



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.
Phase 1 TAK-438 Bismuth Drug Interaction Study

NCT Number: NCT02892409

Protocol Approve Date: 21 November 2016

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PROTOCOL

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 TAK-438 Bismuth Drug Interaction Study

Sponsor: Takeda Development Center Asia Pte. Ltd.
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Study Number: TAK-438_115

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: TAK-438

Date: 21 November 2016 **Amendment Number:** 03

Amendment History

Date	Amendment Number	Region
22 Dec 2015	Initial Protocol	Asia Pacific
22 Apr 2016	01	Asia Pacific
20 July 2016	02	Asia Pacific
21 November 2016	03	Asia Pacific

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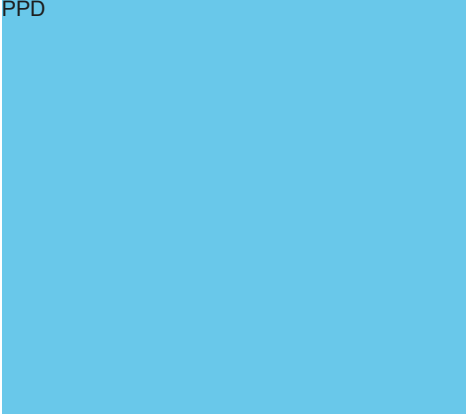
1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center Asia, Pte., Ltd (TDC Asia) sponsored Asian Pacific investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Issue	Asian Regional Contact
Serious adverse event, pregnancy and special interest adverse event reporting Medical Monitor (medical advice on protocol and study drug) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD 

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

Electronic Signatures may be found on the last page of this document.

PPD	_____	Date	PPD	_____	Date
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PPD	_____	Date	PPD	_____	Date
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1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reasons for this amendment are listed below.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see [Appendix F](#).

Changes in Amendment 03

1. Removal of reference to CYP2C19 genotype status from study inclusion criteria.
2. For Exclusion criterion #20, permission for all investigators (including sub investigators) to enter subjects with non-clinically significant electrocardiogram (ECG) abnormalities.
3. For Exclusion Criterion No.22, glomerular filtration rate to be estimated using the Chronic Kidney Disease-Epidemiology Collaboration formula.
4. Clarification to indicate that the time point for pharmacokinetic (PK) analysis will be Day 14.
5. Rescreening and the process of rescreening subjects have been added.
6. Amendments to the CYP2C19 blood collection.
7. The screening procedure of *Helicobacter pylori* (HP) breath test is permitted to be performed at a satellite site.
8. Clarified liver function test monitoring.
9. Clarification of footnotes in the Schedule of Study Procedures (Appendix A).

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- [Appendix B](#) - Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in [Appendix D](#) of this protocol.

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Asia Pte. Ltd.		Compound: TAK-438					
Title of Protocol: 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.		IND No.: Not applicable		EudraCT No.: Not applicable			
Study Number: TAK-438_115		Phase: 1					
Study Design: This is a phase 1, double-blind, parallel group study in subjects with <i>Helicobacter pylori</i> (HP positive) to evaluate the safety, tolerability and pharmacokinetics (PK) of a quadruple therapy with bismuth, clarithromycin, amoxicillin, and TAK-438 versus quadruple therapy with bismuth, clarithromycin, amoxicillin, and lansoprazole. Thirty HP positive subjects aged 19 to 60 years, inclusive, and 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 2 treatment groups as indicated in the schematic below. The treatment phase consists of quadruple therapy twice daily (BID) with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and TAK-438 (20 mg) (Group B) or quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), clarithromycin (500 mg), amoxicillin (1000 mg), and lansoprazole (30 mg) (Group A) from Days 1 to 14. Subjects will be discharged on Day 15 after final PK blood samples are collected and all procedures performed.							
Schematic of Study Design							
Pretreatment		Treatment Period				Follow up	
Screening	Check-in Baseline	←----- Confinement -----→			Check-out	Follow-up call	Follow-up visit
Days -28 to -2	Day -1	Day 1-11	Day 12-13	Day 14	Day 15	Day 17 (+2 days)	Day 42 (+6 days)
		Group A: CA + bismuth + lansoprazole dosing					HP breath test
		Group B: CA + bismuth + TAK-438 dosing					
			TAK-438 PK or lansoprazole PK in plasma				
				Bismuth PK in plasma and urine			
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-438, and lansoprazole. Comparison of Group A and Group B: maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval (AUC_{τ}).							

Primary Objective: 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.		
Subject Population: HP positive subjects aged 19 to 60 years, inclusive.		
Number of Subjects: Estimated total: 30 subjects.	Number of Sites: Estimated total: 1 site in Asia.	
Dose Level(s): TAK-438 (20 mg) Tripotassium bismuth dicitrate (600 mg, equivalent to bismuth 220 mg) Clarithromycin (500 mg) Amoxicillin (1000 mg) Lansoprazole (30 mg)	Route of Administration: Oral	
Duration of Treatment: Quadruple therapy BID for 14 days (Days 1 to 14)	Period of Evaluation: Approximately 70 days (including Screening, Day -1 through Study Exit, Follow-up Call, and Follow-up Visit)	
Main Criteria for Inclusion: <ol style="list-style-type: none"> HP positive male or female subjects aged 19 to 60 years. Subject has a body mass index between >18 and ≤ 30 kg/m² and weighs ≥ 50 kg. 		
Main Criteria for Exclusion: Subjects will be excluded who have: <ol style="list-style-type: none"> A history of hypersensitivity to any excipients of TAK-438 and lansoprazole. A history of gastroesophageal reflux disease (GERD), symptomatic GERD, erosive esophagitis, duodenal ulcer, gastric ulcer, Barrett's esophagus, or Zollinger-Ellison syndrome. Levels of aspartate aminotransferase, alanine aminotransferase, or total bilirubin levels $>$upper limit of normal. 		
Main Criteria for Evaluation and Analyses: - Safety: Standard safety assessments for phase 1 studies will be collected. - Laboratory tests: Standard laboratory tests will be assessed. - Pharmacokinetics: Blood PK samples for TAK-438 and lansoprazole analysis will be collected on Day 12 to 14 at predose (morning and evening). Blood PK samples for bismuth analysis will be collected on Day 14 at predose (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, and 12.0 hours post-morning dose. Urine PK samples for bismuth analysis will be collected on Day 14 at 0 to 12 hours post-morning dose.		
Sample Type	Dosing Day	Time Postdose (hours)
Plasma	12-14	Predose (morning and evening)
Plasma	14	Predose (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
Urine	14	0 to 12 hours post-morning dose

PK variables will be derived from the plasma concentrations of bismuth as required. These will include, where appropriate, AUC_t , C_{max} , time at which C_{max} occurs (t_{max}), terminal elimination rate constant (λ_z), terminal elimination half life ($t_{1/2z}$), apparent clearance (CL/F), and apparent volume of distribution (V_z/F).

PK variables will be derived from the urine concentrations of bismuth as required. These will include amount excreted in urine (Ae_t), the fraction of the dose excreted unchanged in urine (f_e), and renal clearance (CL_R).

- Pharmacogenomics:

Mandatory blood samples will be collected for CYP2C19 genotyping.

- Total volume of blood drawn:

Blood draw is expected to be 203 mL.

Statistical Considerations:

Adverse Events

All treatment-emergent adverse events (TEAEs) will be coded using the Medical Dictionary for Regulatory Activities. Data will be summarized using preferred term and primary system organ class. All TEAEs, drug-related TEAEs and serious TEAEs will be summarized by administration conditions (bismuth with the combination clarithromycin, amoxicillin, and TAK-438 [CAT] and bismuth with the combination clarithromycin, amoxicillin, and lansoprazole [CAL]).

Clinical Laboratory Evaluations, Vital Signs and 12-lead Electrocardiograms

Observed values and changes (from Baseline) for continuous variables will be summarized by administration conditions (bismuth with CAL and bismuth with CAT) over time using descriptive statistics.

For categorical variables, shift tables will be presented for administration conditions (bismuth with CAL and bismuth with CAT).

Pharmacokinetics

Plasma concentrations of bismuth will be summarized at each scheduled sampling point by administration condition (bismuth with CAT and bismuth with CAL) using descriptive statistics (arithmetic mean, SD, median, minimum and maximum). For Days 12 to 14, plasma concentrations of freebase of TAK-438 (TAK-438F) and lansoprazole will be summarized at each scheduled sampling point using descriptive statistics. The plasma and urine PK parameters of bismuth will be summarized by administration conditions (bismuth with CAT and bismuth with CAL) using descriptive statistics. Two-sided 90% and 95% confidence levels (CIs) of the ratio between administration conditions (bismuth with CAT and bismuth with CAL) will be calculated using an analysis of variance with natural log-transformed AUC_t and C_{max} of bismuth to evaluate the impact of TAK-438 on the PK of bismuth compared with the impact of lansoprazole on the PK of bismuth. Statistical analyses of other plasma and urine PK parameters will be performed if appropriate.

Sample Size Justification:

A sample size of 30 (15 subjects per group) will be used in this exploratory study.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

Kyung-Sang Yu, MD, PhD
Professor
Seoul National University Hospital and College of Medicine
Seoul, Korea

3.3 List of Abbreviations

λ_z	terminal elimination rate constant
%CV	percentage coefficient of variation
AE	adverse event
Ae_τ	amount of drug excreted in urine during a dosing interval
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_τ	area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval
AUC_{0-12}	area under the plasma concentration-time curve from time 0 to 12 hours
AUC_∞	area under the plasma concentration-time curve from 0 to infinity
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)
CI	confidence interval
CL/F	apparent clearance
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
CRO	contract research organization
CS	Clinically Significant
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DU	duodenal ulcer
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
f_e	fraction of drug excreted in urine
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	γ -glutamyl transferase
GU	gastric ulcer
H^+,K^+ -ATPase	hydrogen, potassium adenosine triphosphatase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HP	<i>Helicobacter pylori</i>
ICH	International Conference on Harmonisation

ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
K ₂ EDTA	potassium ethylenediamine tetraacetic acid
MedDRA	Medical Dictionary for Regulatory Activities
Med ID	medical identification
NCS	not clinically significant
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PCAB	potassium-competitive acid blocker
PGx	pharmacogenomics
pH4 HTR	pH4 holding time ratio
PK	pharmacokinetic
PPI	proton pump inhibitors
PTE	pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions
t _{1/2z}	terminal elimination half-life
TAK-438F	freebase of TAK-438
TEAE	treatment-emergent adverse event
t _{max}	time to reach C _{max}
ULN	upper limit of normal
V _z /F	apparent volume of distribution during the terminal phase after extravascular administration

3.4 Corporate Identification

TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Helicobacter pylori (HP) is a Gram-negative, microaerophilic bacteria mainly found in the gastric mucus and mucosa, whose causal relationships to gastrointestinal diseases have been extensively studied [1,2] since it has been isolated from the gastric mucosa of a patient with chronic gastritis in 1983 [3]. Since then, HP eradication therapy has been shown to be effective in reducing the recurrence of gastric and duodenal ulcers [4,5], and HP eradication therapy using proton pump inhibitors (PPIs) and antibiotics has been approved in various countries around the world.

In Japan, in September 2000, a triple therapy with lansoprazole/amoxicillin/clarithromycin was the first treatment regimen to gain approval for HP eradication in patients with gastric or duodenal ulcers, and, in August 2007, a triple therapy with PPI/amoxicillin/metronidazole was approved as second-line eradication therapy for patients who failed first-line eradication therapy. These triple therapies for HP eradication were approved in June 2010 also for gastric mucosa associated lymphoid tissue lymphoma, idiopathic thrombocytopenic purpura, and endoscopically-treated early gastric cancers.

Developed at Takeda Pharmaceutical Company Ltd, TAK-438 belongs to a new class of acid-inhibitory agents called potassium-competitive acid blockers (PCABs). TAK-438 is shown not only to inhibit the hydrogen, potassium adenosine triphosphatase (H^+,K^+ -ATPase) enzyme in the final step of acid secretion, as the PPIs do, but does not require the presence of acid for its activation and inhibits the H^+,K^+ -ATPase enzyme in a potassium-competitive fashion. Furthermore, TAK-438 has been shown to be stable in the presence of acid and is water-soluble, requiring no particular pharmacological preparations, such as an enteric coating. Furthermore, TAK-438 is predominantly metabolized by cytochrome P-450 (CYP)3A4 and contribution of polymorphic CYP2C19 is considered to be limited. In contrast to the PPIs, which take 3 to 5 days to produce their maximum acid-inhibitory effects, due to its rapid accumulation in the gastric parietal cell and longer half-life, TAK-438 is expected to produce its maximum acid-inhibitory effects in a much shorter time and therefore have better potential clinical outcomes than the PPIs with its potent and sustained acid-inhibitory effects. TAK-438 is currently marketed in several indications in Japan, including the treatment of reflux esophagitis, gastric ulcer (GU), duodenal ulcer (DU), prevention of recurrence of a GU or DU during nonsteroidal anti-inflammatory drug (NSAID) or aspirin administration and as an adjunct to HP eradication.

