



Title: A Randomized, Double-Blind, Double-Dummy, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily Administration of TAK-438 10 or 20 mg Compared to Lansoprazole 15 mg in the Maintenance Treatment of Subjects With Endoscopic Healing of Erosive Esophagitis

NCT Number: NCT02388737

Protocol Approve Date: 15 November 2016

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PROTOCOL

A Randomized, Double-Blind, Double-Dummy, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily Administration of TAK-438 10 or 20 mg Compared to Lansoprazole 15 mg in the Maintenance Treatment of Subjects With Endoscopic Healing of Erosive Esophagitis

Sponsor: Takeda Development Center Asia Pte. Ltd.
21 Biopolis Road, Nucleos North Tower, Level 4, Singapore 138567

Study Number: TAK-438_305

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

Compound: TAK-438

Date: 15 November 2016 **Amendment Number:** 06

Amendment History

Date	Amendment Number	Region
29 Aug 2012	Initial Protocol	Asia Pacific
31 Oct 2014	01	Asia Pacific
26 Jan 2015	02	Asia Pacific
23 Apr 2015	03	Asia Pacific
14 Dec 2015	04	Asia Pacific
06 Apr 2016	05	Asia Pacific
15 Nov 2016	06	Asia Pacific

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

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

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

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1.2 Approval

REPRESENTATIVES OF TAKEDA

- This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:
- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD



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INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also 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 Clinical Study Site Agreement.
- [Appendix B](#) – Responsibilities of the Investigator.

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

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

1.3 Protocol Amendment 06 Summary of Changes

Rationale for Amendment 06

This document describes the changes in reference to the protocol incorporating Amendment No. 06. The primary reason for this amendment is to add an open-label, single-blind Lansoprazole treatment arm (the Healing Phase) to permit the enrolment of subjects with ongoing erosive esophagitis.

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

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

Changes in Amendment 06

1. Updated study team contacts and approvers.
2. Information from phase 3 clinical studies of TAK-438 has been added.
3. Added a 4- or 8-week, open-label single-arm Lansoprazole 30 mg treatment period (the Healing Phase); new language to distinguish between the open-label Healing Phase and randomized, double-blind Maintenance Phase; defined Healing Phase Failures, and qualified that de novo subjects are no longer eligible to enroll.
4. Added the Healing Phase to the Study Design Schematic.
5. Clarified the primary and secondary objectives.
6. Changed the inclusion criteria.
7. Updated the timings relating to excluded medications and treatments.
8. Stated the dosing instructions for Lansoprazole 30 mg.
9. Stated dosage form, manufacturing, packaging, and labeling for Lansoprazole 30 mg.
10. Clarified dispensing procedures during the Healing Phase.
11. Clarified the total volume of blood collected.
12. Further detailed the site visits for liver function tests.
13. Clarified the classification of endoscopy.
14. Clarified procedures around diary collection on study visit days.
15. Updated compliance instructions to include treatment during the Healing Phase.
16. Clarified that 3 schedules of study-related procedures are included in [Appendix A](#).
17. Clarified the study-related procedures to be conducted during the Screening Phase (Visit 1).
18. Added a description of study procedures during Healing Phase visits.
19. Repeated the discontinuation criteria for liver function abnormalities.

20. Confirmed that the questionnaires used to rate a subject's symptoms and severity of symptoms are the same as that used in the Japanese clinical development program.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Asia Pte. Ltd.	Compound: TAK-438 / Vonoprazan	
Title of Protocol: A Randomized, Double-Blind, Double-Dummy, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily Administration of TAK-438, 10 or 20 mg Compared to Lansoprazole 15 mg in the Maintenance Treatment of Subjects With Endoscopic Healing of Erosive Esophagitis	IND No.: not applicable	EudraCT No.: not applicable
Study Number: TAK-438_305	Phase: 3	
Study Design: This is a phase 3, multicenter, randomized, double-blind, parallel-group study to demonstrate the noninferiority of TAK-438 (10 mg or 20 mg) to Lansoprazole 15 mg in preventing the recurrence of erosive esophagitis in subjects with endoscopically confirmed healing of erosive esophagitis. This study also aims to determine the clinically recommended dose of TAK-438 for maintenance therapy of erosive esophagitis. This study is comprised of 2 treatment periods: An open-label, single-arm period in which subjects with ongoing erosive esophagitis receive Lansoprazole 30 mg for 4 or 8 weeks (Healing Phase), and a double-blind, parallel-group period in which subjects with healed erosive esophagitis are randomized at a 1:1:1 ratio to TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily for up to 24 weeks (Maintenance Phase). To enroll in the study subjects must have ongoing erosive esophagitis or have completed Study TAK-438_303. Subjects with ongoing erosive esophagitis are required to undergo the Healing Phase. Once erosive esophagitis healing is confirmed by endoscopy, these subjects may be randomized to 1 of 3 treatments in the Maintenance Phase. Subjects with endoscopic-confirmed healing of erosive esophagitis following the completion of Study TAK-438_303 will be randomized into the Maintenance Phase without carrying out the open-label Healing Phase. Subjects who previously entered the study (prior to Protocol Amendment 06) after confirmation of healed erosive esophagitis following treatment with a proton pump inhibitor outside Study TAK-438_303, or as part of the Healing Phase of the current study (termed “ <i>de novo</i> ” subjects) are no longer eligible to enter the study; any ongoing subjects may continue being treated in the Maintenance Phase. If relapse of erosive esophagitis has been endoscopically confirmed in any subject during the Maintenance Phase, the subject will complete the study at that time point (to be construed as “complete cases in the Maintenance Phase”, regardless of the time point where relapse of disease is confirmed).		
Primary Objectives: <ul style="list-style-type: none"> • To demonstrate the noninferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a proton pump inhibitor. • To determine the clinically recommended dose of TAK-438 for maintenance therapy in erosive esophagitis in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a proton pump inhibitor. 		
Secondary Objectives: <ul style="list-style-type: none"> • To evaluate the efficacy of TAK-438 during the first 12-weeks of treatment in the Maintenance Phase in subjects with endoscopically confirmed healed erosive esophagitis receiving TAK-438 or a proton pump inhibitor. • To evaluate the safety of TAK-438 versus Lansoprazole in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a proton pump inhibitor. 		

<p>Additional Objectives: To evaluate the effect of TAK-438 on subjective symptoms of erosive esophagitis (heartburn and regurgitation) and improvement in Health Related Quality of Life using the EuroQol (EQ-5D-5L).</p>	
<p>Subject Population: Subjects aged 18 or older (and at least the local age of consent) inclusive with endoscopically confirmed healed erosive esophagitis following completion of Study TAK-438_303, treatment with a proton pump inhibitor during the Healing Phase of the current study, or <i>de novo</i> subjects treated with a proton pump inhibitor outside of Study TAK-438_303 or the current study.</p>	
<p>Number of Subjects: The number of subjects with endoscopically confirmed healed erosive esophagitis to be randomized into the Maintenance Phase: TAK-438 10 mg group: approximately 231 TAK-438 20 mg group: approximately 231 Lansoprazole 15 mg group: approximately 231 Estimated total: approximately 693 randomized</p>	<p>Number of Sites: Estimated total: Approximately 70 sites in multiple countries</p>
<p>Dose Level(s): Subjects entering the study with ongoing erosive esophagitis will receive Lansoprazole (one 30 mg capsule/tablet) given once daily as per the local approved package insert. Following confirmation of endoscopic healing of erosive esophagitis subjects will be randomized to receive: <u>TAK-438 10 mg group:</u> TAK-438 (one 10 mg tablet) + TAK-438 placebo (matching 20 mg tablet) + Lansoprazole placebo (1 capsule) given once daily after breakfast <u>TAK-438 20 mg group:</u> TAK-438 (one 20 mg tablet) + TAK-438 placebo (matching 10 mg tablet) + Lansoprazole placebo (1 capsule) given once daily after breakfast <u>Lansoprazole 15 mg group:</u> TAK-438 placebo (matching 10 mg tablet) + TAK-438 placebo (matching 20 mg tablet) + Lansoprazole (one 15 mg capsule) given once daily after breakfast</p>	<p>Route of Administration: Oral</p>
<p>Duration of Treatment: Up to 8 months (32 weeks).</p>	<p>Period of Evaluation: Healing Phase: up to 2 months (4 or 8 weeks). Maintenance Phase up to 6 months (24 weeks). Follow-up Phase: up to 14 days.</p>
<p>Main Criteria for Inclusion: All subjects are to be evaluated for eligibility for entry in the study based on the following criteria. The subject has endoscopically confirmed erosive esophagitis (LA classification grades A to D) within 84 days of Day 1, and has endoscopically confirmed healed erosive esophagitis after completion of Study TAK-438_303 or completion of 4 or 8 weeks Lansoprazole 30 mg treatment in the open-label arm of the current study (for subjects who have not participated in TAK-438_303 study, this endoscopy must be taken within 14 days before the enrollment in the TAK-438_305 study). Subjects must also have provided (or when applicable their legally acceptable representative has provided) informed consent, are capable of understanding and complying with the study procedures and agree to use appropriate contraception.</p>	

