CLINICAL STUDY PROTOCOL

NCT Number: NCT04198363

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

Study Number: Vonoprazan-3002

Protocol Version and Date:

Version 03: 20-October-2020

TAKEDA PHARMACEUTICALS

PROTOCOL

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

Sponsor:	Takeda Development Center Asia Pte Ltd. 21 Biopolis Road Nucleos North Tower, Level 4 Singapore 138567		
Study Number:	Vonoprazan-3002		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-438/vonoprazan		
Date:	20 October 2020	**Version/Amendment Number:**	03

Amendment History:

Date	Amendment Number	Amendment Type	Region
20 October 2020	03	Nonsubstantial	China
06 May 2020	02	Nonsubstantial	China
28 March 2019	01	Nonsubstantial	China
02 October 2018	Initial protocol		China

[redacted]

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 investigators per individual country requirements 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.

Contact Type/Role	Contact
Serious adverse event and pregnancy reporting	PRA PVS Clinical Operations: Email: MHGSafety@prahs.com Fax: +44 1792 525720
Medical Monitor (medical advice on protocol and study drug)	Medical Director, Clinical Science
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Medical Director, Clinical Science

[redacted]

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 study protocol and 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

[redacted] MD, PhD Date
[redacted] GI TAU
[redacted]

[redacted] MPharm Date
[redacted] GI TAU
[redacted]

[redacted] MSc Date
[redacted] Biostatistics
Biostatistician

1.3 Protocol Amendment 03 Summary of Changes

This section describes the changes in reference to the protocol incorporating Amendment 03. The primary reasons for this amendment are:

- To modify the schedule of study procedures and potentially reduce 1 onsite visit during screening.
- To add COVID terms to medically significant AE list.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 03		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 9.3.2 Randomization (Visit 2) Section 9.3.3 Treatment Period (Visit 3 or Early Termination Visit) Section 9.3.4 Follow up (F/U Visit) Appendix A Schedule of Study Procedures	Modification of Schedule of Study Procedures	Rationale for this change is to streamline study procedures. If the endoscopy was the last procedure during screening period, randomization procedures can now be done after the completion of endoscopy. The study drug will be administrated the day after randomization.
Section 10.1.4 SAEs	Addition of COVID terms to Takeda medically significant AE list	To comply with Takeda policy.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and 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.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator. (Appendix B).

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/Province)

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 Randomized Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of Bismuth-Containing Quadruple Therapy With Oral TAK-438 20 mg Compared to Esomeprazole 20 mg Twice Daily in Subjects With *Helicobacter Pylori* Infection.	**IND No.:** Not applicable	**EudraCT No.:** Not applicable
Study Number: Vonoprazan-3002	**Phase:** 3	

Study Design: This is a randomized, double-blind, phase 3 study to compare the efficacy and safety of bismuth-containing quadruple therapy administered with either oral TAK-438 20 mg or esomeprazole 20 mg twice daily (BID) in all *H pylori*-positive (*HP*+) subjects.

Treatment Period—Dose and Regimen:

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

During the treatment period, the subjects will keep a diary to monitor compliance. Good compliance is defined as taking at least 90% of the study drug by pill counting.

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

Follow-up Period:

The subjects are to be followed-up at Week 4 post-treatment to provide a post-study ^{13}C urea breath test (^{13}C-UBT) to ascertain *HP* eradication status.

Subjects who remain *HP* + at the follow up period will follow eradication regimen as per routine clinical care.

Primary Objectives:

The primary objective of this study:

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

Secondary Objectives:

Secondary objectives of this study are:

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

Subject Population: Subjects aged 18 years or older at the time of signing informed consent, with *HP* infection as determined by ^{13}C-UBT prior to randomization.

Number of Subjects: 425* randomized subjects in total. 400 evaluable subjects in total: 200 evaluable subjects per group* * Based on interim analysis results, the number of randomized subjects may increase up to 510 in total.	**Number of Sites:** Estimated total: approximately 30 sites in China.
Dose Level(s): <u>TAK-438 group:</u> TAK-438 20 mg BID for 2 weeks, given in conjunction with bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) for 2 weeks <u>Esomeprazole group:</u> Esomeprazole 20 mg BID for 2 weeks, given in conjunction with bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) for 2 weeks	**Route of Administration:** TAK-438: Oral Esomeprazole: Oral Amoxicillin: Oral Clarithromycin: Oral Bismuth: Oral
Duration of Treatment: 2 weeks	**Period of Evaluation:** Screening: up to 4 weeks Treatment period: 2 weeks Follow-up period: 4 weeks
Main Criteria for Inclusion: Male or nonpregnant, nonlactating female subjects aged 18 years or older at the time informed consent is signed with *HP* infection as determined by ^{13}C-UBT and who require *HP* eradication in the physician's judgment, who are capable of understanding and complying with the study procedures and who agree to use appropriate contraception.	
Main Criteria for Exclusion: Subjects who have Zollinger-Ellison syndrome or gastric acid hypersecretion or those with a history of gastric acid hypersecretion, or hypersensitivity to TAK-438, or related compounds or to proton pump inhibitors (PPIs), clarithromycin, amoxicillin, bismuth or esomeprazole; or subjects with a liver function test greater than the upper limit of normal; or who have any significant results from physical examinations, or clinical laboratory results as deemed by the investigator. subjects with acute upper gastrointestinal bleeding, active gastric ulcer (GU) or duodenal ulcer characterized by defective mucosa with white coating (with or without adherent blood clots) 3 mm or more in size, or acute gastric mucosal lesion, or acute duodenal mucosal lesion are not eligible.	
Main Criteria for Evaluation and Analyses: <u>Primary Endpoint:</u> • Proportion of all *HP*+ subjects with successful *HP* eradication after the double-blind treatment period, as determined by ^{13}C-UBT at Week 4 post-treatment. <u>Secondary Endpoint:</u> • Proportion of baseline clarithromycin resistant *HP*+ subjects with successful *HP* eradication after the double-blind treatment period, as determined by ^{13}C-UBT at Week 4 post-treatment. <u>Safety Endpoints:</u> • Adverse events (AEs). • Laboratory test values. • Electrocardiogram.	

- Vital signs.

Statistical Considerations: Regarding the primary endpoint for the interim analysis, the noninferiority of TAK-438 to esomeprazole with a noninferiority margin of 10% will be evaluated using Farrington and Manning test. Based on the principle of closed testing procedure, only if the test of the noninferiority is statistically significant, the superiority of TAK-438 to esomeprazole will be evaluated using a score test.

Regarding the primary endpoint for the final analysis, the noninferiority of TAK-438 to esomeprazole with a noninferiority margin of 10% will be evaluated using the Cui-Hung-Wang (CHW) test for noninferiority, which is a linear combination of the 2-stage weighted Farrington and Manning tests. Based on the principle of closed testing procedure, only if the test of the noninferiority is statistically significant, the superiority of TAK-438 to esomeprazole will be evaluated using CHW test for superiority, which is a linear combination of the 2-stage weighted score tests.

Significance level is 1-sided 2.5% for overall. Critical values for the interim analysis and the final analysis will be determined based on the observed information fraction at the interim analysis using the O'Brien-Fleming type alpha spending function.