In Japan, a phase 1 single-dose study (TAK-438/CPH-001), with doses ranging from 1 mg up to 120 mg, and a phase 1, 7-day repeat-dose study (TAK-438/CPH-002), with doses ranging from 10 mg to 40 mg, have been conducted to evaluate safety, pharmacokinetics (PK), and acid-inhibitory effects of TAK-438. TAK-438 was well tolerated at the single daily dose of 40 mg in the 7-day repeat-dose study, and the pH4 holding time ratio (pH4 HTR) of TAK-438 10 mg on Day 7 was comparable to that of lansoprazole 30 mg once daily. TAK-438 exhibited a potent and sustained acid-inhibitory effect, with the pH4 HTR on Day 7 increasing dose dependently reaching over 90% at doses of 30 and 40 mg. Investigation of a possible effect of CYP2C19 on the PK of TAK-438, in the single-dose study, demonstrated no definite trend among the genotypes

examined; this suggested that the PK of TAK-438 is not affected by CYP2C19. In addition, a study evaluating interactions between TAK-438 and various NSAIDs (eg, loxoprofen sodium, diclofenac sodium, or meloxicam) or low-dose aspirin (TAK-438/CPH-003), showed that TAK-438 had no significant effect on the PK of these drugs and these drugs showed no significant effect on the PK of TAK-438 in the repeat dose study.

TAK-438 was also studied in a single-dose study (TAK-438_101) and a repeat-dose study (TAK-438_107) of TAK-438 in the United Kingdom. In the 7-day repeat-dose study to evaluate the safety, PK, and acid-inhibitory effects at doses ranging from 10 to 40 mg once daily, TAK-438 was well tolerated at all doses studied, and the pH4 HTR on Day 7 was similar to that observed in the repeat-dose study conducted in Japan at comparable doses, supporting the potent and sustained acid-inhibitory effects of TAK-438. In a study conducted in the United Kingdom to evaluate interactions between TAK-438 and repeated doses of clarithromycin (TAK-438_110), the maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of TAK-438F (freebase of TAK-438) increased by 1.35-fold and by 1.58-fold, respectively, when used in combination with clarithromycin, a potent inhibitor of the CYP3A4, and TAK-438 was well tolerated.

A 4×4 crossover study of PK drug-drug interactions of triple therapy twice a day (BID) with TAK-438/amoxicillin/clarithromycin or TAK-438/amoxicillin/metronidazole was conducted in healthy Japanese male subjects (TAK-438_CPH-401). In Cohort 1 (triple therapy BID with TAK-438, amoxicillin, and clarithromycin), compared with single-agent use of TAK-438, the mean area under the plasma concentration-time curve from time 0 to 12 hours (AUC_{0-12}) and mean C_{max} for TAK-438F increased approximately 1.8- and 1.9-fold, respectively, when TAK-438 was administered as triple therapy. No difference was observed in the PK of plasma amoxicillin when amoxicillin was administered alone or as triple therapy. Compared with single-agent use of clarithromycin, the mean AUC_{0-12} and mean C_{max} for clarithromycin increased approximately 1.5-fold and 1.6-fold, respectively, when clarithromycin was administered as triple therapy. In Cohort 2 (triple therapy BID with TAK-438, amoxicillin, and metronidazole), no difference was observed in the PK of plasma metronidazole when metronidazole was administered alone or as triple therapy. Compared with the single-agent therapies, the AUC_{0-12} and C_{max} for TAK-438F and clarithromycin increased during triple therapy with TAK-438/amoxicillin/clarithromycin. However, no safety concern was identified with the triple therapy. Although further investigation in more subjects is required, the changes during triple therapy with TAK-438/amoxicillin/clarithromycin or TAK-438/amoxicillin/metronidazole are not considered to be clinically significant.

In a phase 2 dose-ranging study of TAK-438 in Japanese patients with erosive esophagitis (TAK-438/CCT-001), TAK-438, given once daily at doses of 5, 10, 20, and 40 mg for 8 weeks, was evaluated for its dose-response efficacy and safety in a randomized, double-blind, parallel-group comparison with lansoprazole. The primary endpoint of the study was endoscopic healing rate of erosive esophagitis after 4 weeks treatment and was 92.3%, 92.5%, 94.4%, and 97.0% with 5, 10, 20, and 40 mg of TAK-438, respectively, compared with 93.2% with 30 mg of lansoprazole, showing the noninferiority of TAK-438 to lansoprazole at any of the doses examined. No particular safety concerns were noted.

TAK-438 has been studied in a number of acid-related diseases and noninferiority with lansoprazole has been confirmed in several phase 3 studies including reflux esophagitis healing and prevention of recurrence studies, GU/DU ulcer healing and for the prevention of recurrence of a gastric or duodenal ulcer during NSAID or aspirin administration and has subsequently been launched in Japan for these indications. Of note, in a phase 3 HP eradication study, 7-day treatment with TAK-438 20 mg (n=329) or lansoprazole 30 mg (n=321) in combination with amoxicillin 750 mg plus clarithromycin 200 or 400 mg, HP eradication rates were 92.6% and 75.9%, respectively. Furthermore, the first 50 treatment failures with good compliance received second-line triple-therapy with TAK-438 20 mg (in combination with amoxicillin 750 mg and metronidazole 250 mg) in an open-label manner and an eradication rate of 98% was observed. All treatments were well-tolerated.

4.2 Rationale for the Proposed Study

TAK-438 is a novel, orally active PCAB, which was launched for a number of acid-related diseases in Japan in February 2015. Unlike PPIs, TAK-438 is acid-stable and does not require an acid-protective formulation. The compound is metabolized mainly by CYP3A4, in contrast to PPIs, which are metabolized mainly by CYP2C19, an enzyme with genetic polymorphism. Therefore, the degree of interpatient variability in response to treatment is not expected to be as high with TAK-438.

TAK-438 was recently launched in Japan for several acid-related disease indications including adjunct to HP eradication and is currently in clinical development in Asia where there are 2 ongoing studies (reflux esophagitis and prevention of recurrence) and 2 phase 3 studies planned (GU/DU healing) and 2 phase 1 trials planned. TAK-438_115 is one of the planned phase 1 trials planned in Asia. In China, HP eradication guidelines recommend quadruple therapy for HP eradication consisting of 2 antibiotics, a PPI and bismuth [6]. As a replacement for PPIs in China, TAK-438 would be expected to be used as part of a quadruple treatment regimen and a drug interaction study is required to confirm the tolerability of TAK-438 quadruple therapy for HP eradication.

It has been reported that with increasing pH of the stomach an increase in bismuth absorption is observed with the exposure to bismuth increasing by 3- to 7-fold when administered with histamine-2 receptor antagonists and PPIs [7]. Increased levels of bismuth may be associated with increased potential for neurotoxicity [8]. As TAK-438 achieves high stomach pH over a full 24-hour period, an evaluation of drug interaction potential and tolerability when TAK-438 and bismuth are coadministered is warranted.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

The objectives of this study are:

- 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).

5.2 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 STUDY DESIGN AND DESCRIPTION

6.1 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 6.a](#). 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 6.a](#). A schedule of assessments is listed in [Appendix A](#).

Figure 6.a Schematic of Study Design

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

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-438, and lansoprazole.
 Comparison of Group A and Group B: C_{max} and AUC_{τ} .

6.2 Justification for Study Design, Dose, and Endpoints

As bismuth is minimally absorbed and renally excreted, it is not expected to have an effect on the PK of TAK-438, clarithromycin or amoxicillin and the combination of clarithromycin and amoxicillin are not expected to have an effect on bismuth concentrations [9]. However, as an increase in bismuth concentration is observed when administered with PPIs, which is associated with increased stomach pH [7], it is expected that when bismuth is coadministered with TAK-438 there may be an increase in bismuth exposure. Coadministration of clarithromycin and amoxicillin with TAK-438 has already been evaluated in study TAK-438/CPH-401 (TAK-438/CPH-401), where an approximate 2-fold increase in TAK-438 concentrations was observed in healthy male subjects. The absorption of bismuth is affected by intragastric pH, which in turn is affected by HP status. In HP-positive subjects, the intragastric pH could be increased and downstream effects on safety related to an increase in bismuth exposure could occur. HP positive subjects are also more representative of the HP status of the patient population to be treated. Therefore, HP positive only subjects will be included.

This drug interaction study has also been designed to evaluate the relative impact of TAK-438 on the PK of bismuth compared with the impact of lansoprazole on the PK of bismuth. Bismuth PK on Day 14 administered with TAK-438 will be compared with bismuth coadministered with lansoprazole. The population will comprise of HP positive subjects. No clinically relevant difference in exposure between male and females has previously been established in study TAK-438_109, therefore the study will enroll both.

According to the HP local treatment guideline for HP in China, the recommended dose of bismuth is 220 mg BID [6]. Therefore, tripotassium bismuth dicitrate 600 mg has been chosen in this study

as it is equivalent to bismuth 220 mg (hereafter referred to as bismuth 220 mg). Bismuth potassium citrate is the synonym of tripotassium bismuth dicitrate. Bismuth is minimally absorbed with bioavailability <0.3%, a time to reach C_{max} (t_{max}) of 0.5 hour and is excreted through urinary and biliary routes. It is highly distributed throughout the body and displays multicompartment elimination with multiple half-lives: an initial half-life of 1-4 hours, a more prolonged half-life of 5-11 days, and a more extended half-life [11,12]. There are several half-lives reported for bismuth, however, 1 article indicates that plasma level of bismuth approach an apparent steady-state after 30 - 40 days after multiple dose of bismuth. This study could not be simulated using physiologically-based PK modeling due to the number of regimens used.

The local treatment guidance in China proposes the use of quadruple therapy consisting of 2 antibiotics, bismuth 220 mg BID, and PPI BID for 14 days. A number of different antibiotic regimens are proposed; however clarithromycin (500 mg BID) and amoxicillin (1000 mg BID) have been chosen in the upcoming phase 3 program as this regimen will offer optimal eradication rates [13,14]. TAK-438 20 mg BID is the chosen dose as at this dose there is good pH control and 20 mg BID has been observed to give good HP eradication rates when administered as triple therapy in Japanese patients.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the sponsor, an institutional review board (IRB)/ independent ethics committee (IEC), or regulatory authority elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization or first dose or other.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures, including requesting that a subject fast for any laboratory evaluations.
3. The subject is HP positive at Screening.
4. The subject is male or female and aged 19 to 60 years, inclusive, at the time of informed consent and first study medication dose.
5. The subject weighs at least 50 kg and has a body mass index (BMI) >18 and ≤ 30 kg/m², inclusive at Screening and Day -1 (Check-in).
6. A female subject of childbearing potential who is sexually active with a nonsterilized male partner agrees to use routinely adequate contraception* from signing of informed consent and throughout the duration of the study and for 1 month after last dose of the study medication.

*Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

7. The subject is willing to abstain from strenuous exercise from 72 hours before first dose (Day 1) until the Follow-up call on Day 17.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 90 days prior to providing their informed consent.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has uncontrolled, clinically significant cardiovascular, or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the study results.

5. The subject has a known hypersensitivity to any component of the formulation of TAK-438, penicillins, macrolides, bismuths, and lansoprazole, for example, d-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide, and iron sesquioxide.
6. The subject has a positive urine drug result for drugs of abuse at Screening or Check-in (Day -1).
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 21 units or more units per week) at any time prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study (up to Day 17).
8. The subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table listed in Section 7.3 of the protocol, except where over-the-counter (OTC) medication has been pre-approved by Takeda.
9. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
10. The subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-438, or contraindicate any drug used to reduce acid secretion by the stomach or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
11. The subject has a history of gastroesophageal reflux disease (GERD), symptomatic GERD, erosive esophagitis, DU, GU, Barrett's Esophagus, or Zollinger-Ellison syndrome or has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs.
12. Subjects who have undergone therapeutic upper gastrointestinal endoscopic therapy (eg, endoscopic hemostasis or excision including biopsy) within 30 days prior to Screening.
13. Subjects who have undergone major surgical procedures within the past 1 month or are scheduled to undergo surgical procedures that may affect gastric acid secretion (eg, abdominal surgery, vagotomy, or craniotomy).
14. The subject has any known disease or is taking any medication that is contraindicated with bismuth, clarithromycin, or amoxicillin.
15. The subject has a history of cancer, except basal cell carcinoma or Stage 1 squamous cell carcinoma of the skin that has been in remission for at least 5 years prior to Day 1.

16. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen at Screening.
17. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 6 weeks prior to Check-in. Cotinine test is positive at Screening or Check-in.
18. The subject has poor peripheral venous access.
19. The subject has donated or lost 450 mL or more of his blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to Day 1.
20. The subject has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by both the investigator and the contract research organization (CRO) medical monitor.
21. The subject has abnormal Screening or Check-in laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities: alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin >the upper limit of normal (ULN).
22. The subject has reduced renal function assessed by having an estimated glomerular filtration rate <90 mL/min/1.73 m² (as estimated by Chronic Kidney Disease-Epidemiology Collaboration) at Screening or Check-in.

7.3 Excluded Medications, Dietary Products

Use of the agents in [Table 7.a](#) (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities (Day 17).

Table 7.a Prohibited Medications

6 weeks prior to Check-in (Day -1)	28 days prior to Check-in (Day -1)	7 days prior to Check-in (Day -1)	72 hours prior to Check-in (Day -1)
Nicotine-containing products	Prescription medications	OTC medications including salicylates (a)	Products containing caffeine or xanthine
Immunization/vaccines	St. John's wort, ginseng, kava, ginkgo biloba, Chinese herbs, melatonin, other herbal or homeopathic preparations or other nutraceuticals.	Vitamin supplements CYP3A4 Inhibitors/inducers	
		Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juices, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	
		Alcohol containing products	

(a) Occasional use of acetaminophen/paracetamol (≤ 1 g/day) or other medication is allowed.

Subjects must be instructed not to take any medications including OTC products, without first consulting with the investigator.

Use of concomitant medications will not be allowed during the study (up to Day 17) except for those approved by CRO/Takeda medical monitor on a case-by-case basis, unless deemed necessary in a medical emergency. Concomitant medications will include all medications the subject has taken from signing of informed consent to the Follow-up call (Day 17).