Main Criteria for Exclusion:

Subjects who have hypersensitivity to TAK-438 or related compounds and Lansoprazole, a significant history of central nervous system (CNS), cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine or hematological disease, or any significant results from physical examinations, subjects with a liver function test > upper limit of normal, or clinical laboratory results as deemed by the investigator. Subjects that have any co-morbidities, medical or surgical history that may affect the esophagus or have an acute upper gastrointestinal bleeding, gastric or duodenal ulcer within 30 days, with history or treatment of malignancy within 5 years are also excluded.

Main Criteria for Evaluation and Analyses:

Efficacy:

The primary efficacy endpoint for this study is the rate of recurrence of erosive esophagitis as confirmed on endoscopy during the 24-week Maintenance Phase.

The secondary efficacy endpoint for this study is the rate of recurrence of erosive esophagitis during the first 12 weeks of treatment in the Maintenance Phase.

Other efficacy endpoints include subjective symptoms of erosive esophagitis (heartburn and regurgitation) and Health-Related Quality of Life measures.

Safety:

The safety endpoints of this study include adverse events, laboratory test values, electrocardiogram (ECG), vital signs, serum gastrin and pepsinogen I/II values.

Statistical Considerations:

Efficacy Analysis:

For the primary efficacy endpoint of rate of endoscopic recurrence of erosive esophagitis during the 24-week Maintenance Phase, a 2-sided 95% confidence interval (CI) will be constructed for the difference between each TAK-438 group and Lansoprazole and its upper bound will be compared to the noninferiority margin of 10%.

The secondary endpoint of rate of endoscopic recurrence of erosive esophagitis during the first 12 weeks of treatment in the Maintenance Phase will be compared between each TAK-438 group and Lansoprazole by constructing a 2-sided 95% CI for the recurrence rate difference.

The additional endpoints related to GERD symptoms that occur during treatment in the Maintenance Phase will be compared between treatment groups using Wilcoxon rank-sum tests. Analysis of Health-Related Quality of Life endpoints will be conducted with an Analysis of Covariance model with treatment and baseline EE grade (A/B vs C/D) as factors and baseline as a covariate.

Statistical inference will be performed at a 2-sided 0.05 level of significance or via 2-sided 95% CIs. The primary endpoint will be tested for TAK-438 20 mg and 10 mg groups, sequentially, versus Lansoprazole.

Safety Analysis:

Safety analysis will be performed by summarizing the incidence of adverse events, clinical laboratory tests including gastrin and pepsinogen I/II levels, vital signs, and ECGs in the Maintenance Phase. No statistical testing or inferential statistics will be generated.

Sample Size Justification:

Assuming that the true Week 24 recurrence rate is 30.4% for Lansoprazole, 22.0% for TAK-438 10 mg, and 13.6% for TAK-438 20 mg, and assuming that the dropout rate is approximately 30%, a sample size of 208 subjects per group will provide an overall power of 90% to establish noninferiority using a 2-sided 95% CI with a 10% noninferiority margin. 231 subjects per group will be included to allow adequate numbers for the regulatory requirements of various countries.

The assumption of the true recurrence rate is based on a phase 3 study that showed a Week 24 recurrence rate of 30.4% for Lansoprazole 15 mg and 13.6% for Lansoprazole 30 mg.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Principal Investigator/Coordinating Investigator

Takeda Development Center Asia, Pte. Ltd 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 medication, 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.

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3.3 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
BUN	blood urea nitrogen
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CK/CPK	creatine phosphokinase
Cl	chlorine
C _{max}	maximum observed plasma concentration
CNS	central nervous system
eCRF	electronic case report form
CRO	contract research organization
CYP	cytochrome P450 enzyme
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
EE	erosive esophagitis
EM	extensive metabolizers
FDA	Food and Drug Administration
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	γ -glutamyl transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HCV-RNA	hepatitis C virus- ribonucleic acid
HIV	human immunodeficiency virus
H. pylori	Helicobacter pylori
HRQoL	Health-Related Quality of Life
IC	informed consent
ICH	International Conference on Harmonisation

ID	identification
IEC	independent ethics committee
INN	International Nonproprietary Name
INR	international normalized ratio
IRB	institutional review board
IU	International unit(s)
IUDs	intrauterine devices
IVRS	interactive voice response system
IWRS	interactive web response system
LA classification	Los Angeles classification
LDH	lactate dehydrogenase
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NERD	non-erosive reflux disease
NSAIDs	non-steroidal anti-inflammatory drugs
P-CAB	potassium-competitive acid blockers
pH4 HTR	pH4 holding time ratio
PM	poor metabolizers
PPI	proton pump inhibitor
PPS	per-protocol analysis set
PTP	Press Through Package
QD	quaque die, every day
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
TBil	total bilirubin
TBC	to be confirmed
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

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
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

Erosive esophagitis is among the gastric acid-related disorders in which gastric acid reflux to the esophagus leads to problems in affected individuals. In 1994, the concept of a “mucosal break,” defined as “an area of slough or an area of erythema with a discrete lined demarcation from the adjacent or normal looking mucosa,” was introduced in the Los Angeles classification for diagnosis and grading of erosive esophagitis. Erosive esophagitis is graded in severity into 4 grades (A-D) based on the extent of mucosal breaks. Acid reflux induces prolonged, unpleasant subjective symptoms, such as heart burn or gastric acid reflux, in symptomatic patients with erosive esophagitis, often aggravating their Health-Related Quality of Life.

Due to westernization of diet in Asia, there is an increase in the patients with erosive esophagitis.

The proton pump inhibitors (PPIs), such as Lansoprazole, represent the drugs of first choice for erosive esophagitis, and are being widely used all over the world.

The PPIs inhibit the H^+ , K^+ -ATPase enzyme (proton pump) which represents the final step in acid secretion by the parietal cells in the gastric mucosa, and produce potent anti-secretory efficacy for acid-related disorders.

However, even with these potent acid-inhibitory effects, the PPIs are not without their limitations and have not necessarily produced adequate improvements in extent and speed of symptom relief [1]. Indeed, the PPIs appear to leave room for improvement, the reason being that:

1. Being less resistant to acid exposure and provided as enteric-coated drugs, the PPIs vary in time for onset of their action;
2. About 3 to 5 days are required to obtain maximum acid-inhibitory effects with the PPIs;
3. Acid-inhibitory effects with the PPIs appear to be satisfactory during daytime, but not adequate to inhibit acid regurgitations from the stomach to the esophagus occurring during nighttime, leading to nocturnal acid breakthroughs in some individuals;
4. Metabolized by CYP2C19 associated with polymorphisms, the PPIs are associated with varying serum concentrations, thus producing disparate acid-inhibitory effects in extensive metabolizers (EM) versus poor metabolizers (PM).