If the test for noninferiority is statistically significant at the interim analysis, noninferiority will not be tested at the final analysis again, but the superiority will be tested at the final analysis if the study is continued. If the test for noninferiority does not reach statistical significance at the interim analysis, noninferiority will be tested at the final analysis again.

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

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

Interim Analysis: An interim analysis will be conducted after approximately 200 evaluable subjects in total have been assessed for the primary endpoint. Conditional powers for noninferiority and superiority test will be evaluated at the interim analysis, and early stopping for noninferiority, superiority or study continuation will be determined. Conditional powers will be calculated based on the estimated eradication rates of the interim data.

The interim analysis will be carried out by an independent statistical center. The interim analysis results including conditional powers will be presented to an independent statistician for review. The independent statistician will compare the conditional powers based on the interim data with the pre-specified sample size adaptation rule and recommend to the sponsor the final sample size. The interim results will not be shared with the sponsor.

Further details on the interim analysis will be documented in a statistical analysis plan for the interim analysis. An Interim Analysis Charter will be signed-off prior to randomization of the first subject.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities except for 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 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

[redacted] from [redacted] has been selected as coordinating investigator.

3.3 List of Abbreviations

^{13}C-UBT	^{13}C-urea breath test
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
CHW	Cui-Hung-Wang (test)
COVID-19	coronavirus disease 2019
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	case report form (electronic or paper)
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HP	*Helicobacter pylori/H pylori*
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IRB	institutional review board
LFT	liver function tests
O/E	overencapsulated
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PTE	pretreatment adverse event
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reactions
TB	total bilirubin
ULN	upper limit of normal

3.4 Corporate Identification

TDC Japan	Takeda Development Center Japan
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
TPC	Takeda Pharmaceutical Company Limited
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 found mainly in the gastric mucus and mucosa, whose causal relationship to gastrointestinal diseases has been extensively studied [1] since it was isolated from the gastric mucosa of a patient with chronic gastritis in 1983 [2]. Since that time, *HP* eradication therapy has been shown to be effective in reducing the recurrence of gastric and duodenal ulcers (GUs and DUs) [3,4] and *HP* eradication therapy using proton pump inhibitors (PPIs) and antibiotics has been approved in various countries around the world.

Esomeprazole is available in several pharmaceutical forms including different formulations across regions (namely tablets in the European Union and capsules in the United States) for the treatment of erosive esophagitis healing and maintenance; healing of GU and DU; the prevention of recurrence of GU or DU associated with administration of low-dose aspirin or nonsteroidal antiinflammatory; and for the eradication of *HP* infection as a component of triple therapy (coadministered with 2 antibiotics). A recent study has compared the efficacy and tolerability of the standard and the so called 'optimized' concomitant regimen (new generation PPIs at high doses of esomeprazole 40 mg twice daily (BID) and longer treatment duration 14 days), demonstrating higher eradication rates with the optimized regimen [5].

TAK-438 is a novel class of acid suppressants, referred to as a potassium-competitive acid blocker, which was developed by Takeda Pharmaceutical Company Limited (TPC). TAK-438 inhibits H+, K+-adenosine triphosphatase in the final step of acid secretion from stomach parietal cells. Unlike PPIs, TAK-438 inhibits H+, K+- adenosine triphosphatase competitively with potassium ions without activation by acid. Acid-stability and water-solubility of TAK-438 enable a smaller variability in time-of-onset of action compared to PPIs without requiring pharmaceutical dosage form such as enteric-coated formulations. TAK-438 is predominantly metabolized by cytochrome P450 (CYP) 3A4, and the contribution of polymorphic CYP2C19 is considered to be limited. Whereas PPIs require 3 to 5 days to exert their maximum acid-inhibitory effects, TAK-438 is expected to exhibit its maximum acid-inhibitory effects in a much shorter time compared with PPIs, and to exert potent and sustained acid-inhibitory effects, which warrant better treatment outcomes and greater adjunctive effect to *HP* eradication therapy.

The latest China *HP* guideline 2017 recommends bismuth containing quadruple therapy, including PPI+bismuth+amoxicillin+clarithromycin as empirical therapy. The main role of bismuth is to increase the additional eradication rate by 30% to 40% for *HP*-resistant strains [6]. Bismuth quadruple therapy had shown higher eradication rates compared to clarithromycin triple therapy in many literatures cited in the international guidelines [5,7-9].

4.2 Rationale for the Proposed Study

The role of PPIs in *HP* eradication therapy is to increase the intragastric pH to the neutral range and to act as an adjunct to eradication.

In a phase 1, multiple-dose study in healthy male adults in Japan (TAK-438/CPH-002), the once-daily administration of TAK-438 40 mg for 7 days was well tolerated. The acid-inhibitory effect of TAK-438 was as potent and sustained as that of Lansoprazole; the 24-hour pH 4 holding time ratio after 7 days of once daily administration was comparable between TAK-438 10 mg and Lansoprazole 30 mg, while it was higher in subjects receiving TAK-438 20 mg than in subjects receiving Lansoprazole 30 mg. TAK-438 is thus a promising acid suppressant that acts as an adjunct to eradication of *HP* as effectively as PPIs do.

In a phase 3, randomized, double-blind, double dummy, multicenter, parallel group comparison study (TAK-438/CCT-401):

- The noninferiority of triple therapy with TAK-438/amoxicillin/clarithromycin in *HP* eradication effect to triple therapy with lansoprazole/amoxicillin/clarithromycin was verified in *H pylori*-positive (*HP+)* patients with cicatrized GU or DU.
- The superiority of TAK-438-based triple therapy to the lansoprazole-based triple therapy was indicated in additional analyses.
- The safety profile of triple therapy with TAK-438/amoxicillin/clarithromycin was similar to that of triple therapy with lansoprazole/amoxicillin/clarithromycin.
- Triple therapy with TAK-438/amoxicillin/metronidazole was effective in second line *HP* eradication and safe in patients for whom the first line eradication was unsuccessful.
- Triple therapy with TAK-438/amoxicillin/clarithromycin and triple therapy with TAK-438/amoxicillin/metronidazole were effective, safe, and well tolerated in *HP*+ patients with cicatrized GU or DU.

A phase 1 study (TAK-438_115 study) was conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of quadruple therapy BID for 14 days with tripotassium bismuth dicitrate (600 mg), amoxicillin (1 g), clarithromycin (500 mg), and TAK-438 (20 mg) versus quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), amoxicillin (1 g), clarithromycin (500 mg), and lansoprazole (30 mg) in HP+ subjects. No remarkable changes in either plasma or urine PK of bismuth were observed between the 2 treatment groups and no potential safety concerns were identified because of the possibility of a drug-drug interaction between bismuth and treatment with TAK-438 or lansoprazole.