If the subject reports taking any medication or if administration of any medication becomes necessary during the course of this study (up to Day 17), the CRO/Takeda Medical Monitor must be notified. All medications must be recorded in the source documents as well as on the appropriate electronic case report form (eCRF) along with dosage information, dates of administration, and reasons for use.

7.4 Diet, Fluid, Activity Control

Subjects will be confined to the clinic for the duration of the treatment period (Day -1 until check-out on Day 15).

During the confinement period, subjects will be given a menu for the dosing period that includes 3 meals, each containing approximately 30% fat (relative to the total calories). The meals served on the day of dosing should be identical for each treatment group in the study. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study.

If a blood draw or any study procedure coincides with a meal, the study procedure will take precedence followed by the blood draw and then the meal.

Subjects should be fasted overnight for a minimum of 8 hours prior to dosing. Breakfast and dinner should be given at approximately the same time each day on Days 1 to 14. TAK-438, lansoprazole and bismuth should be administered 0.5 hours before breakfast/dinner. Breakfast and dinner should be completed within 0.5 hours and then clarithromycin and amoxicillin should be administered 0.5 hours after the start of breakfast/dinner on Days 1 to 14. They should take all doses with 240 mL water (120 mL with bismuth and TAK-438 or lansoprazole dosing and 120 mL with clarithromycin and amoxicillin doses) and refrain from drinking for at least 1 hour post-clarithromycin and amoxicillin dose, after which water can be given freely.

Subjects will refrain from strenuous exercise from 72 hours prior to the first dose through Day 17 Follow-up Call.

Blood donation is not allowed for at least 12 weeks after the final examination of this study (Day 17).

If a subject visits another medical institution during the study period, the investigator should be informed of the circumstances and therapy, and should communicate with the medical institution about the subject's participation in the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.15.

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

- Liver Function Test Abnormalities

Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study medication treatment:

- ALT or AST or total bilirubin $>2 \times$ ULN.
2. Significant protocol deviation. The discovery postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
 3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
 4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.10.

7. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by

the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to TAK-438, lansoprazole, tripotassium bismuth dicitrate, clarithromycin and amoxicillin.

8.1.1.1 Investigational Drug

The chemical name of TAK-438 is:

1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methyl methanamine monofumarate. Note that the generic name assigned to TAK-438 is vonoprazan.

The chemical name of lansoprazole (AG-1749) is:

(*RS*)-2-({[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridylmethyl]sulfinyl} benzimidazole.

TAK-438 and lansoprazole investigational drug will be foil/foil blistered packaged into 1-dose child-resistant blister cards. Each blister card will contain 1 tablet and 1 capsule. Each dose consists of 1 tablet and 1 capsule. 30 blister cards with the same medication identification (Med ID) will be dispensed to each subject.

The carton box and each blister card will be labeled in a blinded fashion with a single panel label. The labels will include pertinent study information and country-specific regulatory caution statement.

Amoxicillin, clarithromycin, and tripotassium bismuth dicitrate will be purchased by the clinical site, or provided by sponsor or CRO.

Table 8.a Investigational Drug

Name, Strength, and Dose Form	Description	Manufacturer
TAK-438 20 mg tablets	Pale red film-coated tablet scored on both sides	Takeda Pharmaceutical Company Limited, Osaka, Japan
TAK-438 20 mg matching placebo tablet	Pale red film-coated tablet scored on both sides	Takeda Pharmaceutical Company Limited, Osaka, Japan
Lansoprazole 30 mg capsule	White capsule	Takeda Pharmaceutical Company Limited, Osaka, Japan
Lansoprazole 30 mg matching placebo capsule	White capsule	Takeda Pharmaceutical Company Limited, Osaka, Japan
Tripotassium bismuth dicitrate 300 mg (equivalent to bismuth 110 mg) tablets	Locally sourced	
Clarithromycin 500 mg tablets	Locally sourced	
Amoxicillin 500 mg capsules	Locally sourced	

8.1.2 Storage

TAK-438, lansoprazole and each matching placebo investigational drug should be stored at 25°C; with excursions permitted 15°C to 30°C. Protect from moisture and humidity. Sponsor-supplied drugs are to remain in the white carton box and the blister sheet until time of dosing.

Tripotassium bismuth dicitrate, clarithromycin, and amoxicillin should be stored as instructed on the label.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All clinical study material must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Temperature excursion must be reported to the sponsor or designee.

8.1.3 Dose and Regimen

Each subject who qualified to enter into the double-blind treatment on Day 1 will be assigned to 1 of 2 treatment groups (Group A or Group B).

Subjects will be dosed the morning and evening of Day 1 to 14 for each BID dosing. The last dose will be on the evening of Day 14.

Breakfast and dinner should be given at approximately the same time each day on Days 1 to 14 and completed within 0.5 hour. Tripotassium bismuth dicitrate, TAK-438, and lansoprazole should be administered 0.5 hour before breakfast/dinner. Clarithromycin and amoxicillin should be administered 0.5 hour after the start of breakfast/dinner on Days 1 to 14.

Water, 240 mL, will be accompanied with each study medication administration for all dosing (120 mL with bismuth and TAK-438 or lansoprazole dosing and 120 mL with clarithromycin and amoxicillin doses) and the subjects will refrain from drinking for at least 1 hour post-clarithromycin and amoxicillin dose, after which water can be given freely. Subjects must drink all of the water provided with the dose of study drug. Following administration of the study drug, hand and mouth checks will be performed to ensure that the dose was swallowed.

For each dose, the subject's actual dose date and time of administration will be recorded, to the nearest minute in the subject's source documents and transcribed on the eCRF.

[Table 8.b](#) describes the dose and tablet count that will be provided to each subject.

Table 8.b Sponsor-Supplied Drug

Day 1-11	Day 12-13	Day 14
Group A: CA + Bismuth + Lansoprazole Dosing		
Group B: CA + Bismuth + TAK-438 Dosing	TAK-438 or Lansoprazole PK	TAK-438 or Lansoprazole PK Bismuth PK

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.

8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

Serious adverse events (SAEs) associated with overdose should be reported according to the procedure outlined in Section 10.2.2, Collection and Reporting of SAEs.

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the blinded randomization schedule allocated to the site. The Randomization Sequence Number and Med ID will be entered onto the eCRF.

Subjects will be assigned to receive a 4-digit randomization sequence number. The number will be assigned by the clinic site personnel in sequential order beginning with 1001 and ending with 1030. This 4-digit number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number that is assigned at the time the informed consent is obtained and that is used for all other procedures to identify the subjects throughout the study.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

A blinded randomization schedule will be provided to the site pharmacist or authorized study designee prior to the start of this study. The medical identification (Med ID) to be dispensed to each subject will be provided in this schedule.

8.4 Investigational Drug Blind Maintenance

The investigator will receive the subject's investigational drug blind information in the form of a sealed envelope which will reveal the subject's study treatments if opened. The site-designated study personnel will maintain the investigational drug blind information. During regularly scheduled monitoring visits, a study monitor from the sponsor or a designee will perform an inventory of blinded investigational drug unassigned and assigned treatment packages, sealed envelopes. All treatment packages will be reconciled and returned to the sponsor or a designee before study closure.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. All study assessments and causality should be performed, if possible, prior to unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by opening sealed envelope.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

No change should be made to any assessment of the subject after unblinding.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-438 20 mg and matching placebo; lansoprazole 30 mg and matching placebo) and locally sourced study drugs (tripotassium bismuth dicitrate 600 mg;

clarithromycin 500 mg and amoxicillin 1000 mg), the investigator or designee must maintain records of all study drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs and locally sourced drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee (drug label).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.
- A site representative or unblinded pharmacy monitor, otherwise uninvolved with study conduct, will review the randomization schedule and subject dosing log prior to Day 1 dosing and following dosing to ensure all subjects received the correct dose of study medication.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator or designee must record the current inventory of all study drugs (TAK-438 20 mg tablets and matching placebo; lansoprazole 30 mg capsule and matching placebo; tripotassium bismuth dicitrate 600 mg; clarithromycin 500 mg and amoxicillin 1000 mg) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed, including initials of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of supplies already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. The Schedule of Study Procedures is located in [Appendix A](#).

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

If the subject is to undergo the urea breath test (one of the screening procedures) at a satellite site, the subject must sign the informed consent form prior to performing this test.

A unique subject identification number (subject number) will be assigned to each subject at the time informed consent is obtained; this subject number will be used throughout the study.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

The sampling of whole blood for CYP2C19 genotyping analysis is mandatory; every subject must sign the informed consent in order to participate in this study. The informed consent for the CYP2C19 genotyping analysis is a component of the overall study informed consent.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include age, sex, alcohol and caffeine consumption, and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the condition/disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.7](#)).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system*; (10) lymph nodes; (11) genitourinary system; and (12) other.

* A neurological examination of the nervous system will be performed daily.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the investigational drug (Day 1) must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

9.1.4 Weight, Height, and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated using metric units with the formula provided below.

The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

$$\text{Metric:} \quad \text{BMI} = \text{weight (kg)/height (m)}^2$$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $\text{BMI} = 79.2 / 1.76^2 = 25.6 \text{ kg/m}^2$

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral or tympanic measurement), sitting blood pressure (systolic and diastolic, resting more than 5 minutes), respiration rate, and pulse (bpm).

Vital signs may be repeated. All measurements will be recorded on the source documents and in the eCRF.

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study (Day 17), and all medication including vitamin supplements, OTC medications, and oral herbal preparations, must be recorded in the eCRF.

Documentation will include generic medication name, dose, unit, frequency, route of administration, start and end dates, and reason for use.

9.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening examination. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 106 mL, and the approximate total volume of blood for the study is 203 mL for safety laboratory samples. Laboratory samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Study Procedures ([Appendix A](#)).

[Table 9.a](#) lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBCs	ALT (a, b)	pH
WBCs (with differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes)	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase (a)	Protein
Hematocrit	Amylase	Glucose
Platelets	AST (a, b)	Nitrites
PT/INR	GGT	Bilirubin
aPTT	Total bilirubin (a, b, c)	Hemoglobin
Reticulocyte count	Direct bilirubin (a, b)	Ketones
	Uric acid	Leucocytes
	Total protein	Urobilinogen
	Triglycerides (a)	
	Serum creatinine	
	Blood urea nitrogen	
	Creatine kinase	Microscopic Analysis (for abnormal urinalysis result):
	Creatine kinase MB	
	Potassium	RBC/high power field
	Sodium	WBC/high power field,
	Glucose	Epithelial cells, casts, crystals and organisms)
	Chloride	
	Calcium	
	Magnesium	
	Cholesterol (HDL and LDL) (a)	
	LDH (d)	

Diagnostic Screening:

Serum	Urine
HIV test	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, and opiates.
Hepatitis panel, including HBsAg and anti-HCV	
Breath Test	Female subjects of child-bearing potential only:
HP (e)	hCG (for pregnancy)
Alcohol	

aPPT=activated partial thromboplastin time, GGT= γ -glutamyl transferase, hCG=human chorionic gonadotropin, HDL=high-density lipoprotein, INR=international normalized ratio, LDH=lactate dehydrogenase, LDL=low-density lipoprotein, PT=prothrombin time, RBC=red blood cell, WBC=white blood cell.

(a) To be measured under fasting conditions.

(b) Included in liver function tests.

(c) Direct bilirubin will be measured if total bilirubin is $>1.5 \times \text{ULN}$.

(d) LDH1/LDH5 (in % and total) will be measured if clinically significant increase in LDH is reported.

(e) A breath test will be performed at the Screening and must be positive at Screening. A follow-up breath test will be performed on Day 42.

The phase 1 unit's local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience an increase in any one of ALT, AST or total bilirubin $>2 \times \text{ULN}$ then trial medication should be stopped due to the criteria for discontinuation has been met (please refer to Section 7.5 for discontinuation criteria). Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) to monitor recovery should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted.

Please refer to Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests as an SAE.

All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator's assessment of not clinically significant before proceeding with enrollment/randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 4 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with a follicle-stimulating hormone >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

Intrauterine devices (IUDs):

- Cap (plus spermicidal cream or jelly) PLUS male condom.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom.
- Copper T.

*Barrier methods are only applicable in countries where spermicide is commercially available.

Subjects can continue to use contraceptive medications and/or devices as long as they use additional contraceptive precautions as highlighted above. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova during the course of the study.

During the course of the study, regular serum or urine hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures ([Appendix A](#)). In addition to a negative hCG pregnancy test at Screening, subjects must also have a negative hCG pregnancy test at Randomization prior to receiving first dose of double blind investigational drug.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (vonoprazan, lansoprazole, bismuth, clarithromycin, and amoxicillin) should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Day 1 (Randomization) or within 4 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in [Section 1.0](#).

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

12-lead ECGs printed in standard format will be collected at Screening, Check-in, and on Days 1, 3 and 7 at pre-morning dose, Day 14 at pre-morning dose and 1, 2 and 4 hours post-morning dose, and at check out day or the Early Termination of the study for safety assessment.

The investigator will be responsible for providing the interpretation of all safety ECGs (normal/abnormal). These results will be reviewed by the investigator for subject safety and will be provided in an appropriate format with the clinical study report.

9.1.12 Pharmacogenetic Sample Collection for CYP2C19 Genotyping

The sample of whole blood for CYP2C19 genotyping analysis is mandatory. Every subject must sign the informed consent in order to participate in this study. If subjects who initially screen fail this study have performed deoxyribonucleic acid (DNA) blood collection for CYP2C19 genotyping analysis, it is not required to be collected again.