Developed at Takeda Pharmaceutical Company Ltd, TAK-438 belongs to a new class of acid-inhibitory agents called “potassium-competitive acid blockers” (P-CAB). TAK-438 is shown not only to inhibit the H^+ , K^+ -ATPase enzyme in the final step of acid secretion, as the PPIs do, but does not require the presence of acid for its activation and inhibits the H^+ , K^+ -ATPase enzyme in a potassium-competitive fashion. Furthermore, TAK-438 is shown to be stable in the presence of acid, is water-soluble, and requires no particular pharmacological preparations, such as an enteric coating, suggesting that the time to onset of action of TAK-438 may be less variable compared with PPIs. Furthermore, in contrast to the PPIs which take 3 to 5 days to produce their maximum acid-inhibitory effects, TAK-438 is expected to produce its maximum acid-inhibitory effects in a

much shorter time and to produce better outcomes than the PPIs with its potent and sustained acid-inhibitory effects.

In Japan, TAK-438 has been evaluated for the doses ranging between 1 mg and 120 mg in a phase 1 study (TAK-438/CPH-001) as well as for safety, pharmacokinetics, and acid-inhibitory effects in a 7-day repeated-dose study (TAK-438/CPH-002) at the doses ranging between 10 mg and 40 mg. TAK-438 has been found to be well tolerated when given at the dose of 40 mg in the 7-day repeated-dose study, where the pH4 holding time ratio (pH4 HTR) with TAK-438 10 mg on day 7 was shown to be similar to that with Lansoprazole 30 mg. However pH4 HTR was found to increase greatly with TAK-438 15 mg and 20 mg, and exceed 90% and remain stable with TAK-438 30 mg and 40 mg, thus providing evidence of TAK-438's potent and sustained acid-inhibitory effects. Furthermore, no specific trend was found with any of the CYP2C19 polymorphisms, suggesting that these polymorphisms lead to very little difference in the pharmacokinetics of TAK-438. Additionally, in a study evaluating interactions between TAK-438 and various non-steroidal anti-inflammatory drugs (NSAIDs) (eg, loxoprofen sodium, diclofenac sodium, meloxicam) (TAK-438/CPH-003), none of these drugs were shown to significantly affect the pharmacokinetics of TAK-438.

Studies of single-dose (TAK-438_101) and repeated-dose (TAK-438_107) TAK-438 were conducted in the UK as well, where TAK-438 was evaluated for its safety, pharmacokinetics and acid-inhibitory effects in the 7-day repeated-dose study at the doses ranging between 10 mg and 40 mg. TAK-438 was shown to be well tolerated at the dose of 40 mg in the repeated-dose study, with the pH4 HTR on day 7 shown to be similar to that in the repeated-dose study conducted in Japan at either of the doses examined, supporting the potent and sustained acid-inhibitory effects of TAK-438. Again, in a study evaluating interactions between TAK-438 and clarithromycin conducted in the UK (TAK-438_110), repeated-dose clarithromycin was examined for its influence on the pharmacokinetics of TAK-438, where, while the serum concentration of TAK-438F increased by 1.35-fold for C_{max} and by 1.58-fold for AUC in combination with clarithromycin, a potent inhibitor of the CYP3A4 enzyme, TAK-438 was shown to be well tolerated.

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

TAK-438 has been studied in a number of acid-related diseases and noninferiority with Lansoprazole has been confirmed in several phase 3 studies including reflux esophagitis healing and prevention of recurrence studies, gastric/duodenal ulcer healing and for the prevention of

recurrence of a gastric or duodenal ulcer during NSAID or aspirin administration and has subsequently been launched in Japan for these indications. All treatments were well-tolerated.

4.2 Rationale for the Proposed Study

In a phase 2 dose-ranging study of TAK-438 in subjects with erosive esophagitis (TAK-438/CCT-001), dose-response efficacy was shown for TAK-438, showing TAK-438 to be non-inferior to Lansoprazole at either of the doses tested (5 mg, 10 mg, 20 mg, and 40 mg), with no particular safety concerns identified. Furthermore, 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, which led to the clinically recommended dose of TAK-438 for erosive esophagitis being determined as 20 mg.

In light of these considerations, it was decided that a phase 3 double-blind study would be conducted to validate the noninferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 20 mg, following PPI treatments, or Lansoprazole 30 mg. This study will further examine the effectiveness and safety of TAK-438 in Asian subjects outside of Japan for the maintenance treatment of subjects with endoscopically confirmed healed erosive esophagitis.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

- To demonstrate the noninferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.
- To determine the clinically recommended dose of TAK-438 for maintenance therapy in erosive esophagitis in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.

5.1.2 Secondary Objectives

- To evaluate the efficacy of TAK-438 during the first 12-weeks of treatment in the Maintenance Phase in subjects with endoscopically confirmed healed erosive esophagitis receiving TAK-438 or a PPI.
- To evaluate the safety of TAK-438 versus Lansoprazole in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.

5.1.3 Additional Objectives

- To evaluate the effect of TAK-438 on subjective symptoms of erosive esophagitis (heartburn and regurgitation) and improvement in Health Related Quality of Life using the EuroQol (EQ-5D-5L).

5.2 Endpoints

5.2.1 Primary Endpoints

The primary efficacy endpoint for this study is the rate of recurrence* of erosive esophagitis as confirmed on endoscopy during the 24-week Maintenance Phase.

**Recurrence: defined as subjects endoscopically confirmed to have erosive esophagitis (LA classification grades A to D) during the Maintenance Phase (24 weeks).*

5.2.2 Secondary Endpoints

The secondary efficacy endpoint for this study is the rate of recurrence* of erosive esophagitis during the first 12 weeks of treatment in the Maintenance Phase. Safety endpoints for this study include adverse events (AEs), clinical laboratory test results, ECG, vital signs, serum gastrin and pepsinogen I/II levels.

**Recurrence: defined as subjects endoscopically confirmed to have erosive esophagitis (LA classification grades A to D) during the Maintenance Phase (12 weeks).*

5.2.3 Additional Endpoints

Other efficacy endpoints include subjective symptoms of erosive esophagitis (heartburn and regurgitation) as recorded in subject diaries and Health-Related Quality of Life measures.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

6.1.1 Study Description

This is a phase 3, multicenter, randomized double-blind, parallel-group study to demonstrate the noninferiority of TAK-438 (10 mg or 20 mg) to Lansoprazole 15 mg in preventing the recurrence of erosive esophagitis in subjects with endoscopically confirmed healing of erosive esophagitis. This study also aims to determine the clinically recommended dose of TAK-438 for maintenance therapy of erosive esophagitis.

This study is comprised of 2 treatment periods: An open-label, single-arm period in which subjects receive Lansoprazole 30 mg for up to 8 weeks (Healing Phase), and a double-blind, parallel-group period in which subjects are randomized at a 1:1:1 ratio to TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily for up to 24 weeks (Maintenance Phase). To enroll in the study subjects must have ongoing erosive esophagitis or have completed Study TAK-438_303. Subjects with ongoing erosive esophagitis are required to undergo the Healing Phase. Once erosive esophagitis healing is confirmed by endoscopy, these subjects may be randomized to 1 of 3 treatments in the Maintenance Phase. Subjects with endoscopic-confirmed healing of erosive esophagitis following the completion of Study TAK-438_303 will be randomized into the Maintenance Phase without carrying out the open-label Healing Phase. Subjects who previously entered the study (prior to Protocol Amendment 06) after confirmation of healed erosive esophagitis following treatment with a proton pump inhibitor (termed “*de novo*” subjects) are no longer eligible to enter the study; any ongoing subjects may continue being treated in the Maintenance Phase. A schematic of the study design is included in [Figure 6.a](#). A schedule of assessments is listed in [Appendix A](#).

If relapse of erosive esophagitis has been endoscopically confirmed in any subject, the subject will complete the study at that time point (to be construed as “complete cases in the Maintenance Phase”), regardless of the time point where relapse of disease is confirmed.

This study will be conducted at a total of around 70 sites across Asia with an estimated total of 231 subjects randomized to each treatment group during the Maintenance Phase (totaling 693 subjects entering the Maintenance Phase for the study).

The study will consist of a Screening Phase of up to 28 days duration (Visit 1), a Healing Phase (for those subjects with ongoing erosive esophagitis only) of 4 or 8 weeks duration (Visits 2_{HP} and 3_{HP}), followed by a Maintenance Phase of up to 24 weeks (Visits 2-8), and a Follow-up Period of up to 14 days duration. With the exception of the Follow-up (which will be carried out by phone), all visits will occur at the clinic. The total duration of treatment is up to 6 months (24 weeks) in subjects entering from Study TAK-438_303, and up to 8 months (32 weeks) in subjects entering the study with ongoing erosive esophagitis.

