_{τ}	$f_{e,\tau}$	CL_R

Visit: Day 14

Analytical Methods: **(1) Summary of Urine PK Parameters**

Descriptive statistics for PK parameters will be provided.

7.10 OTHER OUTCOMES

HP Breath Test

Analysis Set: Safety Analysis Set

Analysis Variable: HP Breath Test

Visit: Screening and Day 42

Analytical Methods: **(1) Summary of HP Breath Test**

Frequency distributions will be provided by treatment group and overall.

7.11 SAFETY ANALYSIS

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

Categories: Relationship to Study Drug

Relationship to TAK-438/ Lansoprazole	[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 (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)
9) Significant Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
10) Relationship of Significant Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2), 6) and 10)
  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), 6) and 10)
  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.

7.11.1.2 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.

Drug-related TEAEs will be summarized for TAK-438/ Lansoprazole, 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

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

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

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

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.

7.11.1.3 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.

7.11.2 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 ($\times 10^{9}$/L)

Serum Chemistry

ALT (U/L)	Alkaline phosphatase (U/L)	AST (U/L)
GGT (U/L)	Total Bilirubin (µmol/L)	LDH (U/L)
Creatine kinase (U/L)	Creatine kinase MB (µg/L)	Albumin (g/L)

	Total Protein (g/L)	Serum creatinine (umol/L)	Blood urea nitrogen (mmol/L)
	Uric Acid (mmol/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)	

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.

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.

7.11.3 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 1at Pre–evening dose, Day 2 to 14 at Pre–morning dose, Day 2 to 14 Pre–evening dose, , Day 15

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.

7.11.4 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"]

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.

7.11.5 Other Observations Related to Safety

Not applicable

7.12 INTERIM ANALYSIS

Not applicable

7.13 CHANGES IN THE STATISTICAL ANALYSIS PLAN

Time intervals in 7.1.5 and 7.1.6 were modified from SAP version 1.0 to include all records for pre-morning dose, pre-evening dose, and Day 15 as well as to correct misspecification for post-morning dose.

8.0 REFERENCES

Not applicable

9.0 APPENDIX

9.1 CRITERIA FOR MARKEDLY ABNORMAL VALUES

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

For each parameter, all evaluable data (i.e., 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

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	-

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
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

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

12-lead ECG

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

9.1.2 12-lead ECG (Upper MAV Criteria of QTcF Interval)

All evaluable data (i.e., 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	17-May-2017 08:17 UTC
	Pharmacovigilance Approval	17-May-2017 13:37 UTC
	Clinical Science Approval	18-May-2017 00:51 UTC
	Biostatistics Approval	19-May-2017 08:39 UTC
	Biostatistics Approval	22-May-2017 01:59 UTC