One whole blood sample (3 mL) for DNA isolation will be collected at Day -1 from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K₂EDTA) spray-coated tubes, and stored under frozen condition. A second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation into the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the PK/clinical efficacy of TAK-438 and lansoprazole.

9.1.13 PK Sample Collection

9.1.13.1 Collection of Blood for PK Sampling

Blood samples for PK analysis of TAK-438F, lansoprazole, and bismuth will be collected into Vacutainers containing anticoagulant sodium heparin according to the schedule in [Appendix A](#). Instructions for sample processing and shipment are provided in [Appendix E](#).

Serial blood samples for determination of TAK-438F, lansoprazole, and bismuth will be collected according to [Table 9.b](#).

Table 9.b Collection of Blood Samples for PK Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
TAK-438F	Plasma	12-14	Pre-dose (morning and evening).
Lansoprazole	Plasma	12-14	Pre-dose (morning and evening).
Bismuth	Plasma	14	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.

The actual time of sample collection will be recorded on the source document and eCRF.

9.1.13.2 Collection of Urine for PK Sampling

Urine samples for PK analysis of bismuth will be collected according to [Table 9.c](#).

Table 9.c Collection of Urine Samples for PK Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Bismuth	Urine	14	0 to 12 hours post-morning dose.

Instructions for sample processing and shipment are provided in [Appendix E](#).

9.1.13.3 Bioanalytical Methods

Plasma concentrations of TAK-438F and lansoprazole will be measured by high-performance liquid chromatography with tandem mass spectrometry.

Plasma and urine concentrations of bismuth will be measured by inductively coupled plasma mass spectrometry.

9.1.14 PK Parameters

The PK parameters of bismuth will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated for plasma concentration values of bismuth:

Symbol/Term	Definition
Plasma	
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval, calculated using the linear trapezoidal rule.
C_{max}	Maximum observed plasma concentration.
CL/F	Apparent clearance after extravascular administration, calculated as Dose/ AUC_{τ} after multiple dosing.
λ_z	Terminal elimination rate constant, calculated as the negative of the slope of the log-linear regression of the natural logarithm concentration-time curve during the terminal phase.
$t_{1/2z}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$.
t_{max}	Time to reach C_{max} .
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration, calculated as $(CL/F)/\lambda_z$.

The following urine PK parameters of bismuth will be derived from urine concentrations:

Urine	
Ae_{τ}	Amount of drug excreted in urine during a dosing interval (τ).
f_e	Fraction of drug excreted in urine, calculated as $Fe=(Ae_{\tau}/dose)\times 100$.
CL_R	Renal clearance, calculated as $CL_R=Ae_{\tau}/AUC_{\tau}$.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be reused. If a subject fails screening, but is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will

be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRF. An inventory of the study medication supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in [Appendix A](#). Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening (Day -28 to -2)

Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures. Subjects who initially screen fail for the study are permitted to rescreen following re-consent, with the exception of subjects who at the initial screening visit failed due to abnormal clinical laboratory values that were investigator-defined as clinically significant. All screening procedures with the possible exception of DNA blood collection for CYP2C19 genotyping analysis (if this has been collected it is not required to be collected again) will be repeated. The subject must meet all inclusion and none of the exclusion criteria at the time of rescreening in order to qualify for the study. Procedures to be completed at Screening include:

- Informed consent.
- Inclusion/exclusion criteria assessment.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs.
- Weight, height, and BMI.
- Concomitant medications.
- Concurrent medical conditions.
- PTE assessment.
- Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis).
- Fasting liver function tests.
- Hepatitis and HIV panel assessment.
- ECG procedure.

- Breath test for alcohol.
- Urine drug screen.
- Urine pregnancy test (in female subjects of childbearing potential only).

HP breath test. Providing the subject has signed the informed consent form, sites can choose to conduct the urea breath test at a satellite site. The urea breath test may only be performed at a satellite site after the Sponsor has reviewed and approved the site's procedures. All other screening procedures, and all other study visits are required to be conducted at the main Phase 1 unit.

9.3.2 Check-in (Day -1)

Screening will be completed at the Check-in Day -1 visit. If a subject has previously undergone DNA blood collection for CYP2C19 genotyping analysis, it is not required to be collected again. The following procedures will be performed and documented during this Check-in Visit:

- Inclusion/exclusion criteria assessment.
- Physical examination, including baseline neurological examination of the nervous system.
- Vital signs.
- Weight and BMI.
- Concomitant medications.
- Concurrent medical conditions.
- PTE assessment.
- Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis).
- Fasting liver function tests.
- DNA blood collection for CYP2C19 genotyping analysis.
- ECG procedure.
- Urine drug screen.
- Urine pregnancy test (in female subjects of childbearing potential only).
- Confinement will begin once subjects' eligibility is confirmed after study assessments. Randomization will take place on Day -1 after all procedures are completed and the subject remains confined to the phase 1 unit.

9.3.3 Quadruple Therapy Dosing (Day 1 to 11)

The following procedures will be performed and documented after randomization while the subject remains in confinement:

- Vital signs.

- Neurological examination of the nervous system.
- Concomitant medications.
- ECG procedure (pre–morning dose on Days 1, 3, and 7).
- Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis) at Day 5 and Day 8 pre–morning dose.
- Fasting liver function tests at Day 5 and Day 8 pre–morning dose.
- AE assessment.
- Study drug dispense and administration.

9.3.4 Quadruple Therapy Dosing/TAK-438 PK and Lansoprazole PK (Day 12 to 13)

The following procedures will be performed and documented during Days 12 to 13 while subject remains in confinement:

- Vital signs.
- Neurological examination of the nervous system.
- Concomitant medications.
- AE assessment.
- Predose blood PK sampling collection (morning and evening).
- Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis).
- Fasting liver function tests.
- Study drug dispense and administration.

9.3.5 Quadruple Therapy Dosing/TAK-438 PK, Lansoprazole PK and Bismuth PK (Day 14)

The following procedures will be performed and documented during Day 14 while the subject remains in confinement:

- Vital signs and weight.
- Neurological examination of the nervous system.
- Concomitant medications.
- Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis).
- Fasting liver function tests.
- ECG procedure (predose and 1, 2, and 4 hours post–morning dose).
- AE assessment.

- Predose blood PK sampling collection for TAK-438 and lansoprazole (morning and evening).
- Pre- and post-morning dose blood PK sampling collection for bismuth.
- Post-morning dose urine PK sampling collection for bismuth.
- Study drug dispense and administration.

9.3.6 Check-out (Day 15)

The Check-out Visit will be performed on Day 15.

The following procedures will be performed and documented:

- Vital signs.
- Physical examination.
- Concomitant medications.
- Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis including pregnancy test).
- Fasting liver function tests.
- ECG procedure.
- AE assessment.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page. Subjects should avoid antibiotics, PPIs, bismuth preparations until Day 42 (HP breath test).

9.3.7 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The following procedures will be performed and documented:

- Vital signs.
- Physical examination.
- Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis including pregnancy test).
- Concomitant medications.
- ECG procedure.
- AE assessment.

For all subjects receiving study medication, the investigator must complete the End of Study eCRF page.

9.3.8 Follow-up Call (Day 17)

A follow-up phone call will be made after the Final Visit or Early Termination and will continue at approximately 2 days after Check-out to update safety information and concomitant medications. Subjects may be brought back to the unit at the principal investigator's discretion if any laboratory test abnormalities or other abnormalities are deemed clinically significant at the Check-out or Early Termination Visit.

9.3.9 Follow-up Visit (Day 42)

Subjects will be invited back to the phase 1 unit for a follow-up visit on Day 42 (4 weeks after last dose of quadruple therapy) for a HP breath test. The following procedure will be performed and documented:

- HP breath test.

9.4 Blood Volume

Total blood sampling volume for an individual subject is shown in [Table 9.d](#)

Table 9.d Approximate Blood Volume

Sample Type	Sample Volume (mL)	Volume per Period (mL)						Total Volume
		Screening	Check-in/ Baseline	CA + Bismuth + TAK-438 or Lansoprazole Dosing	CA + Bismuth + TAK-438 or Lansoprazole Dosing/TAK-438 or Lansoprazole PK	CA + Bismuth + TAK-438 or Lansoprazole Dosing/TAK-438 or Lansoprazole and Bismuth PK	Check-out	
		Days -28 to -2	Day -1	Day 1 to 11	Day 12-13	Day 14	Day 15	
Safety laboratory samples	10	10	10	20 (Day 5 and 8 only)	20	10	10	80
Pharmacokinetic samples: bismuth	6	-	-	-	-	84	-	84
Pharmacokinetic samples: TAK-438/lansoprazole	6	-	-	-	24	12	-	36
CYP2C19 samples	3	-	3	-	-	-	-	3
Total blood volume								203

- = not applicable.

The maximum volume of blood at any single day is approximately 106 mL, and the approximate total volume of blood for the study is 203 mL.

Direct venipuncture is the preferred method of blood collection; however, a catheter with a single saline flush may be used.

If a catheter with a normal saline flush is used, the 203 mL total blood volume does not include discarded blood from predraws (assuming minimally the catheter dead volume plus 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed 203 mL.

9.5 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section [9.1.12](#). The genetic material will be sent to a testing laboratory to determine the CYP2C19 metabolic status of each subject. Any remaining sample after testing will be destroyed.

The Sponsor and researchers working with the Sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the Sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as 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 medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre existing conditions underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

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

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).
- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, “worsening of...”).

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
 - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List ([Table 10.a](#)).

Table 10.a Takeda Medically Significant AE List

	Term
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation/ventricular tachycardia	Acute liver failure Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product Neuroleptic malignant syndrome/malignant hyperthermia Spontaneous abortion/stillbirth and fetal death

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

- Mild: The event is transient and easily tolerated by the subject.
Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.
Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs

The relationship of each AE to study medication(s) will be assessed using the following categories:

- Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
Not Related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as not related.

10.1.8 Start Date

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

10.1.9 Stop Date

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

10.1.10 Frequency

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

10.1.11 Action Concerning Study Medication

Drug withdrawn – a study medication is stopped due to the particular AE.

Dose not changed – the particular AE did not require stopping a study medication.

Unknown – only to be used if it has not been possible to determine what action has been taken.

Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until the Follow-up telephone call.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

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

10.2.2 Collection and Reporting of SAEs

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

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

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

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

If during the treatment or follow-up period a subject is noted to have ALT or AST $>3 \times$ ULN and total bilirubin $>2 \times$ ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, a Liver Function Test Abnormality Form must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information is not available at the time of the first report and becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply investigative sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last

approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

In this study, 2 kinds of analysis sets are defined: safety analysis set and PK analysis set. 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, completed the minimum protocol specified procedures with no significant protocol deviations, and were evaluable for the PK. The definition of each analysis set will be described in the SAP.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized using the safety analysis set and PK analysis set.

13.1.3 Pharmacokinetic Analysis

The following analyses will be performed in the PK analysis set.

Plasma concentrations of bismuth will be summarized at each scheduled sampling point on Day 14 by administration condition (bismuth with the combination CAL and bismuth with the combination CAT) using descriptive statistics (arithmetic mean, SD, median, minimum and maximum, geometric mean, and %CV). For Days 12 to 14, plasma concentrations of TAK-438F and lansoprazole will be summarized at each scheduled sampling point using descriptive statistics. Concentration-time profiles of bismuth for individual subjects and mean concentration-time profiles with standard deviations will be provided for both administration conditions (bismuth with CAL and bismuth with CAT). Individual plasma concentration data versus time will be presented in a data listing.

The plasma and urine PK parameters of bismuth will be summarized by administration conditions (bismuth with CAL and bismuth with CAT) using descriptive statistics. In addition, geometric mean and coefficient of variation will be computed for C_{\max} and AUCs from plasma PK.

Two-sided 90% and 95% confidence levels (CIs) 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 to evaluate the impact of TAK-438 on the PK of bismuth compared with the impact of lansoprazole on the PK of bismuth. Statistical analyses of other plasma and urine PK parameters will be performed if appropriate.

A more detailed analysis will be presented in the SAP.

13.1.4 Safety Analysis

All summaries of safety data will be presented based on the safety analysis set. No statistical testing or inferential statistics will be generated.

Adverse Events

A TEAE is defined as an AE whose date of onset occurs on or after the start of study drug.

All TEAEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. All TEAEs, drug-related TEAEs and serious TEAEs will be summarized by administration conditions (bismuth with CAL and bismuth with CAT).

Clinical Laboratory Evaluations, Vital Signs, and 12-lead ECGs

Observed values and changes (from Baseline) for continuous variables will be summarized by administration conditions (bismuth with CL and bismuth with CAT) over time using descriptive statistics.

For categorical variables, shift tables will be presented for administration conditions (bismuth with CAL and bismuth with CAT).

Method of Data Conversion and Handling of Missing Data

No imputation of missing data or of excluded data in accordance with the SAP will be applied. Values below the lower limit of quantification will be handled as 0.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 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=percentage coefficient of variation.

These calculations allow for up to 2 dropouts per group and are based on estimates of %AUC 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}) [15].

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda using the Protocol Deviation Form.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 14.a Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 10 minutes predose (a)	0 hour
±5 (b)	immediately postdose to ≤6 hours
±10 (b)	>6 hours to ≤12 hours postdose

(a) For TAK-438, lansoprazole, and bismuth PK samples.