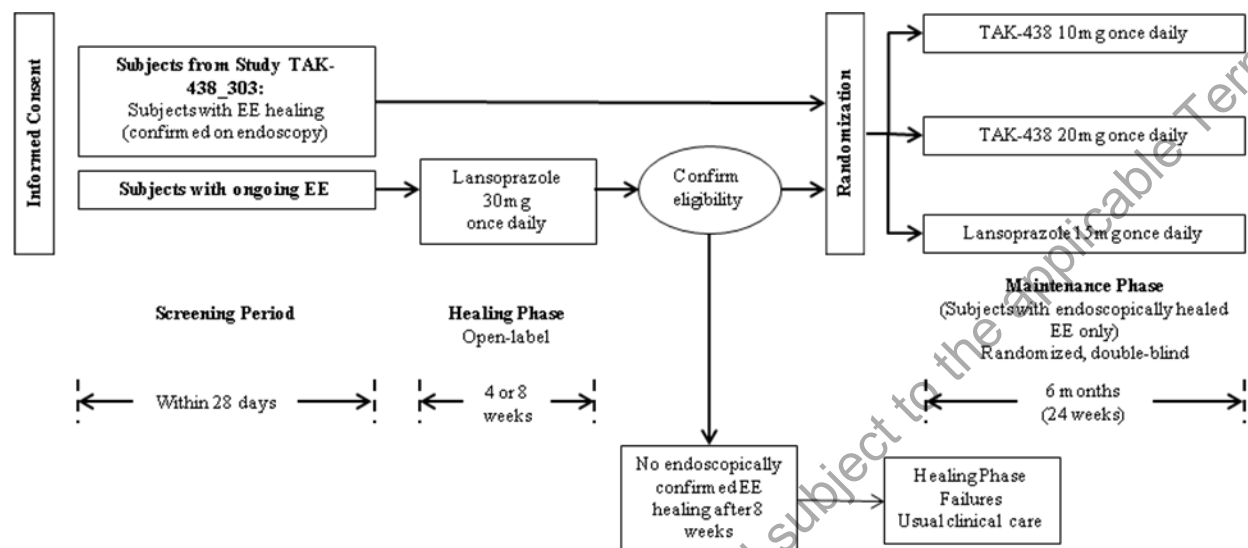
Subjects with ongoing erosive esophagitis: Subjects who have ongoing erosive esophagitis will enter the Healing Phase and administration of Lansoprazole 30 mg once daily will commence

following the completion of all required assessments at Visit 2_{HP}. Subjects will then undergo a visit at Week -4 (Visit 3_{HP}), where the subject may undergo endoscopy to confirm healing of erosive esophagitis. This is an optional procedure where the decision to perform endoscopy is based on the investigator's clinical judgment of a subject's symptoms of healing. Subjects who do not show endoscopic healing at Visit 3_{HP} may continue in the Healing Phase and undergo endoscopy at Day 1 (Visit 2). Subjects with endoscopically confirmed healing of erosive esophagitis at Week -4 or at Day 1 will be eligible to enter the Maintenance Phase. Where the results from clinical laboratory tests confirming eligibility for the Maintenance Phase at Week -4 are not immediately available, subjects should continue to receive Lansoprazole 30 mg for up to 14 days. Subjects healed at Day 1 should be immediately randomized. Subjects who do not have endoscopic-confirmed healed erosive esophagitis after 8 weeks treatment (Healing Phase Failures) will not be randomized into the Maintenance Phase and should be treated using routine clinical care.

Subjects with healed erosive esophagitis: Subjects with healed erosive esophagitis will undergo a randomization visit (Visit 2), and dosing for the Maintenance Phase will commence following the completion of all required assessments on Day 1. Visits will then occur at 2 week intervals after the initiation of treatment in the Maintenance Phase. As a result of Protocol Amendment 06, subjects with healed erosive esophagitis following treatment with a proton pump inhibitor outside Study TAK-438_303 or the Healing Phase of the current study (*de novo* subjects) are no longer eligible to enter the study; any ongoing subjects may continue to be treated in the Maintenance Phase.

All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks. For subjects entering the Maintenance Phase of the current study within 7 days of completing Study TAK-438_303, the requirement for 8 weeks of monitoring can be totalled across the 2 studies. Further detail on the LFT monitoring requirements is available in Section 9.1.8.

Figure 6.a Schematic of Study Design



Subjects entering the study from Study TAK-438_303 with endoscopic-confirmed healing of erosive esophagitis (EE) will be immediately randomized into the double-blind Maintenance Phase. Prior to randomization into the Maintenance Phase, subjects with ongoing EE will receive open-label Lansoprazole 30 mg once daily for 4 or 8 weeks (the Healing Phase) until healing of EE is confirmed by endoscopy performed at either Week -4 and/or Day 1. Subjects who do not have endoscopic-confirmed healed EE after 8 Weeks treatment (Healing Phase Failures) will not be randomized and should be treated using routine clinical care.

6.2 Justification for Study Design, Dose, and Endpoints

For the patient population studied

To evaluate the efficacy and safety of TAK-438 as maintenance therapy for healed erosive esophagitis, this study plans to enroll subjects who were confirmed on endoscopy to have erosive esophagitis (LA classification grades A to D) and in whom endoscopic healing of erosive esophagitis has been confirmed either after treatment with TAK-438 or Lansoprazole in the TAK-438_303 study, or following up to 8 weeks treatment with open-label Lansoprazole in the current study.

The LA classification system is used to confirm the severity of erosive esophagitis, as this is a widespread method of classification, as well as used during an earlier Phase 2 dose-ranging study of TAK-438 (TAK-438/CCT-001).

For study design and sample size used

1. Study design.

To evaluate the efficacy and safety of TAK-438 as maintenance therapy for healed erosive esophagitis, the present study was designed as a randomized, double-blind, parallel-group study comparing the efficacy and safety of TAK-438 10 mg and 20 mg versus the PPI Lansoprazole 15 mg, a drug of first choice for maintenance therapy for erosive esophagitis.

In light of the results of a phase 2 dose-ranging study of TAK-438 (TAK-438/CCT-001) demonstrating a lower rate of endoscopically confirmed healing in subjects with the baseline LA classification grades C/D than those with grades A/B; similarly, in maintenance therapy, relapse is expected to be more common among those with endoscopically confirmed severe disease. Therefore, the present study planned to stratify the subjects by baseline endoscopic findings (grades A/B or C/D) at the start of the Maintenance Phase for those who have participated in Study TAK-438_303, and prior to open-label Lansoprazole during the Healing Phase in those subjects who did not first complete Study TAK-438_303. Moreover, to ensure sufficient enrolment of subjects with severe disease and to perform subgroup analysis, at least 15% LA Grades C/D subjects should be enrolled in this study.

For those subjects entering the study with ongoing erosive esophagitis, a treatment period of 4 or 8 weeks has been selected as the duration of treatment for Lansoprazole 30 mg during the Healing Phase. Lansoprazole 30 mg once daily has been shown to heal erosive esophagitis in 92% of subjects within 4 weeks treatment (Study TAK 438/CCT-002). A treatment duration of up to 8 weeks is consistent with the approved product label for Lansoprazole in Malaysia, China and Taiwan and a treatment duration of 8 weeks is recommended in Korea.

2. Sample size.

For a description of the rationale for sample size determination, refer to Section 13.3.

For doses of the study medications 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, when given once daily at doses 5 mg, 10 mg, 20 mg, and 40 mg for 8 weeks, and demonstrated its noninferiority to Lansoprazole 30 mg at either of the doses examined, with no particular safety concerns identified. 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.

The proton pump inhibitors as the standard of care for erosive esophagitis have been approved for use at the same dose used in the treatment of erosive esophagitis or half the dose in the maintenance treatment of erosive esophagitis.

As TAK-438 is an anti-secretory agent similar to the proton pump inhibitor Lansoprazole, the dose strengths to be tested for maintenance treatment have been determined as the recommended dose of TAK-438 for treatment of erosive esophagitis (20 mg) and half that dose (10 mg).