This study will evaluate the efficacy of quadruple therapy with TAK-438 20 mg BID given in conjunction with amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) for 2 weeks by verifying its noninferiority to quadruple therapy with esomeprazole 20 mg BID given in conjunction with amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) for 2 weeks.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study:

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

5.1.2 Secondary Objectives

Secondary objectives of this study are:

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

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint for this study is the:

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

5.2.2 Additional Endpoint

The additional endpoint for this study is the:

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

5.2.3 Safety Endpoints

Safety endpoints for this study include:

- Adverse events (AEs).
- Laboratory test values.
- Electrocardiogram (ECG).
- Vital signs.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

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

Treatment Period—Dose and Regimen:

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

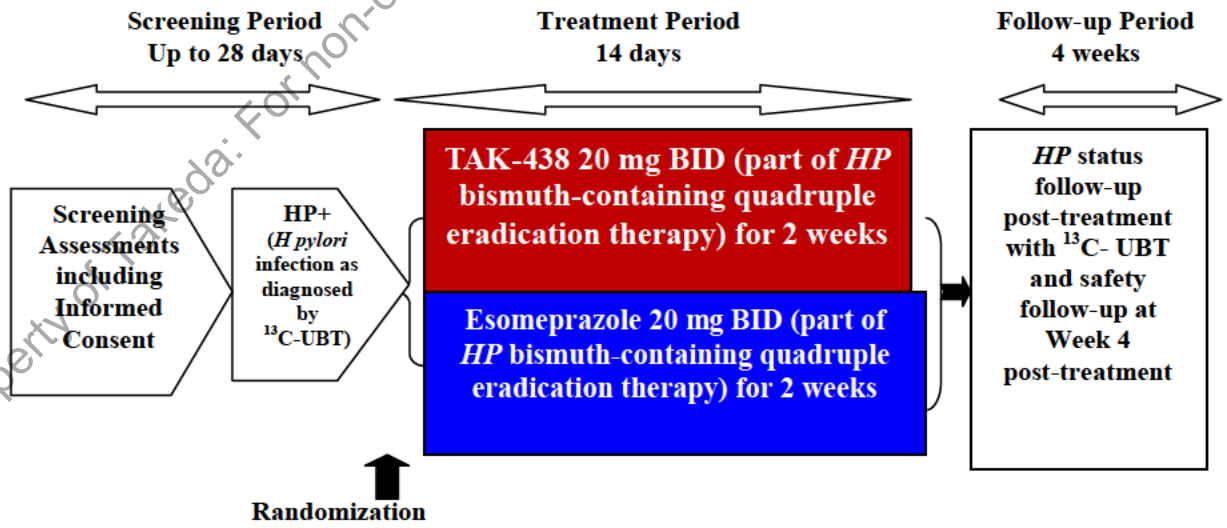
During the treatment period, the subjects will keep a patient diary to monitor compliance. Good compliance is defined as taking at least 90% of the study drug by pill counting.

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

Follow-up Period:

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

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

For the subject population studied

Subjects aged 18 years or older at the time of signing informed consent will be used in the study if they have an *HP* infection as determined by ^{13}C-UBT prior to randomization.

For study design and sample size

1. Study design

This phase 3 study is designed as a randomized, double-blind study is aimed at evaluating the efficacy and safety of TAK-438 in *HP* + subjects. The study design allows for independent assessment of efficacy and safety in these subjects to support registration.

Diagnosis of *HP* by ^{13}C-UBT is a well-accepted method.

While PPIs require 3 to 5 days to exert their maximum acid-inhibitory effects, TAK-438 is known to exhibit its maximum acid-inhibitory effects in a much shorter time compared with PPIs, and to exert potent and sustained acid-inhibitory effects, which warrant better treatment outcomes and greater adjunctive effect to *HP* eradication therapy.

2. Sample size

Justification for sample size can be found in Section 13.3.

For the doses of the study drugs used

In a phase 2 dose-ranging study of TAK-438 in subjects with erosive esophagitis (TAK-438/CCT-001), TAK-438 exhibited a dose-response efficacy at doses 5, 10, 20, and 40 mg, and demonstrated its noninferiority to lansoprazole 30 mg at either of the doses examined after 4 weeks of treatment. Additionally, given that the rate of endoscopic healing of erosive esophagitis in subjects with more severe disease (LA classification grades C/D) was 95% or higher with TAK-438 at doses 20 mg or higher compared to 87% with lansoprazole 30 mg, the clinically recommended dose of TAK-438 for erosive esophagitis was determined as 20 mg. As the clinically recommended dose of TAK-438 for gastric ulcer and duodenal ulcer is the same as that for erosive esophagitis (20 mg).

The quadruple therapy consisting of 2 antibiotics, a PPI, and bismuth is recommended by the Fifth China HP consensus. As a replacement for PPIs, TAK-438 would be expected to be used as part of a quadruple-treatment regimen.

A phase 1 study (TAK-438_115) was conducted to evaluate the safety, tolerability, and PK of quadruple therapy BID for 14 days with tripotassium bismuth dicitrate (600 mg), amoxicillin (1 g), clarithromycin (500 mg), and TAK-438 (20 mg) versus quadruple therapy BID with tripotassium bismuth dicitrate (600 mg), amoxicillin (1 g), clarithromycin (500 mg), and lansoprazole (30 mg) in HP+ subjects. No remarkable changes in either plasma and urine PK of bismuth were observed between the 2 treatment groups and no potential safety concerns were identified because of the possibility of a drug-drug interaction between bismuth and treatment with TAK-438 or lansoprazole. The quadruple therapy is a well-established treatment regimen in conjunction with a

PPI for the treatment of *HP* infection. The doses for companion drugs, namely bismuth, clarithromycin and amoxicillin are consistent with the recommendation of the Fifth China *HP* consensus. Esomeprazole 20 mg BID is the approved dose for treatment of *HP* infection in China.

6.3 Premature Termination or Suspension of Study or Study 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 drug that indicates a change in the known risk/benefit profile for the product, 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.
- Study-specific criteria for terminating the study (eg, study meets predefined rule for futility or benefit).

6.3.2 Criteria for Premature Termination or Suspension of Study 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 Study Site(s)

If 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 a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study 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.

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.
3. Subjects aged 18 years or older at the time of signing informed consent (For subjects >70 years old, the investigators need to perform a benefit-risk assessment to determine the eligibility of subject participation in the study).
4. *HP*+ subjects as determined by ^{13}C-UBT at the start of the study (Visit 1 [screening]) and who require *HP* eradication in physician judgment (indications for *HP* eradication recommended by Chinese Society of Gastroenterology in Table 7.a).

Table 7.a Indications for *HP* Eradication

***HP*+**	**Strongly Recommended**	**Recommended**
Peptic ulcer (regardless of activity or complications)	√	
Gastric mucosa-associated lymphoid tissue	√	
Chronic gastritis with dyspepsia		√
Chronic gastritis with mucosal atrophy erosion		√
Early gastric cancer resected endoscopically or by subtotal gastrectomy		√
Long-term use of PPIs		√
Family history of gastric cancer		√
Planning to take long-term NSAIDs (including low dose aspirin)		√
Iron deficiency anemia with unknown causes		√
Idiopathic thrombocytopenic purpura		√
Other HP-related diseases (eg, lymphocytic gastritis, gastric hyperplasia, polyps, menetrier disease)		√
HP infection confirmed		√

HP: *Helicobacter pylori*; NSAID: nonsteroidal anti-inflammatory drug; PPI: proton pump inhibitors.
Source: Fifth Chinese National Consensus Report on the Management of *H pylori* Infection [6].

5. 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 throughout the duration of the study and 4 weeks after last dose of study drug.

*Definitions and highly effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10.