(b) For bismuth PK samples only.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the “Responsibilities of the Investigator” that are listed in [Appendix B](#). The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol’s review and approval. This protocol, the Investigator’s Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB’s or IEC’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives drug/notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator’s final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on www.ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, country, and recruiting status will be registered and available for public viewing. For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will minimally post the results of clinical trials conducted in patients, regardless of outcome, on www.ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ TAK-438 PK or Lanso PK	Quadruple Therapy Dosing /Bismuth PK and TAK-438 PK or Lanso PK	Check-out/Early Termination (j)	Follow-up	
			Day -1	Day 1				Day 2 to 11	Day 12 to 13
Confinement		X	X	X	X	X	X		
Informed consent	X								
Inclusion/exclusion criteria assessment	X	X							
Medical history and demographics (a)	X								
Medication history and concurrent medical conditions	X	X							
Physical examination	X	X					X		
Neurological examination	X	X	X	X	X	X	X		
Vital signs (b)	X	X	X	X	X	X	X		
Body weight and height (c)	X	X				X			
BMI calculation	X	X							
Clinical laboratory tests (d)	X	X		X	X	X	X		
Liver function tests (e)	X	X		X	X	X	X		
Urine drug screen (f)	X	X							
Urine pregnancy test (hCG) (g)	X	X					X		
HP breath test	X								X
Alcohol breath test	X								
Hepatitis panel and HIV panel	X								
Randomization		X							
12-lead ECG (h)	X	X	X	X		X	X		
PTEs monitoring	X	X	X						
AE monitoring			X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	
PK sampling (i)					X	X			
CYP2C19 sample collection (m)		X							
Dispense study medication			X	X	X	X			

Footnotes are on the following page.

Lanso=lansoprazole.

- (a) Demographics are collected at Screening only. All medical history updates should include tobacco, alcohol, and caffeine use.
- (b) Vital signs will include body temperature (oral or tympanic measurement), sitting blood pressure (after 5 minutes resting), respiration rate and pulse (bpm) at Screening, Day -1 and predose from Day 1 to 15.
- (c) Height is only collected at the Screening Visit.
- (d) Fasting clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be collected at Screening, Check-in and Days 5, 8, 12, 13, 14, and 15. If any results are clinically significant at Day 15, subjects may be requested to return for repeat tests.
- (e) Liver function tests are comprised of AST, ALT, total and direct bilirubin, and measurements are to be taken at Screening, Check-in and Days 5, 8, 12, 13, 14, and 15. If any results are clinically significant at Day 15, subjects may be requested to return for repeat tests.
- (f) Drug screen including: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methadone, and opiates.
- (g) Urine hCG test to be performed only in female subjects of childbearing potential.
- (h) ECGs will be collected on Screening, Check-in, and on dosing Days 1, 3, and 7 at pre-morning dose, Day 14 at pre-morning dose and 1, 2, and 4 hours post-morning dose, and at Check-out.
- (i) Blood PK samples for TAK-438 or lansoprazole analysis will be collected on Day 12 to Day 14 at predose (morning and evening). Blood PK samples for bismuth analysis will be collected on Day 14 at 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, and 12.0 hours post-morning dose. Urine PK samples for bismuth analysis will be collected on Day 14 at 0 to 12 hours post-morning dose.
- (j) In the event of Early Termination, all Check-out procedures should be done at the time of withdrawal.
- (k) A follow-up phone call will be made approximately 2 days after Check-out to update safety information including AEs and concomitant medications. Subjects may be brought back to the unit at the principal investigator's discretion if any laboratory test abnormalities or other abnormalities are deemed clinically significant at the Check-out Visit.
- (l) A Follow-up Visit will be arranged after approximately 4 weeks for HP breath test.
- (m) Mandatory collection of 1 whole blood sample (3 mL) for DNA CYP2C19 genotyping will be taken at Day -1. If subjects who initially screen fail for this study have performed DNA blood collection for CYP2C19 genotyping analysis, it is not required again.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that study results are published.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Plasma Samples for PK Analysis of TAK-438 or Lansoprazole

1. Collect 6 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer at room temperature. All TAK-438 or lansoprazole blood samples should be collected into Vacutainers containing sodium heparin.
2. Gently invert the vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the vacutainers for 10 minutes at approximately 1100 to 1300 (relative centrifugal force [RCF]) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-438_115), sample matrix (ie, plasma), analyte (TAK-438F or lansoprazole), randomization sequence number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower until shipment to the correct laboratory as noted in Step 12 of the shipping instructions. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Plasma Samples for PK Analysis of Bismuth

1. Collect 6 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer. All Bismuth blood samples should be collected into vacutainers containing sodium heparin.
2. Gently invert the vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-438_115), sample matrix (ie, plasma), analyte (Bismuth), randomization sequence number, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower until shipment to PPD, Osaka, Japan. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Urine Samples for PK Analysis of Bismuth

1. Collect urine into polypropylene containers. During the collection interval, the urine will be stored at approximately 4°C,
2. Stir the urine in the polypropylene container vigorously.
3. Measure the urine volume within 2 hours of the end of the collection period.
4. Transfer approximately 10 mL aliquots of urine in duplicate into appropriate polypropylene containers. Container should be filled to within 60% to 80% of the nominal value. Labeling may include protocol number (TAK-438_115), sample matrix (ie, urine), analyte (bismuth), randomization sequence number, nominal day and time, and either “SET 1” (for original sample) or “SET 2” (for duplicate sample).
5. Freeze the urine sample immediately and store frozen at approximately -70°C or lower. Keep samples frozen at approximately -70°C or lower until shipment to ^{PPD} [REDACTED], Osaka, Japan.

Shipping of Plasma and Urine Samples

The following instructions are recommended unless they differ from the site’s standard operating procedures for labeling, packaging, or shipping of PK samples.

1. Plasma samples for TAK-438, lansoprazole and Bismuth will be collected separately and sent to different analytical labs.
2. Biological samples (ie, plasma or urine) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
3. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject’s samples as follows:
4. Separate the duplicate SET 2 samples from the SET 1 samples.
5. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
6. Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma or urine), number of samples, and “SET 1” on each self-sealing bag.
7. Place the bags of individual subject’s samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked “SET 2.”
8. An inventory of individual samples should accompany each shipment and should include the Sponsor’s name (Takeda), study medication (TAK-438), protocol number (TAK-438_115),

investigator's name, sample type (ie, plasma or urine), randomization sequence number, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.

9. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
10. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
11. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
12. Follow Central Laboratory Manual for shipping samples.

Plasma Samples for TAK-438

PPD



Plasma Samples for Lansoprazole

PPD



Plasma and Urine Samples for Bismuth

PPD



13. Affix a carbon dioxide label on each carton, specifically:

Carbon Dioxide Solid UN-1845

Class 9 PKG GR III

Quantity _____

(fill in weight to nearest lb/kg and specify unit of measure used)

CONFIDENTIAL

14. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.
15. Obtain the airway bill number and a receipt of shipment from the carrier.
16. After shipping of the TAK-438 samples, **please contact (name) at e-mail** to notify her of next day delivery. When calling, provide the following information:
 - Name of courier or transport company
 - Time and date the shipment left the clinical site
 - Airway bill number

Collection of PGx Samples

Sample Collection

1. Mandatory Collection for CYP2C19 Genotyping:

One 3 mL whole blood sample for DNA isolation and CYP2C19 genotyping will be collected from each subject during the screening period, into a plastic tube spray coated with K₂EDTA.

Appendix F Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 03 are indicated. The corresponding text has been revised throughout the protocol

Change 1: Removal of reference to CYP2C19 genotype status from study inclusion criteria.

The primary change occurs in: Section [7.1 Inclusion Criteria](#):

Initial wording:	3. The subject is HP positive and a CYP2C19 EM (genotypes 1/*1, *1/*2, and *1/*3) at Screening.
------------------	-------------------------------------------------------------------------------------------------

Amended or new wording:	3. The subject is HP positive and a CYP2C19 EM (genotypes 1/*1, *1/*2, and *1/*3) at Screening.
-------------------------	------------------------------------------------------------------------------------------------------------

Rationale for Change:

The inclusion criterion #3 has been extended to permit all subjects, regardless of CYP2C19 genotype to be eligible to enter the study. TAK-438 is predominantly metabolized by CYP3A4, therefore, CYP2C19 status does not have an impact on plasma concentrations of TAK-438. Secondly, although exposure to lansoprazole has been shown to be several fold higher in subjects who lack a functional CYP2C19 gene (poor metabolizers), approved dosing information for lansoprazole does not state dose adjustment based on CYP2C19 status. Taken together, the enrolment of subjects with all CYP2C19 genotypes is not anticipated to have an impact on the safety of the subjects or on the objectives and scientific value of the study.

The following sections also contain this change:

- Section [2.0 STUDY SUMMARY](#)
 - Section [6.1 Study Design](#)
 - Section [6.2 Justification for Study Design, Dose, and Endpoints](#)
-

Change 2: For Exclusion criterion #20, permission for all investigators (including sub investigators) to enter subjects with non-clinically significant electrocardiogram (ECG) abnormalities.

The primary change occurs in: Section 7.2 Exclusion Criteria

Initial wording: 20. The subject has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by both the principal investigator and the contract research organization (CRO) medical monitor.

Amended or new wording: 20. The subject has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by both the principal investigator and the contract research organization (CRO) medical monitor.

Rationale for Change:

A site request to allow all appropriately-trained investigators involved in the study to permit entry in case of principal investigator unavailability.

Change 3: For Exclusion Criterion No.22, glomerular filtration rate to be estimated using the Chronic Kidney Disease-Epidemiology Collaboration formula.

The primary change occurs in: Section 7.2 Exclusion Criteria

Initial wording: 22. The subject has reduced renal function assessed by having an estimated glomerular filtration rate $<90 \text{ mL/min/1.73 m}^2$ (as estimated by Modification of Diet in Renal Disease) at Screening or Check-in.

Amended or new wording: 22. The subject has reduced renal function assessed by having an estimated glomerular filtration rate $<90 \text{ mL/min/1.73 m}^2$ (as estimated by ~~Modification of Diet in Renal Disease~~ **Chronic Kidney Disease-Epidemiology Collaboration**) at Screening or Check-in.

Rationale for Change:

Compared with the Modification of Diet in Renal Disease equation for estimating glomerular filtration rate, the Chronic Kidney Disease-Epidemiology Collaboration equation has been shown to be similarly accurate at estimating the glomerular filtration rate in subjects with an estimated glomerular filtration rate of $<60 \text{ ml/min/1.73m}^2$ and substantially more accurate in subjects with eGFR of $>60 \text{ ml/min/1.73m}^2$ (Misuk Ji, Yoon-Hee Lee, Mina Hur, Hyesun Kim, Han-Ik Cho, Hyun Suk Yang, et al. Comparing results of five glomerular filtration rate-estimating equations in the Korean general population: MDRD Study, Revised Lund-Malmö, and three CKD-EPI equations. Ann Lab Med 2016;36:521-528.)

Change 4: Clarification to indicate that the time point for pharmacokinetic (PK) analysis will be Day 14.

The primary change occurs in Section 5.2 Endpoints:

Initial wording:	<ul style="list-style-type: none">– C_{\max} at Day 14.– The area under the plasma concentration-time curve during a dosing interval (AUC_{τ}).– The amount of drug excreted in urine during a dosing interval (Ae_{τ}).
Amended or new wording:	<ul style="list-style-type: none">– 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.

Rationale for Change:

A clarification to indicate the time point for PK analysis.

Change 5: Rescreening and the process of rescreening subjects have been added.

The primary change occurs in Section 9.3.1 Screening (Day -28 to -2):

Initial wording: Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures.

Amended or new wording: Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures.

Subjects who initially screen fail for the study are permitted to rescreen following re-consent, with the exception of subjects who at the initial screening visit failed due to abnormal clinical laboratory values that were investigator-defined as clinically significant. All screening procedures with the possible exception of DNA blood collection for CYP2C19 genotyping analysis (if this has been collected it is not required to be collected again) will be repeated.

The subject must meet all inclusion and none of the exclusion criteria at the time of rescreening in order to qualify for the study.

Rationale for Change:

Given that the inclusion criteria has changed to permit the inclusion of all HP positive subjects, regardless of CYP2C19 status (see Change 1), and the equation for estimating glomerular filtration rate has also changed (see Change 3), the protocol has been updated to provide guidance for the possible rescreening of subjects who had previously been found to be ineligible.

The following sections also contain this change:

- Section 9.1.12 Pharmacogenetic Sample Collection for CYP2C19 Genotyping.
 - Section 9.1.15 Documentation of Screen Failure.
-

Change 6: Amendments to the CYP2C19 blood collection.

The primary change occurs in Section [9.1.12 Pharmacogenetic Sample Collection for CYP2C19 Genotyping](#):

Initial wording: One whole blood sample (3 mL) for DNA isolation will be collected during the screening period from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K₂EDTA) spray-coated tubes, and stored under frozen condition. A second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation into the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the PK/clinical efficacy of TAK-438 and lansoprazole. CYP2C19 metabolic status information will be confirmed with the investigators prior to Day -1.

Amended or new wording: One whole blood sample (3 mL) for DNA isolation will be collected ~~during the screening period~~ **at Day-1** from each subject in the study, into plastic potassium ethylenediamine tetraacetic acid (K₂EDTA) spray-coated tubes, and stored under frozen condition. A second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation into the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the PK/clinical efficacy of TAK-438 and lansoprazole. ~~CYP2C19 metabolic status information will be confirmed with the investigators prior to Day -1.~~

Rationale for Change:

To clarify study procedures.

The following section also contains one of these changes:

- [Table 9.d Approximate Blood Volume.](#)
 - [Appendix A Schedule of Study Procedures.](#)
-

Change 7: The screening procedure of *Helicobacter pylori* (HP) breath test is permitted to be performed at a satellite site.