For the open-label Healing Phase, Lansoprazole 30 mg has been selected as this is the indicated dose for the treatment of erosive esophagitis in all participating countries.

For the route of administration used

In a phase 1 single-dose study of TAK-438 in healthy male volunteers conducted in Japan, which evaluated the influence of diet on the pharmacokinetics of TAK-438 10 mg and 40 mg, the

AUC₀₋₄₈ and the C_{max} was shown to be increased by 1.32-fold (95% CI, 1.18 to 1.48) and by 1.21-fold (95% CI, 0.951 to 1.54), respectively, with TAK-438 10 mg, and by 1.15-fold (95% CI, 1.05 to 1.27) and by 1.08 (95% CI, 0.944 to 1.23), respectively, with TAK-438 40 mg, after meals compared to those seen under fasting conditions, demonstrating that the postprandial increases in AUC and C_{max} with TAK-438 were modest. Again, pharmacological results from the same phase 1 study demonstrated that once-daily dosing of TAK-438 exhibited adequate acid-inhibitory effects that were sustained over a 24-hour period, and Lansoprazole 15 mg has been approved for once daily dosing.

Based on these results, it was decided that TAK-438 would be given after breakfast as a once-daily regimen, as in the earlier phase 2 dose-ranging study of TAK-438 (TAK-438/CCT-001).

For the duration of treatment used

In a double-blind comparative study of Lansoprazole (AG-1749), a drug of first choice for erosive esophagitis, as maintenance therapy for erosive esophagitis (AG-1749/CCT-202: A study of Lansoprazole as maintenance therapy for erosive esophagitis), Lansoprazole, given 15 or 30 mg once daily for 24 weeks, has been shown to be efficacious in subjects in whom endoscopic healing of erosive esophagitis were confirmed after 8 weeks of treatment with Lansoprazole 30 mg orally given once daily.

In this study, which aims to validate the noninferiority of TAK-438 10 mg and 20 mg to Lansoprazole as well as to determine the clinically recommended dose of TAK-438, the duration of maintenance treatment with TAK-438 has been determined as 24 weeks as was the case with Lansoprazole.

For the endpoints used

1. Primary endpoint.

The primary endpoint for this study was defined as the rate of endoscopic recurrence of erosive esophagitis during the 24 weeks of maintenance treatment with TAK-438, as in the above-mentioned study of Lansoprazole as maintenance therapy for erosive esophagitis, as the study aimed to validate the noninferiority of TAK-438 10 mg and 20 mg to Lansoprazole and to determine the clinically recommended dose of TAK-438.

2. Secondary endpoints

To compare early recurrence of erosive esophagitis with TAK-438 and Lansoprazole, the secondary endpoint for this study was defined as the rate of recurrence during the first 12 weeks of maintenance treatment with TAK-438 10 mg and 20 mg versus Lansoprazole 15 mg.

3. Additional endpoints.

Heartburn and gastric acid regurgitation are typical symptoms of erosive esophagitis which could impact the subject's Health-Related Quality of Life. The severity and frequency of those symptoms are recorded via the daily diary by the subjects using the questionnaires outlined in [Table 9.c](#) and

[Table 9.d](#), which were also implemented in the Japanese clinical development program. The HRQoL will be assessed by subjects completing validated questionnaires. The EQ-5D-5L index

score has been previously used to demonstrate that moderate to severe symptoms of GERD are associated with a significant impairment in HRQoL [2, 3]. Consequently those subjective symptoms and health-related quality of life using EQ-5D-5L are considered as additional endpoints in this study.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

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

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

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. The subject has been confirmed on endoscopy to have had erosive esophagitis (LA classification grades A to D) within 84 days of Day 1. At least 15% (104 subjects) of LA grades C/D subjects should be enrolled in this study to ensure sufficient enrollment of subjects with severe disease and to perform subgroup analysis.

Note: The recruitment goal is to enroll subjects so that those with a history of LA classification grade C/D will account for more than 15% of all subjects (104/693) and those with a history of grade A/B will not be recruited further when they account for more than 85% (589/693) of all subjects.

4. If the subject is not rolled over from TAK-438_303 study, he/she has undergone an open-label PPI treatment (Lansoprazole 30 mg, once daily) of 4 or 8 weeks within the TAK-438_305 protocol.
5. The subject has been confirmed on endoscopy to have healing of erosive esophagitis. This endoscopy, if not part of the TAK-438_303 study, must have been within the last 14 days prior to randomization, otherwise the endoscopy must be repeated to confirm healing before randomization in the TAK-438_305 study.
6. The subject is aged 18 years old or older (or the local age of consent if that is older), male or female, at the time of signing an informed consent, and is being treated on an outpatient basis for erosive esophagitis, including those temporarily admitted for examination.
7. 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 for 4 weeks after last dose of study medication.

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

7.2 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 (other than study TAK-438_303) within 84 days prior to screening phase.
2. The subject has received TAK-438 in a previous clinical study (other than study TAK-438_303) or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at Screening.
5. The subject has a history or clinical manifestations of significant CNS, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine or hematological disease.
6. The subject has a history of hypersensitivity or allergies to TAK-438 or to proton pump inhibitors (PPIs) including any associated excipients*.

* D-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide and iron sesquioxide.

7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the start the screening phase.
8. The subject is required to take excluded medications listed in Section 7.3.
9. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.
10. The subject has participated in another clinical study (other than study TAK-438_303) within the past 30 days prior to the screening phase.
11. The subject has co-morbidities that could affect the esophagus (eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal strictures), a history of radiotherapy or cryotherapy for the esophagus; those with corrosive or physiochemical injury (with the possible inclusion in the study of those with Schatzki's ring or Barrett's esophagus).
12. The subject has a history of surgical procedures that may affect the esophagus (eg, fundoplication and mechanical dilatation for esophageal strictures excluding Schatzki's ring) or a history of gastric or duodenal surgery excluding endoscopic removal of benign polyps.

13. The subject developed acute upper gastrointestinal bleeding, gastric ulcer (a mucosal defect with white coating) or duodenal ulcer (a mucosal defect with white coating), within 30 days before the start of the Screening Phase (Visit 1) (with the possible inclusion of those with gastric or duodenal erosion). The subjects requiring NSAIDs or aspirin treatment along with the concomitant PPI therapy to prevent GI bleeding should not be enrolled
14. The subject has Zollinger-Ellison syndrome or gastric acid hypersecretion or a history of gastric acid hypersecretion.
15. The subject is scheduled for surgery that requires hospitalization or requires surgical treatment during his/her participation in the study.
16. The subject has a history of malignancy or was treated for malignancy within 5 years before the start of the Screening Phase (visit 1) (the subject may be included in the study if he/she has cured cutaneous basal cell carcinoma or cervical carcinoma in situ).
17. The subject has acquired immunodeficiency syndrome (AIDS) or hepatitis, including hepatitis virus carriers (HBs-antigen or HCV-antibody-positive) (the subject may be included in the study if he/she is HCV-antigen or HCV-RNA-negative).
18. Laboratory tests performed on visit 1 revealed any of the following abnormalities in the subject:
 - a) Creatinine levels: >2 mg/dL (>177 μ mol/L).
 - b) ALT, AST or total bilirubin levels: \geq the upper limit of normal (ULN).

7.3 Excluded Medications and Treatments

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

Table 7.a Excluded Medications and Treatments

From 12 weeks prior to randomization to study completion	From the start of the Healing Phase through to study completion	From 7 days prior to randomization through to study completion	From start of randomization to study completion
Other investigational drugs or drugs administered due to participation in another clinical trial	H. pylori eradication therapy (ie, PPI + 2 antibiotics) Hormonal contraceptives	H ₂ antagonists (interfere with gastric acid secretion)	Other agents affecting digestive organs including: muscarinic M ₃ receptor antagonists, prokinetics, anticholinergic agents, prostaglandins, antacids, anti-gastrin agents or mucosal-protective agents. Non-study related PPIs. Atazanavir sulfates, Rilpivirine hydrochloride (contraindicated with TAK-438) Surgical procedures that could affect gastric acid secretion (eg, upper gastrointestinal surgery, vagotomy) or for treatment of EE (fundoplication) Bisphosphonates(*)

(*) Except subjects that were using these agents before signing the informed consent form at the screening visit and the dose and administration will not be changed during the study. 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 that have no GI inflammation or history of such.