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 84 days prior to the treatment period including their post-marketing studies, with the exception of study medication in patients:
   - With GU in the phase 3 double-blind trial [TAK-438_302].
   - With erosive esophagitis in the phase 3 double-blind trial [TAK-438_303].
   - With DU in the phase 3 double-blind trial [TAK-438_304].
   - Receiving maintenance therapy for endoscopically healed erosive esophagitis in the phase 3 double-blind trial [TAK-438_305].

   In addition, subjects must not have received the *HP* eradication regimen defined in [TAK-438_302] or [TAK-438_304]).
2. The subject has received TAK-438 in a previous clinical study; however, may be included if he/she:
   - Participated in and completed the phase 3 double-blind trials for erosive esophagitis healing (TAK-438_303) and maintenance (TAK-438_305).
   - Participated in and completed the phase 3 double-blind trials for GU (TAK-438_302) or DU (TAK-438_304).
   - Did not receive *HP* eradication regimen defined in GU (TAK-438_302) or DU (TAK-438_304) trials or as a therapeutic agent.
3. The subject has a history of alcohol abuse, illegal drug use, or drug addiction within the 12 months prior to screening, or regularly consumes >21 units of alcohol (1 unit = 12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine) per week.
4. 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 conduct of this study (eg, spouse, parent, child, sibling) or who may have consented under duress.
5. The subject had any of the following conditions at the start of the study (Visit 1, screening): acute upper gastrointestinal bleeding, active GU or DU characterized by defective mucosa with white coating (with or without adherent blood clots) 3 mm or more in size, acute gastric mucosal lesion, or acute duodenal mucosal lesion. However, subjects with gastritis, gastric or duodenal erosion are permitted to participate.
6. Subjects who have undergone major surgical procedures within 30 days prior to the screening visit or are scheduled to undergo surgical procedures that may affect gastric acid secretion (eg, abdominal surgery, vagotomy or craniotomy). Medicinal therapy was not indicated because the subject's condition accompanied perforation, pyloric stenosis, or severe bleeding, or for other reasons.

7. Subjects with Zollinger-Ellison syndrome or gastric acid hypersecretion or those with a history of gastric acid hypersecretion.
8. The subject has a history of hypersensitivity or allergies to TAK-438, esomeprazole, PPIs, amoxicillin, clarithromycin and bismuth, including any associated excipients. Skin testing may be performed according to local standard practice.
9. Exclusion criterion was deleted in Amendment 02.
10. The subject is required to take excluded medications listed in the protocol.
11. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 4 weeks after participating in this study; or intending to donate ova during such time period.
12. The subject has a history or clinical manifestations of significant central nervous system, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine or hematological disease that, in the opinion of the investigator, would confound the study results or compromise subject safety.
13. The subject has, in the judgment of the investigator, clinically significant abnormal physical examinations, hematological parameters of hemoglobin, hematocrit, or erythrocytes at screening.
14. Exclusion criterion was deleted in Amendment 02.
15. The subject has a history of malignancy or was treated for malignancy within 5 years before the start of the screening visit (the subject may be included in the study if he/she has cured cutaneous basal cell carcinoma or cervical carcinoma in situ).
16. The subject has a known acquired immunodeficiency syndrome or hepatitis infection, including hepatitis virus carriers (hepatitis B surface antigen [HBsAg] or hepatitis C virus [HCV]- antibody-positive).
17. Subjects for whom laboratory tests performed prior to randomization revealed any of the following abnormalities:
    - Creatinine levels: >2 mg/dL (>177 μmol/L).
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin (TB) levels: > the upper limit of normal (ULN). (Note: 1 retest is allowed if the subject has no other abnormal liver function, no liver disease, and the ALT, AST or TB level is > ULN but <2 × the ULN; if the retest level is still > ULN, the subject should be excluded.)

7.3 Excluded Medications

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator. The investigator should review any additions or changes in medications. All medications should be recorded in the source documents or equivalent and then transcribed onto the appropriate electronic case report forms (eCRFs).

Medications and treatments that are not permitted prior to or during the study, including the time periods during which they must be withdrawn are shown in Table 7.b.

Table 7.b Excluded Medications and Treatments

Excluded Medication/Treatment	Beginning of Exclusion	End of Exclusion
Other investigational drugs or drugs administered due to participation in another clinical trial	84 days prior to study treatment	End of follow-up
Medications (excluding PPIs and antibiotics) that may interfere with ^{13}C-UBT (metronidazole, bismuth preparations, ecabet sodium hydrate) [a]	14 days prior to ^{13}C-UBT (at screening)	End of ^{13}C-UBT
Antibiotics	30 days prior to ^{13}C-UBT (at screening)	End of follow-up
Antiprotazoals	30 days prior to study treatment	End of follow-up
Non–study-related *HP* eradication therapy	30 days prior to study treatment	End of follow-up
Medications contraindicated with clarithromycin: pimozide, ergot derivatives, tadalafil, terfenadine, astemizole, cisapride, simvastatin, lovastatin, atorvastatin etc. Note: other statins such as fluvastatin; pravastatin and rosuvastatin may be allowed but used with caution	30 days prior to study treatment	End of *HP* eradication therapy
Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin)	30 days prior to study treatment	End of *HP* eradication therapy
Strong inhibitors or inducers of CYP2C19 (eg, fluconazole, fluoxetine, fluvoxamine, ticlopidine, rifampicin, ritonavir)	30 days prior to study treatment	End of *HP* eradication therapy
Non–study-related PPIs, and H_2 receptor antagonists	14 days prior to ^{13}C-UBT (at screening)	End of follow-up
Surgical procedures that could affect gastric acid secretion (eg, upper gastrointestinal surgery, vagotomy)	Start of study treatment	End of follow-up
NSAIDs [c]	Start of study treatment	End of follow-up
Agents affecting digestive organs including: H_2 antagonists, muscarinic M3 antagonists, prokinetics, anticholinergic agents, prostaglandins, anti-gastrin agents or mucosal-protective agents. [b]	Start of study treatment	End of follow-up
Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with TAK-438)	Start of study treatment	End of follow-up
Corticosteroids [c], anti-platelets (includes low-dose aspirin) [c], anticoagulants [c], psychotropics [c], antidepressants [c], bisphosphonates [c, d], methotrexate and probenecid (contraindicated with bismuth)	Start of study treatment	End of follow-up

Table 7.b Excluded Medications and Treatments

Excluded Medication/Treatment	Beginning of Exclusion	End of Exclusion

^{13}C-UBT: ^{13}C-urea breath test; CYP: cytochrome P450; H_2: histamine-2 (receptor); *HP*: *Helicobacter pylori;* NSAID: nonsteroidal anti-inflammatory drug, PPI: proton pump inhibitor.

[a] Prohibited period is 14 days prior to any ^{13}C-UBT or as otherwise stated in package insert for ^{13}C urea breath testing kit package to be used.

[b] The use of gastric mucosal protective agents (only teprenone capsules and gefarnate tablets are allowed) may be allowed during the follow-up period.

[c] Except subjects that were using these agents before signing the informed consent form at Visit 1 and the dose and administration will not be changed during the study.

[d] Switching between once-daily and weekly regimens is allowed for drugs containing the same active ingredients. Also allowed are compliant subjects on a stable dose (in accordance with the package insert) at the time of signing consent who have no gastrointestinal inflammation or history of such.