The primary change occurs in Section 9.3.1 Screening (Day -28 to -2):

Initial HP breath test.
wording:

Amended HP breath test. **Providing the subject has signed the informed consent form, sites can choose to conduct the urea breath test at a satellite site. The urea breath test or new may only be performed at a satellite site after the Sponsor has reviewed and wording: approved the site's procedures. All other screening procedures, and all other study visits are required to be conducted at the main Phase 1 unit.**

Rationale for Change:

This update to the study protocol has been included to improve the recruitment process by allowing a satellite site to test for HP status, before a subject must travel to the main Phase 1 unit to confirm other eligibility criteria. Satellite sites will use the same urea breath test as the main Phase 1 unit, and staff will be appropriately trained. Therefore, allowing satellite sites to conduct this test will not have an impact on the scientific integrity of the study or subject safety.

The following section also contains this change:

- Section 9.1.1 Informed Consent Procedure.
-

Change 8: Clarified liver function test monitoring.

The primary change occurs in [Table 9.a Clinical Laboratory Tests](#):

Description In the column *Serum Chemistry*: alanine aminotransferase, aspartate of change: aminotransferase, total bilirubin, and direct bilirubin have been highlighted as being included in liver function tests, with a new footnote:

(b) Included in liver function tests.

Rationale for Change:

Highlight the tests involved in liver function monitoring.

The following sections also contain this change:

- Section [9.3 Schedule of Observations and Procedures](#).
 - [Appendix A Schedule of Study Procedures](#).
-

Change 9: Clarification of footnotes in the Schedule of Study Procedures ([Appendix A](#)).

The primary change occurs in [Appendix A Schedule of Study Procedures](#):

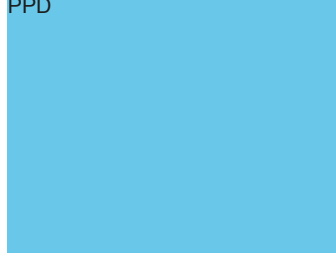
Description In the footnote (b): Vital signs will include body temperature (oral or tympanic of change: measurement), sitting blood pressure (after 5 minutes resting), respiration rate and pulse (bpm) at Screening Day -1 and predose from Day 1 to Day 15. ~~An orthostatic blood pressure measurement will be made at Screening and Check-in (Day -1) based on the difference between sitting and standing [1 minute] systolic blood pressure measurements.~~

Rationale for Change:

To clarify study procedures.

Amendment 03 to 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

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD 	Clinical Pharmacology Approval	23-Nov-2016 11:27 UTC
	Biostatistics Approval	23-Nov-2016 12:20 UTC
	Clinical Science Approval	24-Nov-2016 00:35 UTC
	Medical Monitor Approval	24-Nov-2016 02:42 UTC

Appendix F Detailed Description of Amendments to Text

This document describes changes in reference to the original Protocol (22 December 2015).

Page 2, Section 1.1 Contacts

Existing text

A separate contact information list will be provided to each site.

TDC sponsored Asian Pacific investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Issue	Asian Regional Contact
Serious adverse event, pregnancy and special interest adverse event reporting	<i>To be confirmed</i>
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	<i>To be confirmed</i>
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	<i>To be confirmed</i>

Revised Text

A separate contact information list will be provided to each site.

TDC sponsored Asian Pacific investigators will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Issue	Asian Regional Contact
Serious adverse event, pregnancy and special interest adverse event reporting	PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

Rationale for Amendment

Appropriate contacts have been identified for reporting of adverse events, Medical Monitoring, and the Responsible Medical Officer.

Page 3, Section 1.2 Approvals

Existing Text

SIGNATURES

Electronic Signatures may be found on the last page of this document.

PPD		ate	PPD		Date
[Redacted]			[Redacted]		

PPD		Date	PPD		Date
[Redacted]			[Redacted]		

Revised Text

SIGNATURES

Electronic Signatures may be found on the last page of this document.

PPD		Date	PPD		Date
[Redacted]			[Redacted]		

PPD		Date	PPD		Date
[Redacted]			[Redacted]		

Rationale for Amendment

According to changes in the Takeda process for approval of Protocols and Protocol Amendments, the document should be approved by the Study Clinical Science Lead. As such, ^{PPD} [REDACTED] replaces ^{PPD} [REDACTED].

Page 20, Section 5.1 Objectives

Existing Text

The objectives of this study are:

- 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).
- *To evaluate the 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).*

Revised Text

The objectives of this study are:

- 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).

Rationale for Amendment

The first, bulleted objective stated that the objectives of the study were to evaluate the safety, tolerability, and PK of study drug administration. The second, bulleted objective in the original text was a duplicate of this for PK evaluation and, as such, has been deleted.

Page 25, Section 7.2 Exclusion Criteria

Existing Text

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 90 days prior to providing their informed consent.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

4. The subject has uncontrolled, clinically significant cardiovascular, or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-438, penicillins, macrolides, and bismuths, for example, D-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide, and iron sesquioxide.
6. The subject has a positive urine drug result for drugs of abuse at Screening or Check-in (Day -1).
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 21 units or more units per week) at any time prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study (1 unit=12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine).
8. The subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table listed in Section 7.3 of the protocol, except where over-the-counter (OTC) medication has been pre-approved by Takeda.
9. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
10. The subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-438, or contraindicate any drug used to reduce acid secretion by the stomach or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
11. The subject has a history of gastroesophageal reflux disease (GERD), symptomatic GERD, erosive esophagitis, DU, GU, *dyspepsia*, Barrett's Esophagus, or Zollinger-Ellison syndrome or has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs.
12. The subject has any known disease or is taking any medication that is contraindicated with bismuth, clarithromycin, or amoxicillin.
13. The subject has a history of cancer, except basal cell carcinoma or Stage 1 squamous cell carcinoma of the skin that has been in remission for at least 5 years prior to Day 1.
14. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen at Screening.

15. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 6 weeks prior to Check-in. Cotinine test is positive at Screening or Check-in.
16. The subject has poor peripheral venous access.
17. The subject has donated or lost 450 mL or more of his blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to Day 1.
18. The subject has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by both the principal investigator and the contract research organization (CRO) medical monitor.
19. The subject has abnormal Screening or Check-in laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities: alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin >the upper limit of normal (ULN).
20. The subject has reduced renal function assessed by having an estimated glomerular filtration rate <90 mL/min/1.73 m² (as estimated by Modification of Diet in Renal Disease) at Screening or Check-in.

Revised Text

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 90 days prior to providing their informed consent.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has uncontrolled, clinically significant cardiovascular, or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the study results.
5. The subject has a known hypersensitivity to any component of the formulation of TAK-438, penicillins, macrolides, and bismuths, for example, D-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide, and iron sesquioxide.
6. The subject has a positive urine drug result for drugs of abuse at Screening or Check-in (Day -1).
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 21 units or more units per week) at any time prior to

- the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study (1 unit=12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine).
8. The subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table listed in Section 7.3 of the protocol, except where over-the-counter (OTC) medication has been pre-approved by Takeda.
 9. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
 10. The subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking TAK-438, or contraindicate any drug used to reduce acid secretion by the stomach or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
 11. The subject has a history of gastroesophageal reflux disease (GERD), symptomatic GERD, erosive esophagitis, DU, GU, Barrett's Esophagus, or Zollinger-Ellison syndrome or has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs.
 - 12. Subjects who have undergone therapeutic upper gastrointestinal endoscopic therapy (eg, endoscopic hemostasis or excision including biopsy) within 30 days prior to visit 1.**
 - 13. Subjects who have undergone major surgical procedures within the past 1 month or are scheduled to undergo surgical procedures that may affect gastric acid secretion (eg, abdominal surgery, vagotomy, or craniotomy).**
 14. The subject has any known disease or is taking any medication that is contraindicated with bismuth, clarithromycin, or amoxicillin.
 15. The subject has a history of cancer, except basal cell carcinoma or Stage 1 squamous cell carcinoma of the skin that has been in remission for at least 5 years prior to Day 1.
 16. The subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV) antibody/antigen at Screening.
 17. The subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 6 weeks prior to Check-in. Cotinine test is positive at Screening or Check-in.
 18. The subject has poor peripheral venous access.
 19. The subject has donated or lost 450 mL or more of his blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to Day 1.

20. The subject has a Screening or Check-in abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by both the principal investigator and the contract research organization (CRO) medical monitor.
21. The subject has abnormal Screening or Check-in laboratory values that suggest a clinically significant underlying disease or subject with the following laboratory abnormalities: alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin >the upper limit of normal (ULN).
22. The subject has reduced renal function assessed by having an estimated glomerular filtration rate <90 mL/min/1.73 m² (as estimated by Modification of Diet in Renal Disease) at Screening or Check-in.

Rationale for Amendment

In order to ensure that subjects are recruited with an intact luminal gastrointestinal tract, so that absorption of investigational medicinal product is not compromised, 2 additional criteria (#12 and #13) have been added to Section 7.2 Exclusion Criteria. The additions will exclude subjects with a history of upper gastrointestinal endoscopic therapy (within 30 days of Visit 1) and exclude subjects who have undergone (within 1 month prior to recruitment), or will be undergoing, major surgical procedures that may affect gastric acid secretion. Additionally, as dyspepsia is a common symptom of H. pylori infection, this term has been removed as an exclusion criteria.

Page 28, Section 7.3 Excluded Medication, Dietary Products

Existing Text

Concomitant medications will include all medications the subject has taken from signing of informed consent to the *end of the study* (Day 17).

Revised Text

Concomitant medications will include all medications the subject has taken from signing of informed consent to the **Follow-up call** (Day 17).

Rationale for Amendment

The study end has been corrected to Day 42 from Day 17.

Page 74, Appendix A Schedule of Study Procedures

Existing Text

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ TAK-438 PK or Lanso PK	Quadruple Therapy Dosing /Bismuth PK and TAK-438 PK or Lanso PK	Check-out/Early termination (i)	Follow-up	
			Day 1	Day 2 to 11				Day 12 to 13	Day 14
Confinement		X	X	X	X	X	X		
Informed consent	X								
Inclusion/exclusion criteria assessment	X	X							
Medical history and demographics (a)	X								
Medication history and concurrent medical conditions	X	X							
Physical examination	X	X					X		
Neurological examination	X	X	X	X	X	X	X		
Vital signs (b)	X	X	X	X	X	X	X		
Body weight and height (c)	X	X				X			
BMI calculation	X	X							
Clinical laboratory tests (d)	X	X		X	X	X	X		
Urine drug screen (e)	X	X							
Urine pregnancy test (hCG) (f)	X	X				X	X		
HP breath test	X								X
Alcohol breath test	X								
Hepatitis panel and HIV panel	X								
Randomization		X							
12-lead ECG (g)	X	X	X	X		X	X		
PTEs monitoring	X	X	X						
AE monitoring			X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	
PK sampling (h)					X	X			
CYP2C19 sample collection (l)	X								
Dispense study medication			X	X	X	X			

Revised Text

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ TAK-438 PK or Lanso PK	Quadruple Therapy Dosing /Bismuth PK and TAK-438 PK or Lanso PK	Check-out/Early termination (i)	Follow-up	
	Days -28 to -2	Day -1	Day 1	Day 2 to 11	Day 12 to 13	Day14	Day 15	Day 17 (+2 days) (j)	Day 42 (+6 days) (k)
Confinement		X	X	X	X	X	X		
Informed consent	X								
PGx informed consent			X						
Inclusion/exclusion criteria assessment	X	X							
Medical history and demographics (a)	X								
Medication history and concurrent medical conditions	X	X							
Physical examination	X	X					X		
Neurological examination	X	X	X	X	X	X	X		
Vital signs (b)	X	X	X	X	X	X	X		
Body weight and height (c)	X	X				X			
BMI calculation	X	X							
Clinical laboratory tests (d)	X	X		X	X	X	X		
Urine drug screen (e)	X	X							
Urine pregnancy test (hCG) (f)	X	X					X		
HP breath test	X								X
Alcohol breath test	X								
Hepatitis panel and HIV panel	X								
Randomization		X							
12-lead ECG (g)	X	X	X	X		X	X		
PTEs monitoring	X	X	X						
AE monitoring			X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	
PK sampling (h)					X	X			
CYP2C19 sample collection (l)	X								
Dispense study medication			X	X	X	X			

Rationale for Amendment

A separate PGx informed consent form must be obtained in order to store the remaining DNA sample from the CYP2C19 genotyping. The provision of consent to store the sample for future analysis is independent of consent to the other aspects of the study and any randomized subjects will be provided with a separate PGx informed consent form at Randomization. As such, this will be collected at Day 1, in the Schedule of Study Procedures. Additionally, the procedure for urine pregnancy test on Day 14 has been deleted, as this was included in error. The qualifier (+6 days) has been added to the Follow-up at Day 42, in order to be aligned with the study schematic (Figure 6.a).

Page 81, Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Existing Text

Instructions for Processing of Plasma Samples for PK Analysis of TAK-438 or Lansoprazole

1. Collect 6 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer at room temperature. All TAK-438 or lansoprazole blood samples should be collected into Vacutainers containing sodium heparin.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-438_115), sample matrix (ie, plasma), analyte (TAK-438F or lansoprazole), *subject number, period*, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower until shipment to the correct laboratory as noted in Step 12 of the shipping instructions. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Plasma Samples for PK Analysis of Bismuth

1. Collect 6 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer. All Bismuth blood samples should be collected into Vacutainers containing sodium heparin.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.