7.4 Diet, Fluid, Activity Control

The principal investigator, the co-investigators, and the study collaborators are to explain, and give instructions on, the following before the start of the study or during the study, as well as to check to see if the subjects keep to the instructions at the time of their scheduled visits.

- Every subject should keep to the scheduled visits, seek medical consultation, and undergo predetermined laboratory tests.
- With the exception of Lansoprazole 30 mg during the Healing Phase (where applicable), which should be administered according to the approved local package insert, the subject should ensure that all study medications are swallowed with 240 ml water soon after breakfast according to the administration, dose and dosing schedule. Subjects should be instructed according to Section 8.1.3.3 (Missed Doses) and Section 9.2 (Compliance). Details of any missed or forgotten doses should be reported to the investigator or designee at the subsequent study visit.
- The subject should store all medications in a cool, dry, safe place which is out of reach at children and to bring all study supplies (empty / used / unused drug packets and diaries alike) to each study visit.
- The subject should record his/her nighttime (during sleep) subjective symptoms and the previous daytimes subjective symptoms in his/her subject diary upon rising in the morning on

a daily basis. The subject should also record his/her study medication compliance status during the Maintenance Phase of the study.

- Subjects will be required to fast for at least 10 hours before each visit, where fasting blood draw will be taken and/or endoscopy will be performed, after the Informed Consent is signed. Fasting status means no food or nutritional drinks. Water is allowed. Any medication that needs to be taken with food, and study medications, should be held until after the fasting blood draw has been taken and/or endoscopy has been performed. Medication that does not need to be taken with food should be continued. Investigator must instruct the subject accordingly prior to visits in which serum gastrin and pepsinogen I/II levels will be measured, endoscopy will be performed.
- If on any day between study visits the subject failed to eat breakfast, he/she should take the study medication at about the same time as he/she usually does.
- When the subject is to be treated by physicians other than study investigators or taking other medications, such as over-the-counter drugs, beyond those prescribed, he/she should consult the study investigator or designee beforehand. When the subject was treated by a physician other than the investigator or when he/she took other medications such as over-the-counter drugs beyond those prescribed, he/she should report on the treatment received or the medications taken at the next study visit.
- The subject should 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 AE, the subject or his/her family should contact the investigator as soon as possible.
- The subject should use contraception without fail. (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 medication). Pregnancy in a female subject, if found, should be reported immediately.
- The subject should not donate blood during the study, and should report on any such donation immediately.
- The subject should 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 should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.12.

1. Pretreatment event or AE. The subject has experienced a pretreatment event 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 pretreatment event or AE.

- Liver Function Test Abnormalities

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

- ALT, AST or total bilirubin >2 times of upper limit of normal (ULN).
2. Major 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.
 4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

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

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

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

7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational 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, for example: non-compliance.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may terminate 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. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to TAK-438 (10 mg tablets, 20 mg tablets and their matching placebo tablets) and Lansoprazole (15 mg capsules and matching placebo capsules, as well as Lansoprazole 30 mg capsules/ tablets) defined below. Study medication will be packaged in a blinded fashion for the Maintenance Phase and in an open fashion for the Healing Phase.

8.1.1.1 Investigational Drug

The chemical name of TAK-438 is:

1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1*H*-pyrrol-3-yl]-*N*-methyl methanamine monofumarate. The code name is TAK-438. The International Nonproprietary Name (INN) is vonoprazan. Note that there is no generic name assigned at the time of writing this protocol. TAK-438 10 mg, 20 mg and their matching placebo investigational drug is manufactured by Takeda Pharmaceutical Company, Osaka, Japan and will be supplied as pale yellow and pale red respectively, film-coated tablets.

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

(*RS*)-2-({[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridylmethyl]sulfinyl} benzimidazole. Lansoprazole 15 mg will have a dual supply chain. The Lansoprazole 15 mg and 30 mg for the study conducted in China is manufactured locally by Tianjin Takeda, Tianjin China. Lansoprazole 15 mg and 30 mg for all other countries and matching placebo for Lansoprazole 15 mg is manufactured by Takeda Pharmaceutical Company, Osaka, Japan. All Lansoprazole 15 mg and matching placebo will be supplied as a white colored capsule. Lansoprazole 30 mg will be supplied as a white colored capsule with the exception of the Malaysia marketed version where Lansoprazole 30 mg will be supplied as a white-to-yellowish white uncoated tablet with orange-to-dark brown speckles.

For the Healing Phase, Lansoprazole 30 mg will be foil/foil blistered packaged into 35-day (4 weeks plus 7 extra days) child-resistant blister cards for sites in Korea and Taiwan. The daily dose will be 1 capsule. The country-specific marketed version of Lansoprazole 30 mg will be supplied for sites in China and Malaysia respectively. These products will be labelled in an open fashion.

For the Maintenance Phase, TAK-438 and Lansoprazole investigational drug will be foil/foil blistered packaged into 20-day (2 weeks plus 6 extra days) child-resistant blister cards. Each blister card will include 20 TAK-438 10 mg or placebo tablets; 20 TAK-438 20 mg or placebo

tablets and 20 Lansoprazole 15 mg or placebo capsules. The daily dose will be 2 tablets and 1 capsule. Each blister card will be labeled in a blinded fashion. For all investigational treatments, each blister card will be accompanied by a single panel or multi language booklet label appropriate to the countries in which it will be used. The labels will include pertinent study information and country-specific regulatory caution statement.

An Interactive Web Response System (IWRs) program will be used to manage inventory, assist the site in dispensing the proper investigational drug to the subjects, record accountability and support the return to sponsor or designee of these investigational drugs after study completion.

Table 8.a Investigational Drug

Study medication form	Description	Manufacturer and Location
Healing Phase		
Lansoprazole 30 mg capsule/tablet*	White capsule White to yellowish white with orange to dark brown speckles uncoated tablet *	Tianjin Takeda Pharmaceuticals Co., Ltd, China(for the study in China) / Takeda Pharmaceutical Company Limited, Osaka, Japan (for the study in countries except for China)
Maintenance Phase		
TAK-438 10 mg tablet	Pale yellow film-coated tablet	Takeda Pharmaceutical Company Ltd, Japan
TAK-438 10 mg matching placebo tablet	Pale yellow film-coated tablet	Takeda Pharmaceutical Company Ltd, Japan
TAK-438 20 mg tablet	Pale red film-coated tablets with score on both side	Takeda Pharmaceutical Company Ltd, Japan
TAK-438 20 mg matching placebo tablet	Pale red film-coated tablets with score on both side	Takeda Pharmaceutical Company Ltd, Japan
Lansoprazole 15 mg capsule	White capsule	Tianjin Takeda Pharmaceuticals Co., Ltd, China(for the study in China) / Takeda Pharmaceutical Company Limited, Osaka, Japan (for the study in countries except for China)
Lansoprazole 15 mg matching placebo capsule	White capsule	Takeda Pharmaceutical Company Ltd, Japan

*In Malaysia, marketed Lansoprazole 30 mg is supplied as a tablet.

All active medications and their matching placebo are difficult to distinguish from their appearance.

8.1.1.2 Ancillary Materials

Daily subject diaries will be dispensed to all subjects entering the study.

8.1.1.3 Sponsor-Supplied Drug

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

8.1.2 Storage

TAK-438, Lansoprazole 15 mg and each matching placebo investigational drug should be stored at 25°C; with excursions permitted 15°C to 30°C). Please follow the instruction on the marketed drug (Lansoprazole 30 mg) label. Protect from moisture and humidity. Study medication is to remain in the blister card until time of dosing.

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

Temperature excursion must be reported to the sponsor or designee.

8.1.3 Dose and Regimen

8.1.3.1 Healing Phase

The Healing Phase is not applicable for subjects rolled over from TAK-438_303 study.

Subjects who have ongoing erosive esophagitis and meet all of the inclusion criteria and none of the exclusion criteria will receive open-label Lansoprazole 30 mg administered once daily.

Subjects will receive Lansoprazole 30 mg for 4 or 8 weeks and will self-administer according to guidelines provided in the local package insert.