7.4 Diet, Fluid, Activity Control

Subjects should be instructed as follows:

- To adhere closely to the scheduled visits, seek medical consultation, and undergo predetermined laboratory tests.
- To take study drug(s) twice daily at about the same time as he/she usually does with approximately 240 mL water. To ensure that bismuth and TAK-438 or esomeprazole are to be taken 0.5 hour before breakfast and dinner. Breakfast and dinner should be completed within 0.5 hour before taking clarithromycin and amoxicillin, ie, 1 hour after bismuth and TAK-438 or esomeprazole dosing.
- To present to the clinic in a fasting state when he/she is scheduled for laboratory tests and/ or endoscopy. On such study visit days, subjects will be instructed to take their dose of study drug(s) (if appropriate) after study procedures are completed.
- Subjects should be instructed according to Section 9.2 at every study visit. Details of any missed or forgotten doses should be reported to the Investigator or designee at the subsequent study visit.
- To store all medications in a cool, dry, safe place which is out of reach of children and to bring all study supplies (empty / used / unused drug packets) to each study visit.
- If during study participation the subject is prescribed medication by a nonstudy physician or other healthcare professional, he/she should consult the investigator beforehand. Such treatment or consultation, or the use of over-the-counter medicine should be reported at the next study visit.
- To report on all subjective or objective symptoms experienced with regard to their details, day of onset, severity, outcome, and day of outcome at every visit. In case of emergency, such as

occurrence of a serious adverse event (SAE), the subject or his/her family should contact the investigator as soon as possible.

- To use contraception without failure. (A female subject of childbearing potential from signing of informed consent throughout the duration of the study and 4 weeks after the final dose of the study drug.) Pregnancy in a female subject should be reported immediately.
- Not to donate blood during the study, and to report on any such donation immediately.
- To refrain from excessive drinking and eating, an extreme diet change (eg, change to an extremely high-fat diet) or excessive exercise throughout 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 drug should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.15.

1. AE. The subject has experienced a pretreatment adverse event (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 (LFT) Abnormalities

     Study drug 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 drug treatment:
     - ALT or AST or TB >2 times the ULN.
     - (Note: If ALT/AST/TB: > ULN but <2 × ULN, retest LFT in 1 week to monitor abnormal LFT).
2. Protocol deviation. The discovery post-randomization 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 in the subject's source documents.
4. Voluntary withdrawal by subject. The subject wishes to withdraw from the study.
5. Study terminated by the sponsor.
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. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
8. 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 STUDY MATERIAL MANAGEMENT

This section contains information regarding all medications 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 study material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term "study drugs" refers to any and all of the drugs administered as part of the study, including TAK-438 or esomeprazole as well as the companion drugs given for *HP* infection eradication in *HP*+ subjects. TAK-438 (20 mg tablets) and esomeprazole (20 mg tablets) will be O/E and identical in appearance. Properties of TAK-438 O/E 20 mg tablets and esomeprazole O/E 20 mg tablets are described in Table 8.a. The companion drugs refer to amoxicillin (500 mg capsules), clarithromycin (250 mg tablets) and bismuth potassium citrate (300 mg capsules [equivalent to 110 mg bismuth]) which will be packaged in an open fashion.

8.1.1.1 TAK-438 and Esomeprazole

TAK-438 and esomeprazole will be foil/foil blistered packaged into child-resistant blister cards. Each blister card will contain 32 O/E TAK-438 20 mg tablets or 32 O/E esomeprazole 20 mg tablets.

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

TAK-438 20 mg O/E Tablets

The chemical name of TAK-438 is:
1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methyl methanamine monofumarate. The generic name for TAK-438 is vonoprazan. TAK-438 tablets will be manufactured by TPC, Hikari, Japan. TAK-438 tablets will be O/E by Fisher Suzhou.

Esomeprazole 20 mg O/E Tablets

The chemical name of esomeprazole is:
Bis{5-methoxy-2-[(*S*)-(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1*H*-benzimidazol-1-yl}monomagnesium trihydrate. Esomeprazole 20 mg tablets will be manufactured by AstraZeneca. Esomeprazole tablets will be O/E by Fisher Suzhou.

Table 8.a Study Medications and Dose Regimen

Study Medication [a]	Product, Dose, Strength, and Form	Mode of Administration
TAK-438 20 mg	O/E TAK-438 20 mg tablets BID for 2 weeks, given in conjunction with bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) for 2 weeks	Oral
Esomeprazole 20 mg	O/E esomeprazole 20 mg tablets BID for 2 weeks, given in conjunction with bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) for 2 weeks	Oral

[a] Subjects should take the first dose of study medication 1 day after the randomization visit (Visit 2).

8.1.1.2 Companion Drugs

Bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg BID) will be provided by sponsor or sourced by other means.

8.1.1.3 Sponsor-Supplied Study Drugs

All drugs referenced in Section 8.1.1.1 and Section 8.1.1.2 of this protocol will be supplied by the sponsor.

8.1.2 Storage

TAK-438 and esomeprazole tablets (O/E) will be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. TAK-438 tablets (O/E) should be stored at 20°C to 25°C; with excursions permitted 15°C to 30°C. Esomeprazole tablets (O/E) should be stored at 20°C to 25°C; with excursions permitted 15°C to 30°C. Protect from moisture and humidity. Study medication is to remain in the blister card until time of dosing.

Temperature excursion must be reported to the sponsor or designee.

Companion medication will be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Amoxicillin capsules will be stored at 10°C to 30°C, Clarithromycin tablets will be stored at 2°C to 20°C, and Bismuth capsules will be stored at 10°C to 30°C. All of these medications will remain in their original containers until dispensed.

A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Overdose

An overdose is defined as a known deliberate or accidental administration of study 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, 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.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

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

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to the study schedule. The Subject Number will be entered onto the eCRF.

The investigator or the investigator's designee will access the interactive web response system (IWRS) at screening to obtain the subject study number. The investigator or the investigator's designee will utilize the IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The medication identification (ID) number of the study drug and other sponsor-supplied drugs to be dispensed will then be provided by the IWRS. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IWRS. (Refer to IWRS manual provided separately.)

8.3 Randomization Code Creation and Storage

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

Subjects will be assigned in a 1:1 ratio to TAK-438 or esomeprazole group.

8.4 Study Drug Blind Maintenance

The blinding for TAK-438 and esomeprazole will be maintained using the IWRS.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment 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 study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be obtained by the investigator, by accessing the IWRS.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents/ Record of Early Blind-Breaking, and the same information (except the time) must be recorded on the eCRF.

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

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 [list all that apply], the investigator or designee must maintain records of all sponsor-supplied 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/by recording in IWRS. 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 must maintain 100% accountability for all sponsor-supplied 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 (drug label).
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot (or Med ID or job number) 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.

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

The current inventory of all sponsor-supplied drugs will be maintained in IWRS. 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 or retest date, 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 drugs. The IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drugs are dispensed.

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

All boxes (including used and unused) of study drug must be returned to the study sponsor according to the standard practice. Destruction of such supplies will be documented, and the sponsor or its designee will verify disposition records.

No other utilization of study drugs intended for use in this study is authorized by the sponsor. The on-site pharmacist will immediately return unused study drugs to the sponsor after the study is closed at the study site.

The investigator will be notified of any expiry date or retest date extension of clinical study material 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 clinical study material for return to the sponsor or its designee for destruction.