3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-438_115), sample matrix (ie, plasma), analyte (Bismuth), enrollment number, period, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower until shipment to ^{PPD} Osaka, Japan. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Urine Samples for PK Analysis of Bismuth

1. Collect urine into polypropylene containers. During the collection interval, the urine will be stored at approximately 4°C,
2. Stir the urine in the polypropylene container vigorously.
3. Measure the urine volume within 2 hours of the end of the collection period.
4. Transfer approximately 10 mL aliquots of urine in duplicate into appropriate polypropylene containers. Container should be filled to within 60% to 80% of the nominal value. Labeling may include protocol number (TAK-438_115), sample matrix (ie, urine), analyte (bismuth), enrollment number, period, nominal day and time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Freeze the urine sample immediately and store frozen at approximately -70°C or lower. Keep samples frozen at approximately -70°C or lower until shipment to ^{PPD} Osaka, Japan.

Shipping of Plasma and Urine Samples

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of PK samples.

1. Plasma samples for TAK-438, lansoprazole and Bismuth will be collected separately and sent to different analytical labs.
2. Biological samples (ie, plasma or urine) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
3. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:

4. Separate the duplicate SET 2 samples from the SET 1 samples.
5. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
6. Using a permanent marker, write the 4-digit enrollment number, sample matrix (ie, plasma or urine), number of samples, and “SET 1” on each self-sealing bag.
7. Place the bags of individual subject’s samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked “SET 2.”
8. An inventory of individual samples should accompany each shipment and should include the Sponsor’s name (Takeda), study medication (TAK-438), protocol number (TAK-438_115), investigator’s name, sample type (ie, plasma or urine), subject enrollment number, period, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as “SET 2.” Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
9. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
10. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
11. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
12. Follow Central Laboratory Manual for shipping samples. The PK samples will be shipped to the central laboratory and the central laboratory will ship to the designated laboratories for analysis of TAK-438, lansoprazole or bismuth.

Plasma Samples for TAK-438

PPD



PPD



Plasma and Urine Samples for Bismuth

PPD



13. Affix a carbon dioxide label on each carton, specifically:
Carbon Dioxide Solid UN-1845
Class 9 PKG GR III
Quantity _____
(fill in weight to nearest lb/kg and specify unit of measure used)
14. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.
15. Obtain the airway bill number and a receipt of shipment from the carrier.
16. After shipping of the TAK-438 samples, **please contact (name) at e-mail** to notify her of next day delivery. When calling, provide the following information:
Name of courier or transport company
Time and date the shipment left the clinical site
Airway bill number

Revised Text

Instructions for Processing of Plasma Samples for PK Analysis of TAK-438 or Lansoprazole

1. Collect 6 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer at room temperature. All TAK-438 or lansoprazole blood samples should be collected into Vacutainers containing sodium heparin.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.

4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-438_115), sample matrix (ie, plasma), analyte (TAK-438F or lansoprazole), **randomization sequence number**, nominal day and time, and either “SET 1” (for original sample) or “SET 2” (for duplicate sample).

5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower until shipment to the correct laboratory as noted in Step 12 of the shipping instructions. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Plasma Samples for PK Analysis of Bismuth

1. Collect 6 mL of venous blood for the plasma into a Becton-Dickinson Vacutainer. All Bismuth blood samples should be collected into Vacutainers containing sodium heparin.

2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.

3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at approximately 4°C. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer’s instruction for proper centrifugation force and time.

4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-438_115), sample matrix (ie, plasma), analyte (Bismuth), **randomization sequence number**, nominal day and time, and either “SET 1” (for original sample) or “SET 2” (for duplicate sample).

5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower until shipment to ^{PPD} Osaka, Japan. No more than 45-60 minutes will elapse between blood collection and freezing the plasma sample.

Instructions for Processing of Urine Samples for PK Analysis of Bismuth

1. Collect urine into polypropylene containers. During the collection interval, the urine will be stored at approximately 4°C,

2. Stir the urine in the polypropylene container vigorously.

3. Measure the urine volume within 2 hours of the end of the collection period.

4. Transfer approximately 10 mL aliquots of urine in duplicate into appropriate polypropylene containers. Container should be filled to within 60% to 80% of the nominal value. Labeling may include protocol number (TAK-438_115), sample matrix (ie, urine), analyte (bismuth), **randomization sequence number**, nominal day and time, and either “SET 1” (for original sample) or “SET 2” (for duplicate sample).

5. Freeze the urine sample immediately and store frozen at approximately -70°C or lower. Keep samples frozen at approximately -70°C or lower until shipment to PPD [REDACTED] Osaka, Japan.

Shipping of Plasma and Urine Samples

The following instructions are recommended unless they differ from the site's standard operating procedures for labeling, packaging, or shipping of PK samples.

1. Plasma samples for TAK-438, lansoprazole and Bismuth will be collected separately and sent to different analytical labs.
2. Biological samples (ie, plasma or urine) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.
3. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
 4. Separate the duplicate SET 2 samples from the SET 1 samples.
 5. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
 6. Using a permanent marker, write the 4-digit **randomization sequence number**, sample matrix (ie, plasma or urine), number of samples, and "SET 1" on each self-sealing bag.
 7. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."
8. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study medication (TAK-438), protocol number (TAK-438_115), investigator's name, sample type (ie, plasma or urine), **randomization sequence number**, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
9. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.

10. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
11. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
12. Follow Central Laboratory Manual for shipping samples.

Plasma Samples for TAK-438

PPD



PPD



Plasma and Urine Samples for Bismuth

PPD



13. Affix a carbon dioxide label on each carton, specifically:
 - Carbon Dioxide Solid UN-1845
 - Class 9 PKG GR III
 - Quantity _____
 - (fill in weight to nearest lb/kg and specify unit of measure used)
14. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.
15. Obtain the airway bill number and a receipt of shipment from the carrier.
16. After shipping of the TAK-438 samples, **please contact (name) at e-mail** to notify her of next day delivery. When calling, provide the following information:
 - Name of courier or transport company
 - Time and date the shipment left the clinical site
 - Airway bill number

Rationale for Amendment

In order to align with Section 8.2, Investigational Drug Assignment and Dispensing Procedures, the term 'randomization sequence number' has replaced 'enrollment number, period', where appropriate. Additionally, for the shipping of PK samples to the designated laboratories (for TAK-438, lansoprazole, and bismuth analysis), the specific names of individuals have been deleted in order to minimize any further protocol amendments.

Appendix F Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Amendment 01 (22 April 2016).

Throughout the Protocol Amendment 02

Revised Text

Wording that references measurement of bismuth PK parameters (in both plasma and urine) at steady state (eg, $C_{\max ss}$) has been removed (eg, C_{\max}).

Rationale for Amendment

In the original protocol, and protocol amendment 01, the sponsor stated that, following oral administration, bismuth is highly distributed throughout the body and displays multicompartment elimination with an effective half-life of 10.2 hours [15], indicating that the plasma concentration could almost reach steady state in a few days after multiple dosing. However, following discussions with the Korean agency (MFDS), in which the time for bismuth to reach steady state could vary from 5 to 28 days, in some literature, it has been agreed that measurement of PK parameters (in both plasma and urine) will now not be calculated on the assumption that steady state has been reached.

Throughout the Protocol Amendment 02

Revised Text

(up to Day 17)

Rationale for Amendment

Qualification of study end as Day 17 regarding prohibited medications for exclusion criteria (Section 7.2), excluded medications/dietary products (Section 7.3), blood draw (Diet, Fluid, and Activity Control, Section 7.4), and documentation of concomitant medications (Section 9.1.6).

Page 2, Section 1.1 Contacts

Existing Text

Medical Monitor (medical advice on protocol, *compound*, and *medical management of subjects*)

Revised Text

Medical Monitor (medical advice on protocol and **study drug**)

Rationale for Amendment

Adopted the protocol template language.

Page 3, Section 1.2 Approval

Existing Text

Richard Jenkins, *PhD*
Global Development Lead, GI TAU, Senior Scientific Director

Revised Text

Richard Jenkins, **DPhil**
Global Development Lead, GI TAU, Senior Scientific Director

Rationale for Amendment

Correct qualification assigned.

Page 13, Section 2.0 Study Summary

Existing Text

Main Criteria for Exclusion

A history of hypersensitivity to any excipients of TAK-438.

Pharmacogenomics:

Mandatory blood samples will be collected for CYP2C19 genotyping. The storage of remaining DNA samples from the CYP2C19 genotyping test for future analysis will be optional.

- Total volume of blood drawn:

Blood draw is expected to be 206 mL.

Revised Text

Main Criteria for Exclusion

A history of hypersensitivity to any excipients of TAK-438 **and lansoprazole.**

Pharmacogenomics:

Mandatory blood samples will be collected for CYP2C19 genotyping.

- Total volume of blood drawn:

Blood draw is expected to be **203** mL.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed.

Page 21, Section 5.2 Endpoints

Existing Text

- Additional safety endpoints will be examined.
- 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):
 - The maximum observed steady-state plasma concentration ($C_{\max,ss}$) at Day 14.
 - The area under the plasma concentration-time curve during a dosing interval (AUC_T).
 - The amount of drug excreted in urine during a dosing interval (Ae_T).

- Additional PK endpoints for tripotassium bismuth dicitrate (600 mg), TAK-438 and lansoprazole.

Revised Text

- 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}).
 - The amount of drug excreted in urine during a dosing interval (Ae_{τ}).

Rationale for Amendment

As a consequence of lack of specificity, 2 endpoints ('Additional safety endpoints will be examined.' and 'Additional PK endpoints for tripotassium bismuth dicitrate (600 mg), TAK-438 and lansoprazole.') have been removed.

Page 24, Section 6.2 Justification for Study Design, Dose, and Endpoints

Existing Text

According to the HP local treatment guideline for HP in China, the recommended dose of bismuth is 220 mg BID [6]. Therefore, tripotassium bismuth dicitrate 600 mg has been chosen in this study as it is equivalent to bismuth 220 mg (hereafter referred to as bismuth 220 mg). Bismuth potassium citrate is the synonym of tripotassium bismuth dicitrate. Bismuth is minimally absorbed with bioavailability <0.3%, a time to reach C_{\max} (t_{\max}) of 0.5 hour and is excreted through urinary and biliary routes. It is highly distributed throughout the body and displays multicompartment elimination with an *effective* half-life of 10.2 hours [11], *indicating that the plasma concentration could almost reach steady state in a few days after multiple dosing*. This study could not be simulated using physiologically-based PK modeling due to the number of regimens used.

Revised Text

According to the HP local treatment guideline for HP in China, the recommended dose of bismuth is 220 mg BID [6]. Therefore, tripotassium bismuth dicitrate 600 mg has been chosen in this study as it is equivalent to bismuth 220 mg (hereafter referred to as bismuth 220 mg). Bismuth potassium citrate is the synonym of tripotassium bismuth dicitrate. Bismuth is minimally absorbed with bioavailability <0.3%, a time to reach C_{\max} (t_{\max}) of 0.5 hour and is excreted through urinary and biliary routes. It is highly distributed throughout the body and displays multicompartment elimination with **multiple half-lives: an initial half-life of 1-4 hours, a more prolonged half-life of 5-11 days, and a more extended half-life [11,12]. There are several half-lives reported for bismuth, however, one article indicates that plasma level of bismuth approach an apparent steady-state after 30 - 40 days after multiple dose of bismuth**. This study could not be simulated using physiologically-based PK modeling due to the number of regimens used.

Rationale for Amendment

Following extended literature review, the half-life for bismuth has been revised and supported by 2 new references (Benet 1991; Froomes et al. 1989).

Page 27, Section 7.2 Exclusion Criteria

Existing Text

5. The subject has a known hypersensitivity to any component of the formulation of TAK-438, penicillins, macrolides, *and* bismuths, for example, D-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide, and iron sesquioxide.

7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 21 units or more units per week) at any time prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study (*1 unit=12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine*).

12. Subjects who have undergone therapeutic upper gastrointestinal endoscopic therapy (eg, endoscopic hemostasis or excision including biopsy) within 30 days prior to *Day -28*.

Revised Text

5. The subject has a known hypersensitivity to any component of the formulation of TAK-438, penicillins, macrolides, bismuths, **and lansoprazole**, for example, D-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide, and iron sesquioxide.

7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 21 units or more units per week) at any time prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.

12. Subjects who have undergone therapeutic upper gastrointestinal endoscopic therapy (eg, endoscopic hemostasis or excision including biopsy) within 30 days prior to **Screening**.

Rationale for Amendment

The exclusion criterion regarding known hypersensitivity to medicines provided by the sponsor for administration during the study has been expanded to include lansoprazole, which will be administered as an active comparator.

The qualification for alcohol units will now be calculated by the study site.

To be consistent with other exclusion criteria, Day -28 was rephrased to Screening.

Page 34, Section 8.2 Investigational Drug Assignment and Dispensing Procedures

Existing Text

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the randomization schedule allocated to the site. The Randomization Sequence Number will be entered onto the eCRF. *Med ID will be assigned by the Site Pharmacist*

or authorized study designee based on the randomization schedule and medication schedule allocated to the site.

Revised Text

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the **blinded** randomization schedule allocated to the site. The Randomization Sequence Number **and Med ID** will be entered onto the eCRF.

Rationale for Amendment

The randomization schedule and Med ID list will be provided to a blinded pharmacist at the site in order to dispense the drug.

Page 35, Section 8.3 Randomization Code Creation and Storage

Existing Text

Randomization personnel of the sponsor or designee will generate the randomization schedule and will provide it to the site pharmacist or authorized study designee prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

Revised Text

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

A blinded randomization schedule will be provided to the site pharmacist or authorized study designee prior to the start of this study. The Med ID to be dispensed to each subject will be provided in this schedule.