8.1.3.2 Maintenance Phase

Following endoscopic confirmation of healed erosive esophagitis, each subject who meets all the inclusion criteria and none of the exclusion criteria will be randomly assigned via the IWRS to receive daily TAK-438 10 mg, TAK-438 20 mg, or Lansoprazole 15 mg.

Blinding will be achieved using double-dummy, therefore at each dosing time-point subjects will take 2 tablets and 1 capsule, one will be active and the other two will be placebos. All subjects will self-administer the study medications at approximately the same time each morning after breakfast.

Subjects will receive study drug for up to 24 weeks, thereafter subjects will move into the follow-up phase. A follow-up phone call will be completed at 7-14 days after the last dose.

The subject will take the first dose of study medication at Visit 2 after completion of all assessments but before leaving the clinic. At all subsequent study visits during the Maintenance Phase (Weeks 2, 4, 6, 8, 12 and 24) the subject should be instructed to present to the clinic for study visits without taking the study medication. The daily dose of the study medication on those days will be taken by the subject after completion of assessments.

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

Table 8.b Sponsor-Supplied Drug During the Maintenance Phase

Treatment Group	Dose	Treatment Description	
		Active	Placebo
A	10 mg TAK-438 QD	One 10 mg TAK-438 tablet	One placebo tablet for TAK-438 20 mg plus one placebo for 15 mg Lansoprazole capsule
B	20 mg TAK-438 QD	One 20 mg TAK-438 tablet	One placebo tablet for TAK-438 10 mg plus one placebo for 15 mg Lansoprazole capsule
C	15 mg Lansoprazole QD	One 15 mg Lansoprazole capsule	One placebo for 20 mg TAK-438 tablet and one placebo for 10 mg TAK-438 tablet

8.1.3.3 Missed Doses

Subjects should be instructed that all doses of study medication (TAK-438 or Lansoprazole) should be taken on time. Subjects should also be instructed that if any dose is missed inadvertently it is acceptable for that dose to be taken within 12 hours of the time that it was due. If longer than 12 hours have passed since the dose was due, it should not be taken but noted instead in the subject's diary that the dose was missed.

8.1.4 Overdose

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

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0, Pretreatment Events and Adverse Events.

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

In the event of drug overdose in the subject should treat the subject symptomatically.

8.2 Investigational Drug Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IWRS at the Screening Visit after the subject provides informed consent in order to obtain a subject number.

Healing Phase: The investigator or investigator's designee will access IWRS in order to record the number of Lansoprazole cartons/wallet cards that will be dispensed at Week -8 and Week -4 in order to provide enough study medication to cover the duration until the next visit. Lansoprazole

30 mg provided for Healing Phase has a different count of capsules/tablets in a carton/wallet card depending on the country. Please refer to the IWRS manual on how many cartons/wallet cards will need to be dispensed.

Maintenance Phase: Following confirmation of healed erosive esophagitis and study eligibility at Visit 2, 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 Med ID number of the investigational drug to be dispensed will then be provided by the IWRS.

If sponsor-supplied drug (TAK-438 10 mg and 20 mg tablet or their matching placebo tablet, Lansoprazole 15 mg capsule or matching placebo capsule) is lost or damaged, the site can request a replacement from IWRS. (Refer to IWRS manual provided separately.) The Med ID number will be entered onto the eCRF at each dispensing visit for the Maintenance Phase.

At subsequent drug-dispensing visits, the investigator or designee will again contact the IWRS to request additional investigational drug for a subject. The IWRS will provide 2 Med ID numbers for dispensing to subjects for a 4-week treatment duration at Visit 2, 4 Med ID numbers for an 8 week treatment duration at Visit 3, and 6 Med ID numbers for a 12 week treatment duration at Visit4.

8.3 Randomization Code Creation and Storage

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

Subjects will be assigned in a 1:1:1 ratio to TAK-438 10 mg, TAK-438 20 mg or Lansoprazole 15 mg treatment groups. Subject randomization will be stratified by LA classification grades A/B vs C/D at the time of erosive esophagitis diagnosis.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IWRS

8.5 Unblinding Procedure

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

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

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

If any site personnel is unblinded, investigational 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 approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (TAK-438, Lansoprazole, or matching placebo), the investigator 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 is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment 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 investigator must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry 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 drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform 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.

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 should be obtained including date of birth, sex, race as described by the subject, smoking status, and history of alcohol use and caffeine-containing drinks, history of H. pylori eradication therapy (eg, triple therapy with PPI + amoxicillin + clarithromycin) and date of completion of such therapy (within the past 1 year/more than 1 years) 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 disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.7](#)). Medical history will include the following:

- Erosive esophagitis.
- Other upper gastrointestinal diseases including gastric ulcer, duodenal ulcer, erosive esophagitis, non-erosive gastroesophageal reflux disease or procedures.

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 90 days prior to signing the ICF. Medication history will include the following:

- PPIs.
- Histamine H₂ receptor antagonists.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the pretreatment assessment immediately prior to the start of investigational drug) 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. All subsequent physical examinations should assess clinically significant changes from the baseline examination.

9.1.4 Weight, Height and BMI

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

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

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral, tympanic or infra-axillary measurement), sitting blood pressure (5 minutes), and pulse (bpm). Vital signs will be assessed at all time points specified in the Study Schedule ([Appendix A](#)).

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

9.1.6 Documentation of Concomitant Medications

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

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, electrocardiogram (ECG), or physical examination abnormalities noted at screening (Visit 1) or baseline (Visit 2) 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. Except for Hepatitis B and C analysis, all other samples will be analyzed at the designated central laboratory.

The maximum volume of blood to be collected at any single visit for central laboratory analysis is approximately 3.5 to 19.5 mL. Additionally, the volume of blood to be collected for Hepatitis B and C tests at the Screening visit is up to 10 mL and the approximate total volume of blood to be collected for the study is 79.5~96.0 mL for those subjects entering directly in to the Maintenance Period and 96.0~112.5 mL for those subjects entering the Healing Phase and Maintenance Phase.

Details of these procedures and required safety monitoring will be given in the central laboratory manual.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells	ALT(*)	Protein (qualitative)
White blood cells	ALP	Sugar (qualitative)
Hemoglobin	AST(*)	
Hematocrit	GGT	
	Gastrin(*)	
	Pepsinogen I/II(*) (\$)	
Platelets	Total bilirubin(*)	Hepatitis B and C Analysis (#)
	Direct bilirubin(*)	
White blood cell fractions (neutrophils, eosinophils, basophils, monocytes, lymphocytes)	LDH	HBsAg
	CK (CPK)	HCV-antibody
	Albumin	HCV-antigen (+)
	Total protein	HCV-RNA(+)
	Creatinine	
	BUN	
	Uric acid	
	Total cholesterol	
	Triglycerides(*)	
	Glucose(*)	
	Potassium	
	Sodium	
	Magnesium	
	Calcium	
	Inorganic phosphorus	
	Chloride	
	Serum iron	
	Vitamin B12	
Other:		
Serum		Urine
Female subjects if menopause is suspected only		Female subjects of child-bearing potential only
– Follicle-stimulating hormone (FSH)		– hCG (for pregnancy)

(*) To be measured under fasting conditions.

(\$) This includes pepsinogen I, pepsinogen II and pepsinogen I/II ratio.

(#) To be measured either at the central laboratory or the local laboratory depending on the site capability.

(+) HCV-antigen and HCV-RNA are optional.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The HBV and HCV tests can be done either at the local laboratory or the central laboratory depending on the site capability. The results of the central laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks. For subjects entering the Maintenance Phase of the current study within 7 days of completing Study TAK-438_303, the frequency of the LFT monitoring visits depends on when the subject was healed in Study TAK-438_303. For example, a subject healed at Week 2 of Study TAK-438_303 would complete LFT monitoring visits at Weeks 2, 4, and 6 of the current study, whereas a subject healed at Week 4 of Study TAK-438_303 would complete LFT monitoring visits at Weeks 2 and 4 of the current study. Subjects entering the Maintenance Phase of the current study more than 7 days after completing antecedent study TAK-438_303, as well as subjects entering the Maintenance Phase after completing the Healing Phase, and *de novo* subjects (an eligible route of entry prior to protocol amendment 6), will be required to complete LFT monitoring visits every 2 weeks from Day 1 (at Weeks 2, 4, 6, and 8).