In the event of expiry date extension of supplies already at the study site, supplies may be relabeled with the new expiry date at that site. In such cases, sponsor 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. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. 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.

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

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth (or age in countries where collection of birth date is not allowed), sex, race, alcohol and caffeine consumption and smoking classification 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 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 and (11) other.

9.1.4 Weight, Height, and Body Mass Index

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Body mass index (BMI) is calculated by sponsor or its designee using metric units with the formula provided below.

BMI = weight (kg) / height $(m)^2$

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral, tympanic, or axillary measurement), sitting blood pressure (after 5 minutes resting), respiration rate, and pulse (bpm). On dosing days, vital sign measurements should be taken at predose in the morning, and it is recommended that for the remaining days, measurements should be taken at approximately the same time as on the dosing days.

When vital signs are scheduled at the same time as blood draws, vital signs will be obtained before 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), and all medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Documentation will include dose and frequency (although only 'total daily dose' may be captured on the eCRF), as

well as generic medication name, unit, 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 or Day -1 examinations. 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. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Erythrocytes (RBC)	ALT	Protein (qualitative)
Leukocytes (WBC)	ALP	Glucose (qualitative)
Hemoglobin	AST	
Hematocrit	γ-GTP	
Platelets	TB	
Leukocyte differentials (neutrophils, eosinophils, basophils, monocytes, and lymphocytes)	Direct bilirubin	
	LDH	
	CK (CPK)	
	Albumin	
	Protein (Total protein)	
	Creatinine	
	BUN	
	Urate	
	Cholesterol (Total cholesterol)	
	Triglycerides (fasting)	
	Glucose (fasting)	
	Potassium	
	Sodium	
	Magnesium	
	Calcium	
	Phosphate	
	Chloride	
	Hepatitis B & C Analysis	
	HBsAg	
	anti-HBc	
	IgM anti-HBc	
	anti-HBs	
	HCV-antibody	

Other: Human chorionic gonadotropin (hCG), for pregnancy test in female subjects with childbearing potential, FSH, for female subjects if menopause is suspected only.

ALP: alkaline phosphate; ALT: alanine aminotransferase; anti-HBc: hepatitis B core antibody; anti-HBs: hepatitis B surface antibody; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CK: creatine kinase; CPK: creatine phosphokinase; FSH: follicle-stimulating hormone; HBsAg: hepatitis B virus surface antigen; HCV: hepatitis C virus; IgM anti-HBc: IgM antibody to hepatitis B core antigen; γ-GTP: gamma-glutamyl transferase; LDH: lactate dehydrogenase; RBC: red blood cell; TB: total bilirubin; WBC: white blood cell.

The central 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 ALT or AST or TB >2 × ULN, the study drug shall be stopped due to the discontinuation criteria for risk minimization having been met (Section 7.5).

Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, TB, gamma-glutamyl transferase, and the international normalized ratio) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

Abnormalities of LFTs should be monitored until such abnormalities (and any associated symptoms) have returned to normal or there is a satisfactory explanation to discontinue monitoring.

(Note: If ALT/AST/TB: > ULN but <2 × ULN, retest LFT in 1 week to monitor abnormal LFT.)

The investigator or designee is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

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 an follicule-stimulating hormone (FSH) > 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, where medications and devices containing hormones are excluded, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse) where applicable[a]:	**Intrauterine devices (IUDs):**
• Cap (plus spermicidal cream or jelly) PLUS male condom. • Diaphragm (plus spermicidal cream or jelly) PLUS male condom.	• Copper T.

[a] Barrier methods are only applicable in countries where spermicide is available.

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, and sperm donation during the course of the study.

During the course of the study, regular 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). Female subjects must have a negative urine hCG pregnancy test on Day 1 prior to receiving any dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug (TAK-438 20 mg tablets or Esomeprazole 20 mg tablets) should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Day 1 or within 30 days 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.

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 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

A standard 12-lead ECG will be recorded. The investigator will interpret the ECG using 1 of the following categories: normal or abnormal. If the interpretation is abnormal, the investigator (or a qualified observer at the investigational site) will judge if it is clinically significant. The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval QT interval and QRS interval.

9.1.12 Documentation of Subjects Who Fail Screening

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible prior to randomization, the investigator should complete the eCRF. The IWRS should be contacted as a notification of screen failure.

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

- AE.
- Screen failure (Did not meet inclusion criteria or did meet exclusion criteria).
- Protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal by subject.
- Study terminated by sponsor.
- Other.

Subject numbers assigned to subjects who fail screening should not be reused.

9.1.13 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the double-blind treatment period.

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

If the subject is found to be eligible the subject will be randomized to either TAK-438 or esomeprazole using IWRS. Instructions on accessing and using the IWRS will be provided in a separate manual. Blinded details of subject treatment allocation (MED ID numbers) will be provided via the IWRS.

9.1.14 ^{13}C-UBT

To establish *HP* infection status, a ^{13}C-UBT will be performed via the laboratory. Exhaled air samples will be taken in accordance with instructions for use of central analysis to test for *HP* infection status determination.

9.1.15 Antibiotic Susceptibility Test

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

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication bottles/unused medications to each dispensing site visit.

If a subject is persistently noncompliant with the study medication, it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

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 (Visit 1)

Subjects will be screened within 4 weeks prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.12 for procedures for documenting screening failures.

Procedures to be completed at screening (Visit 1) include:

- Sign informed consent.
- Inclusion/exclusion criteria.
- Record demographics, medical history, and medication history.
- Perform physical examination.
- Measure vital signs, weight, and height.
- Record the use of concomitant medications.
- Document concurrent medical conditions.
- ^{13}C-UBT to confirm *HP*.
- Collect blood and urine samples for laboratory tests (hematology, chemistry including liver function tests, urinalysis, and hepatitis B and C screening tests).
- FSH (when menopause is suspected).
- Urine pregnancy test (for women of child bearing potential).
- Guidance on avoidance of pregnancy.
- ECG.
- Endoscopy and biopsy specimen collection for the purpose of antibiotic susceptibility testing
- Access IWRS to obtain subject number.
- PTE assessment.

9.3.2 Randomization (Visit 2)

Procedures to be completed during randomization (Visit 2).

- Inclusion/exclusion criteria.
- Perform physical examination.
- Measure vital signs.
- Endoscopy and biopsy specimen collection for the purpose of antibiotic susceptibility testing (this can be performed at Visit 2 if it was not performed at Visit 1, but must be done before randomization).
- Record the use of concomitant medications.
- Urine pregnancy test (for women of childbearing potential).
- Guidance on avoidance of pregnancy.

- Randomization with IWRS.
- Dispense study drugs.
- PTE assessment.

9.3.3 Treatment Period (Visit 3 or Early Termination Visit)

Subjects should take the first dose of study medication the next day, after randomization (Visit 2).

Procedures to be completed at Week 2 (Visit 3) or Early Termination visit are shown below. The early termination visit will occur within 14 days of the last dose if study drug is discontinued.

- Perform physical examination.
- Measure vital signs.
- Record the use of concomitant medications.
- Collect blood and urine samples for laboratory tests.
- Urine pregnancy test (for women of child bearing potential).
- Guidance on avoidance of pregnancy.
- ECG.
- Drug return/ accountability/ compliance.
- Register subject as discontinued or completed via IWRS.
- AE assessment.