Rationale for Amendment

A blinded randomization schedule (includes the subject sequence number and which Med ID each subject should receive) will be provided to the pharmacist or designee.

Page 38, Section 9.1.1.1 Pharmacogenomic Informed Consent Procedure

Existing Text

The sampling of whole blood for CYP2C19 genotyping analysis is mandatory; every subject must sign the informed consent in order to participate in this study. The informed consent for the CYP2C19 genotyping analysis is a component of the overall study informed consent.

A separate pharmacogenomic (PGx) informed consent form pertaining to storage of the sample must be obtained in order to store the sample after the study related PGx analysis described in the protocol is completed. The provision of consent to store the sample for future analysis is independent of consent to the other aspects of the study and any randomized subjects will be provided with a separate PGx informed consent form at Randomization. The requirements are described in Section 15.2.

Revised Text

The sampling of whole blood for CYP2C19 genotyping analysis is mandatory; every subject must sign the informed consent in order to participate in this study. The informed consent for the CYP2C19 genotyping analysis is a component of the overall study informed consent.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed. Therefore, there is no longer the need to obtain PGx informed consent.

Page 40, Section 9.1.8 Procedures for Clinical Laboratory Samples

Existing Text

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 106 mL, and the approximate total volume of blood for the study is 206 mL for safety laboratory samples. Laboratory samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Revised Text

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 106 mL, and the approximate total volume of blood for the study is **203** mL for safety laboratory samples. Laboratory samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed, which has reduced the total blood draw from 206 mL to 203 mL.

Page 40, Table 9.a Clinical Laboratory Assessments

Existing Text

Serum Chemistry

ALT (a)
Albumin
Alkaline phosphatase
Amylase
AST
GGT
Total bilirubin (a) (b)
Direct bilirubin (a)
Uric acid
Total protein
Triglycerides
Serum creatinine
Blood urea nitrogen
Creatine kinase
Creatine kinase MB
Potassium
Sodium
Glucose
Chloride
Calcium
Magnesium
Cholesterol (HDL and LDL)
LDH (c)

Revised Text

Serum Chemistry

ALT (a)
Albumin
Alkaline phosphatase (**a**)
Amylase
AST
GGT
Total bilirubin (a) (b)
Direct bilirubin (a)
Uric acid
Total protein
Triglycerides (**a**)
Serum creatinine
Blood urea nitrogen
Creatine kinase
Creatine kinase MB
Potassium
Sodium
Glucose
Chloride
Calcium
Magnesium
Cholesterol (HDL and LDL) (**a**)
LDH (c)

Rationale for Amendment

To be consistent with other protocols in the clinical development program for TAK-438, assessment of alkaline phosphatase, triglycerides, and cholesterol will be measured under fasting conditions, as denoted by the footnote (a).

Page 44, Section 9.1.12 Pharmacogenetic Sample Collection for CYP2C19 Genotyping

Existing Text

The sample of whole blood for CYP2C19 genotyping analysis is mandatory. Every subject must sign the informed consent in order to participate in this study.

Two whole blood *samples* (3 mL *per sample*) for DNA isolation will be collected during the screening period from each subject in the study, into plastic K₂EDTA spray-coated tubes, and stored under frozen condition. A second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation into the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the PK/clinical efficacy of TAK-438 and lansoprazole. CYP2C19 metabolic status information will be *provided to* investigators prior to Day -1.

Revised Text

The sample of whole blood for CYP2C19 genotyping analysis is mandatory. Every subject must sign the informed consent in order to participate in this study.

One whole blood **sample** (3 mL) for DNA isolation will be collected during the screening period from each subject in the study, into plastic K₂EDTA spray-coated tubes, and stored under frozen condition. A second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation into the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the PK/clinical efficacy of TAK-438 and lansoprazole. CYP2C19 metabolic status information will be **confirmed with the** investigators prior to Day -1.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed.

Page 44, Section 9.1.13 PGx Sample Collection for Storage

Existing Text

A separate PGx informed consent form must be obtained in order to store the remaining DNA sample from the CYP2C19 genotyping. The provision of consent to store the sample for future analysis is independent of consent to the other aspects of the study and any randomized subjects will be provided with a separate PGx informed consent form at Randomization.

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a “Pharmacogenomics research study.” Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to vonoprazan
- Finding out more information about how vonoprazan works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to vonoprazan.
- Identifying variations in genes related to the biological target of vonoprazan.

This information may be used, for example, to develop a better understanding of the safety and efficacy of vonoprazan and other study medications, understanding of disease/condition being studied and for improving the efficiency, design and study methods of future research studies.

Each PGx sample for a study subject should be identifiable on the requisition form with a subject identification number.

The samples will be stored for no longer than 15 years after completion of the study and/or until the drug development of TAK-438 is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. “Stored samples” are defined as samples that are key-coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drugs.

Detailed instructions for the handling and shipping of samples are provided in Appendix E.

Rationale for Amendment

Section 9.1.13 PGx Sample Collection for Storage has been removed. The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed. Therefore, there is no longer the need to obtain PGx informed consent.

Page 48, Section 9.3.2 Check-in (Day -1)

Existing Text

- Urine pregnancy test (in female subjects of childbearing potential only).
- *Informed consent for long-term storage of DNA blood collection.*
- Confinement will begin once subjects' eligibility is confirmed after study assessments. Randomization will take place on Day -1 after all procedures are completed and the subject remains confined to the phase 1 unit.

Revised Text

- Urine pregnancy test (in female subjects of childbearing potential only).
- Confinement will begin once subjects' eligibility is confirmed after study assessments. Randomization will take place on Day -1 after all procedures are completed and the subject remains confined to the phase 1 unit.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed. Therefore, there is no longer the need to obtain PGx informed consent.

Page 49, Section 9.3.6 Check-out (Day 15)

Added Text

Subjects should avoid antibiotics, PPIs, bismuth preparations until Day 42 (HP breath test)

Rationale for Amendment

Provision of advice to avoid gastrointestinal disease treatments until the final study procedure (HP breath test), on Day 42, as these may interact with TAK-438, affecting the breath test result.

Page 51, Section 9.4 Blood Volume

Existing Text

Table 9.d Approximate Blood Volume

Sample Type	Sample Volume (mL)	Volume per Period (mL)							Total Volume
		Screening	Check-in/ Baseline	CA + Bismuth + TAK-438 or Lansoprazole Dosing	CA + Bismuth + TAK-438 or Lansoprazole Dosing/TAK-438 or Lansoprazole PK	CA + Bismuth + TAK-438 or Lansoprazole Dosing/TAK-438 or Lansoprazole and Bismuth PK	Check-out		
		Days -28 to -2	Day -1	Day 1 to 11	Day 12-13	Day 14	Day 15		
Safety laboratory samples	10	10	10	20 (Day 5 and 8 only)	20	10	10	80	
Pharmacokinetic samples: bismuth	6	-	-	-	-	84	-	84	
Pharmacokinetic samples: TAK-438/lansoprazole	6	-	-	-	24	12	-	36	
CYP2C19 samples	<u>6</u>	<u>6</u>	-	-	-	-	-	<u>6</u>	
Total blood volume								<u>206</u>	

- = not applicable.

The maximum volume of blood at any single day is approximately 106 mL, and the approximate total volume of blood for the study is 206 mL.

Direct venipuncture is the preferred method of blood collection; however, a catheter with a single saline flush may be used.

If a catheter with a normal saline flush is used, the 206 mL total blood volume does not include discarded blood from predraws (assuming minimally the catheter dead volume plus 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed 206 mL.

Revised Text

Table 9.d Approximate Blood Volume

Sample Type	Sample Volume (mL)	Volume per Period (mL)							Total Volume
		Screening	Check-in/ Baseline	CA + Bismuth + TAK-438 or Lansoprazole Dosing	CA + Bismuth + TAK-438 or Lansoprazole Dosing/TAK-438 or Lansoprazole PK	CA + Bismuth + TAK-438 or Lansoprazole Dosing/ TAK-438 or Lansoprazole and Bismuth PK	Check-out		
		Days -28 to -2	Day -1	Day 1 to 11	Day 12-13	Day 14	Day 15		
Safety laboratory samples	10	10	10	20 (Day 5 and 8 only)	20	10	10	80	
Pharmacokinetic samples: bismuth	6	-	-	-	-	84	-	84	
Pharmacokinetic samples: TAK-438/lansoprazole	6	-	-	-	24	12	-	36	
CYP2C19 samples	3	3	-	-	-	-	-	3	
Total blood volume								203	

- = not applicable.

The maximum volume of blood at any single day is approximately 106 mL, and the approximate total volume of blood for the study is **203** mL.

Direct venipuncture is the preferred method of blood collection; however, a catheter with a single saline flush may be used.

If a catheter with a normal saline flush is used, the **203** mL total blood volume does not include discarded blood from predraws (assuming minimally the catheter dead volume plus 1 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study must not exceed **203** mL.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed. Thus, the total blood draw volume will be 203 mL, instead of 206 mL.

Page 51, Section 9.5 Biological Sample Retention and Destruction

Existing Text

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12. The genetic material will be sent to a testing laboratory to determine the CYP2C19 metabolic status of each subject. *If subjects consent for long-term storage, the remaining PGx samples will be preserved and retained at ^{PPD} [REDACTED], Greenfield, IN, USA for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect*

the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The Sponsor and researchers working with the Sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the Sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers; the samples are stripped of all personal identifying information but a key linking the samples to clinical analysis data exists. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

Subjects who consented and provided a PGx sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis. Notify sponsor of consent withdrawal.

Revised Text

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12. The genetic material will be sent to a testing laboratory to determine the CYP2C19 metabolic status of each subject. **Any remaining sample after testing will be destroyed.**

The Sponsor and researchers working with the Sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the Sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed. Thus, the need for storage and retention no longer applies. After DNA analysis for CYP2C19 genotyping, any remaining sample will be destroyed.

Page 54, Section 10.1.4 SAEs

Existing Text

5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Revised Text

5. Is a CONGENITAL ANOMALY/BIRTH DEFECT.

6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:

- May require intervention to prevent items 1 through 5 above.
- May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Rationale for Amendment

The wording for ‘congenital anomaly/birth defect’ has been amended to be in line with the definition in ICH E2A.

Page 55, Section 10.1.6 Causality of AEs

Existing Text

The relationship of each AE to *each* study medication(s) will be assessed using the following categories:

Revised Text

The relationship of each AE to study medication(s) will be assessed using the following categories:

Rationale for Amendment

To provide clarity.

Page 73, Appendix A Schedule of Study Procedures

Existing Text

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ TAK-438 PK or Lanso PK	Quadruple Therapy Dosing /Bismuth PK and TAK-438 PK or Lanso PK	Check-out/Early termination (i)	Follow-up	
			Day 1	Day 2 to 11				Day 17 (+2 days) (j)	Day 42 (k)
Confinement		X	X	X	X	X	X		
Informed consent	X								
<i>PGx Informed consent</i>			<u>X</u>						
Inclusion/exclusion criteria assessment	X	X							

(l) Mandatory collection of 2 whole blood *samples* (3 mL *each*) for DNA CYP2C19 genotyping will be taken during Screening. *Long-term storage for the remaining sample after testing is optional.*

Revised Text

Study Phase	Screening	Check-in Baseline	Quadruple Therapy Dosing (Group A or B)		Quadruple Therapy Dosing/ TAK-438 PK or Lanso PK	Quadruple Therapy Dosing /Bismuth PK and TAK-438 PK or Lanso PK	Check-out/Early termination (i)	Follow-up	
			Day 1	Day 2 to 11				Day 17 (+2 days) (j)	Day 42 (+6 days) (k)
Confinement		X	X	X	X	X	X		
Informed consent	X								
Inclusion/exclusion criteria assessment	X	X							

(l) Mandatory collection of **1** whole blood **sample** (3 mL) for DNA CYP2C19 genotyping will be taken during Screening.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed. Therefore, there is no longer the need to obtain PGx informed consent.

Page 83, Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Existing Text

Collection, *Shipment, and Storage* of PGx Samples

Sample Collection

1. Mandatory Collection for CYP2C19 Genotyping

Two 3 mL whole blood *samples* for DNA isolation and genotyping will be collected from each subject during the screening period, into a plastic tube spray coated with K₂EDTA. *Note long-term storage of the sample is optional.*

Sample Shipment

- 1. DNA PGx samples will be shipped frozen at -20°C after collection.*
- 2. Ship samples only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, to minimize the possibility of samples in transit over a weekend or holiday.*
- 3. The laboratory must confirm arrival of the shipped samples. Storage at the site prior to shipping must be at -20°C or colder.*
- 4. For instructions on shipping, both ambient and refrigerated, and packing follow the laboratory manual and shipping instructions provided by the central laboratory.*
- 5. Before shipping, ensure the sample tubes are tightly sealed. Ship samples to the Central Laboratory Services. Shipping information can be found in the PGx laboratory manual.*

Sample Storage

The central laboratory will initially store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples that have consent for storage and future use will be retained at ^{PPD} for up to but not longer than 15 years or as required by applicable law.

Revised Text

Collection of PGx Samples

Sample Collection

1. Mandatory Collection for CYP2C19 Genotyping:

One 3 mL whole blood **sample** for DNA isolation and **CYP2C19** genotyping will be collected from each subject during the screening period, into a plastic tube spray coated with K₂EDTA.

Rationale for Amendment

The requirement for an optional blood draw (3 mL) for storage purposes for later DNA analysis has been removed. Thus, the need for shipment, storage and retention no longer applies. After DNA analysis for CYP2C19 genotyping, any remaining sample will be destroyed.