9.3.4 Follow up (F/U Visit)

The follow up (F/U) visit will be performed 28 to 35 days after the last dose of study drug irrespective of the completion status of treatment period. The following procedures will be performed and documented:

- Perform physical examination.
- Weight and height.
- Record the use of concomitant medications.
- ^{13}C-UBT to confirm *HP*.
- AE assessment.

10.0 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 drug; 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 value), 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 (pre-existing conditions or 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 drug 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 findings 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 or ECG retest and/or continued monitoring of an abnormal value or finding is 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 etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. 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 medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. 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 the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, 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 intensity of AEs /serious PTEs:

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

Preplanned procedures (surgeries or interventions):

- 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 recorded 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.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

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. 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).

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
COVID-19 pneumonia	Neuroleptic malignant syndrome / malignant hyperthermia
COVID-19-related disease	Spontaneous abortion / stillbirth and fetal death

COVID-19: Coronovirus disease 2019.

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 AEs of Special Interest

A special interest AE (serious or nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda. There are no special interest AEs for this study.

10.1.6 Intensity 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.

10.1.7 Causality of AEs

The relationship of each AE to study drug(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 medications 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 medications and concurrent treatments.

10.1.8 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.

10.1.9 Start Date

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

10.1.10 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.

10.1.11 Pattern of AE (Frequency)

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

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose reduced – the dose was reduced due to the particular AE.
- Dose increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.1.13 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 drug (Day 1) or until screen failure. For subjects who discontinue prior to study drug 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 drug (Day 1). Routine collection of AEs will continue until Day 42 (the end of the 4-week follow-up period).

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 drug 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:

- Event term.
- Start and stop date.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not applicable for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study drug (not applicable for PTEs).
- Outcome of event.
- 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 drug(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. Also, investigators should report any SAE in appropriate format (ie, locally required form) to related authorities, IRB/IECs in accordance with local GCP and/or local regulations.

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

10.2.3 Reporting of Abnormal LFTs

If during the treatment or follow-up period a subject is noted to have ALT or AST >3 × ULN **and** TB >2 × 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 or the sponsor's designee for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Study drug should be discontinued immediately (as per Section 7.4), and follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF 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 but becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax 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 is responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, 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 also will prepare an expedited report for other safety issues that might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

An independent statistical center will be used for evaluation of the interim efficacy analysis. An interim analysis charter will be signed-off prior to randomization of the first subject.

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 medical conditions will be coded using the Medical

Dictionary for Regulatory Activities. Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs (Electronic and Paper)

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

The sponsor or its designee will provide 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.

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 to eCRFs 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.

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 Clinical Study Site Agreement 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) for the interim analysis and the final analysis will be prepared and finalized prior to unblinding of subject's treatment assignment for the interim analysis. These documents will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment for the interim analysis. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

If the study continues after the interim analysis, an additional blinded data review may be conducted and an SAP for the final analysis may be revised as needed, prior to unblinding of subject's treatment assignment for the final analysis.

13.1.1 Analysis Sets

In this study, 3 kinds of analysis sets are defined: full analysis set (FAS), per protocol set, and safety analysis set. The FAS, the main analysis set used for primary efficacy analysis, will be defined as all subjects who were randomized and received at least 1 dose of the study drug.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized overall and by treatment group using the FAS.

13.1.3 Efficacy Analysis

Regarding the primary endpoint for the interim analysis, the noninferiority of TAK-438 to esomeprazole with a noninferiority margin of 10% will be evaluated using the Farrington and Manning test. Based on the principle of closed testing procedure, only if the test of the noninferiority is statistically significant, the superiority of TAK-438 to esomeprazole will be evaluated using a score test.

Regarding the primary endpoint for the final analysis, the noninferiority of TAK-438 to esomeprazole with a noninferiority margin of 10% will be evaluated using Cui-Hung-Wang (CHW) test for noninferiority, which is a linear combination of the 2-stage weighted Farrington and Manning tests. Based on the principle of closed testing procedure, only if the test of the noninferiority is statistically significant (either at the interim or final analysis), the superiority of

TAK-438 to esomeprazole will be evaluated using CHW test for superiority which is a linear combination of the 2-stage weighted score tests.

Significance level is controlled at 1-sided 2.5% for overall using O'Brien-Fleming type alpha spending function. Critical values for the interim analysis and the final analysis as well as the weights for CHW test will be determined based on the observed information fraction at the interim analysis and the initial sample size for the primary analysis of 400.

If the test for noninferiority is statistically significant at the interim analysis, noninferiority will not be tested at the final analysis again, but the superiority will be tested at the final analysis if the study is continued. If the test for noninferiority does not reach statistical significance at the interim analysis, noninferiority will be tested at the final analysis again.

For the additional efficacy endpoints, frequency distributions will be provided by treatment group along with proportions and the 2-sided 95% confidence intervals. The differences in the proportions between TAK-438 and esomeprazole (TAK-438 - esomeprazole) and the 2-sided 95% confidence intervals will be provided.

13.1.4 Safety Analysis

Safety analysis will be performed using the safety analysis set, which consisted of all subjects who received at least 1 dose of study treatment.

The number and proportion of subjects with treatment-emergent adverse events will be summarized by Medical Dictionary for Regulatory Activities System Organ Class and Preferred Term overall, by severity, and by relationship to study drug for each treatment group.

Change from baseline in laboratory test values, vital signs and quantitative ECG variables will be summarized by treatment group. For qualitative ECG assessments, post-baseline results will be tabulated against baseline. Subjects with markedly abnormal values for laboratory tests, vital signs, and ECG parameters will be tabulated.

No statistical testing or inferential statistics will be generated.

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis will be conducted after approximately 200 evaluable subjects in total have been assessed for the primary endpoint. Evaluable subjects for the primary endpoint means subjects with nonmissing ^{13}C-UBT result at Week 4 post-treatment in the FAS. Conditional powers for noninferiority and superiority test will be evaluated at the interim analysis, and early stopping for noninferiority, superiority or study continuation will be determined. Conditional powers will be calculated based on the estimated eradication rates of the interim data.

The interim analysis will be carried out by an independent statistical center. The interim analysis results including conditional powers will be presented to an independent statistician for review.

Table 13.a Interim Analysis Results and Subsequent Action

Zone	Interim analysis result	Subsequent action
1	Noninferiority unfavorable zone	Continue without sample size increase.
2	Noninferiority promising zone	Continue with sample size increase to keep power for noninferiority (up to 510).
3	Noninferiority not significant and noninferiority favorable zone	Continue without sample size increase.
4	Noninferiority significant and superiority unfavorable zone	Noninferiority stop.
5	Superiority promising zone	Continue with sample size increase to keep power for superiority (up to 510).
6	Superiority not significant and superiority favorable zone	Continue without sample size increase.
7	Superiority significant	Superiority stop.

The prespecified sample size adaptation rule is a stepwise function to avoid the back-calculation problem resulting from 1 sample size corresponding to either barely promising or highly promising interim results. The sample size adaptation rule will be designed by the sponsor's independent design statistician and approved by the sponsor's head of biostatistics. Neither the independent design statistician nor the head of biostatistics is involved in the study conduct.

The sample size adaptation rule will be outlined in the Interim Analysis Charter and will not be accessible to the sponsor's study team until completion of the study. The rules will be available only to the sponsor's independent design statistician, the sponsor's head of biostatistics, the independent statistician, and the statistics representative on the sponsor's executive committee (if different from the sponsor's head of biostatistics).

Further details on the interim analysis will be documented in an SAP for the interim analysis. An Interim Analysis Charter will be signed-off prior to randomization of the first subject.

13.3 Determination of Sample Size

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

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

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 will guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information, 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.

The investigator should document all protocol deviations.

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, 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 will 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 Helsinki principles are addressed in the protocol and 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 requirements of each participating region/country. 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 drugs 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 or its designee will notify site once the sponsor or its designee has confirmed the adequacy of site regulatory documentation *and, when applicable, the sponsor has received permission from competent authority to begin the* study. Until the site receives 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 trial database or documentation via a subject 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 the monitor or the sponsor's designee, representatives from any regulatory authority (eg, the Food and Drug Administration, 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 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 study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

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 all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study 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.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/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 study subjects. Refer to the 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.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

	Screening Period	Randomization	Treatment Period			Follow-up Period
Study Day/Week:		**Day -1** [a]	**Day 1** [a]	**Week 2 (Day 15)**	**Early Termination Visit**	**Week 4 Post-treatment**
Visit Windows (Days):	**Day -28 to Day -2**			**15 - 18**	**Within 14 days of last dose**	**28 - 35 days after last dose**
Visit Number:	**1**	**2**		**3**	-	**F/U**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X					
Medication history	X					
Physical examination	X	X		X	X	X
Vital signs	X	X		X	X	
Weight and height	X					X
Concomitant medications	X	X		X	X	X
Concurrent medical conditions	X					
^{13}C UBT test to confirm *HP* infection status [b]	X [c]					X
Hepatitis B and C tests	X					
Clinical laboratory tests (including liver function tests: ALT, AST, total and direct bilirubin) [d]	X			X	X	
Urine pregnancy test [e]	X	X		X	X	
FSH [f]	X					
Guidance on avoidance of pregnancy	X	X		X	X	
ECG	X			X	X	
Endoscopy	X [g]					
Antibiotic susceptibility test	X [h]					
Randomization via IWRS		X				
Obtain subject number via IWRS	X					
Dispense TAK-438/esomeprazole via IWRS		X				

	Screening Period	Randomization	Treatment Period			Follow-up Period
Study Day/Week:		**Day -1 [a]**	**Day 1 [a]**	**Week 2 (Day 15)**	**Early Termination Visit**	**Week 4 Post-treatment**
Visit Windows (Days):	**Day -28 to Day -2**			**15 - 18**	**Within 14 days of last dose**	**28 - 35 days after last dose**
Dispense companion drug via IWRS		X				
Take TAK-438/esomeprazole and companion drugs			X			
Drug return/ accountability/compliance				X	X	
Register subject as discontinued or completed via IWRS				X	X	
PTE assessment [i]	X	----------	X			
AE assessment			X	X	X	X

^{13}C-UBT: ^{13}C-urea breath test; AE: adverse event; ECG: electrocardiogram; F/U: follow-up; FSH: follicle-stimulating hormone; *HP*: *Helicobacter pylori;* IWRS: interactive web response system; PTE: pretreatment event.

[a] The day of first investigational drug administration for treatment period is Day 1. The day before first investigational drug administration for treatment period is Day -1.

[b] Main Criteria for Inclusion section, determined by 13C-UBT. Any local test for HP infection status should be avoided after subjects sign an informed consent form.

[c] If the patient takes PPI prior to UBT test, it may show false negative, for those cases retest can be allowed 2 weeks after the PPI discontinuation when appropriate in investigator's judgment.

[d] Clinical laboratory tests includes hematology, liver function test, renal function test, electrolytes, glucose, lipid test and urinalysis (see Table 9.a).

[e] For women of childbearing potential.

[f] For women if menopause is suspected.

[g] If endoscopy and randomization visit are on the same day, endoscopy should be performed first, before completing the procedures of the randomization visit.

[h] If the patient fails screening, susceptibility test will not be performed with the collected sample.

[i] The PTE assessment will start when the subject signs the informed consent and continue until the first administration of study drug on Day 1, or until screen failure.

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 that 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 or the subject's

legally acceptable representative 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 pharmacogenomic 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 drug(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.
    e) That the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

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 drug.
- 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 Protocol History

Date	Amendment Number	Amendment Type	Region
20 October 2020	03	Nonsubstantial	China
06 May 2020	02	Nonsubstantial	China
28 March 2019	01	Nonsubstantial	China
02 October 2018	Initial protocol		China

Protocol Amendment 03 Summary and Rationale

This section describes the changes in reference to the protocol incorporating Amendment 03. The primary reasons for this amendment are:

- To modify the schedule of study procedures and potentially reduce 1 onsite visit during screening.
- To add COVID terms to medically significant AE list.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 03		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	**Description**	**Rationale**
Section 9.3.2 Randomization (Visit 2) Section 9.3.3 Treatment Period (Visit 3 or Early Termination Visit) Section 9.3.4 Follow up (F/U Visit) Appendix A Schedule of Study Procedures	Modification of Schedule of Study Procedures	Rationale for this change is to streamline study procedures. If the endoscopy was the last procedure during screening period, randomization procedures can now be done after the completion of endoscopy. The study drug will be administered the day after randomization.
Section 10.1.4 SAEs	Addition of COVID terms to Takeda medically significant AE list	Rationale for this change is to comply with Takeda policy.

Rationale for Amendment 02

The primary reason for this amendment is to add TAK-438_115 study results as a rationale for this study, indications of *Helicobacter pylori* (HP) eradication as recommended by the Chinese Society of Gastroenterology, and information for the coordinating investigator. The revisions are nonsubstantial and will not have an impact on subject safety.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 02

1. Addition of coordinating investigator.
2. Addition of the results of TAK-438_115 to the rationale of this study.
3. Revisions to schematic of study design.
4. Addition of information for dose justification.
5. Added indications for HP eradication as recommended by the Chinese Society of Gastroenterology.
6. Removal of drug screen.
7. Removal of a duplicate exclusion criterion referring to history of drug and alcohol abuse.
8. Removal of a duplicate exclusion criterion referring to participation in another clinical study.
9. Correction of excluded medication and treatment timelines.
10. Clarification of pregnancy test during the treatment period is for women of childbearing potential.
11. Correction of the timepoint for the final visit.
12. Clarification of pregnancy test for women of childbearing potential is only at early termination.
13. Addition of the need to register a subject as discontinued or completed via interactive web response system (IWRS) during Visit 3.
14. Correction of the need to register a subject as discontinued or completed via IWRS at Visit 3 instead of only at the final visit or early termination.

Rationale for Amendment 01

The primary reason for this amendment is the correction of the breakpoint resistance for the 2-fold agar dilution method and the storage conditions of the products.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 01

1. The correction of the breakpoint resistance for the 2-fold agar dilution method.
2. The correction of the storage conditions for the products.
3. Removal of hepatitis-C virus (HCV)-viral load-RNA laboratory test.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Science Approval	20-Oct-2020 09:13 UTC
[redacted]	Biostatistics Approval	20-Oct-2020 13:43 UTC
[redacted]	Clinical Science Approval	20-Oct-2020 23:49 UTC