If subjects experience an increase in any one of ALT, AST or total bilirubin $>2 \times \text{ULN}$, the study medication shall be stopped according to the discontinuation criteria. Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) to monitor recovery should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was found. Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests.

Given the possibility that the use of TAK-438 or Lansoprazole may be associated with increases in serum gastrin and pepsinogen I/II levels, the subjects will be examined for gastrin and pepsinogen I/II levels to investigate the magnitude of these increases throughout all applicable treatment periods in the study.

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 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*: **Intrauterine devices (IUDs):**

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

*Barrier methods is only applicable in countries where spermicide is commercially 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 and donation of ova during the course of the study.

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures ([Appendix A](#)). In addition to a negative urine hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test at 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, Lansoprazole, matching placebo and antacid drugs) should be immediately discontinued.

If the pregnancy occurs during administration of active study medication, eg, after Visit 2 or within 4 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section [1.0](#).

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not to be followed.

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

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

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and 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.

As ECG tracings on thermal paper fade over time, any such tracings should be completely photocopied and both the original tracing and the counter-signed copy should be filed in the subject's medical record.

9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at this visit, the investigator should complete the eCRF. 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:

- Healing Phase failure (for subjects enrolled in the open-label Lansoprazole 30 mg Healing Phase only, and who are not healed after 8 weeks of treatment).
- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria <specify reason>.
- Major protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.
- Other <specify reason>.

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

9.1.13 Documentation of Study Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance/randomization into the Maintenance Phase.

If the subject is found to be not eligible for randomization/Maintenance Phase, 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 10 mg, 20 mg or Lansoprazole using the IWRS. Instructions on accessing and using the IWRS will be provided in a separate manual. Blinded details of subject treatment allocation (Med ID numbers) provided by the IWRS should be documented in the subject's medical record and/or eCRF.

9.1.14 Endoscopy

Endoscopy should be performed while subjects are fasted and according to the usual practice of the institution (ie, in regards to pre-medications or concomitant therapies as long as they are not prohibited in Section 7.3 of this protocol).

During endoscopy the investigator, or designee, should ensure that the gastric and esophageal mucosa is observed for a sufficient duration that the subject's eligibility is confirmed and/or ensure that accurate classification of the grade of any erosive esophagitis, Barrett's mucosa or esophageal hiatal hernia observed can be made. Digital images of any esophagus should be captured and stored at the investigational site and they should be available in the event of a future medical or data query, audit or inspection.

The investigator should classify any lesions seen based on the LA classification (Table 9.b), any Barrett's mucosa in accordance with the following criteria:

- At Screening Phase (Visit 1), Visit 3HP, and Day 1: present (3 cm or greater), present (less than 3 cm), absent, unknown.
- Other time points for endoscopy: increased, unchanged, reduced, disappeared, unknown.

And any esophageal hiatal hernia in accordance with the following criteria:

- At Screening Phase (Visit 1), Visit 3HP, and Day 1: present (2 cm or greater), present (less than 2 cm), absent, unknown.

After the endoscopy the investigator should promptly record any findings or observations in the subject's medical record.

Table 9.b Los Angeles (LA) classification for diagnosis and grading of erosive esophagitis

Mucosal break: area with white coating or erythema clearly distinguished from the surrounding mucosa

Grade	Description
Grade O	No mucosal breaks
Grade A	One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
Grade B	One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of esophageal circumference
Grade D	Mucosal breaks which involve at least 75% of esophageal circumference

The investigator (or designee) will record the results of endoscopy (including results of the LA classification and other gradings) in the subject's medical record. For LA Grade O, the investigator is allowed to record the result as either "No mucosal breaks" and/or "Grade O". This reflects the

clinical practice of recording ‘No mucosal breaks’ in medical records, as Grade O is not routinely used.

To ensure the accuracy of EE evaluation according to LA grading, a second review process of the endoscopy image will be established at each site. The first reviewer, ie, the endoscopist should take sufficient images or videotape the process at each endoscopic examination. The second reviewer will evaluate the EE LA grading according to the endoscopic images.

- Preferably, the principal investigator performs as the second reviewer and conducts the second review in a timely manner after the endoscopy is performed by the first reviewer who is a sub-investigator in this study.
- In cases where the principal investigator is the first reviewer, a sub-investigator at the same site can be delegated as the second reviewer and conducts the second review in a timely manner.
- Only investigators (either principal investigators or sub-investigators) can be delegated as the second reviewer.

If the LA grading by the two reviewers are consistent, this result becomes the final report. If not, the two reviewers will discuss their findings and reach a consensus which will then become the final report.

9.1.15 Diary for Gastrointestinal symptoms and Health-Related Quality of Life

Subjective symptoms of erosive esophagitis to be entered in the subject’s diary will include “heartburn”, and “regurgitation”. The subjective symptoms to be surveyed are described in [Table 9.c](#) and the severity in

[Table 9.d](#). Additionally, during all study visits ‘Health-Related Quality of Life’(EQ-5D-5L) questionnaire will be completed as the first priority of all procedures. The subject will be evaluated for HRQoL in the preceding week at every visit scheduled during the Maintenance Phase of the study. The subject diary and EQ-5D-5L questionnaire will be paper-based and provided to the subjects in their local languages. Site staffs are required to check the completeness of the HRQoL questionnaires and patient diaries before subjects leave the site in each visit. The data will be recorded onto the (e)CRFs and considered source data based on the subject’s completion of the paper questionnaires.

The subject will be instructed as to how to enter any subjective symptoms of erosive esophagitis he/she may experience in a subject diary and will be given a copy of the subject diary.

The subject must start entering the subject diary in the next morning (upon rising) after the start of the Screening Phase. Any subjective symptoms experienced should be entered on a once daily basis in accordance with the descriptions given in [Table 9.c](#), throughout the study, describing in the diary the severity of all heartburns or acid regurgitations experienced during the previous daytime and nighttime periods (previous 24 hours), in the morning. The subject must also record the study medication taken on a daily basis in the diary during the Maintenance Phase. On study

visit days, the administration of study medication for that day should be entered into the diary before the diary is returned.

Documentation that subjects are appropriately instructed (and re-instructed as necessary) on how to correctly complete their diary and questionnaire should be completed in the subject's medical record.

Table 9.c Requirements for Subject Diary Entries Regarding Subjective Symptoms

Subjective symptom	Description of symptom	Entry requirements
Heartburn	A burning feeling, pressure or pain in the chest, just behind the breast bone which may rise from the upper part of the stomach upwards towards the throat.	How bad was the heartburn when it was at its worst?
Regurgitation	Flow of sour or bitter fluid into the mouth.	How bad did regurgitation feel when it was at its worst?

Table 9.d Severity of Subjective Symptoms

Subjective symptom	Severity
Heartburn	No symptoms
Regurgitation	Mild Moderate Severe

* Please refer to [Appendix E](#) for definition of each 'severity' grade.

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication containers to each dispensing site visit. Investigators or designee should perform subject treatment compliance checks by reviewing the subject's diary and returned medications.

If a subject is persistently noncompliant with the study medication (Lansoprazole 30 mg during the Healing Phase or TAK-438 10 mg, 20 mg or Lansoprazole 15 mg and their matching placebos during the Maintenance Phase) (eg, at more than 2 consecutive compliance checks to have taken less than 75% or more than 133% of the study medication), it may be appropriate to withdraw the subject from the study.

At each applicable study visit it should be documented in the subject's medical record that study medication was dispensed or collected, or checked for compliance. All subjects should be re-instructed 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](#). Individual schedule of study-related procedures are presented separately for subjects entering the current study at the Healing Phase ([Appendix A1](#)), subjects entering the current study within 7 days of completing Study TAK-438_303 ([Appendix A2](#)), and subjects entering the current study more than 7 days after completing Study TAK-438_303 ([Appendix A3](#)). Ongoing *de novo* subjects (an eligible route of entry prior to protocol amendment 06), should follow the schedules outlined in [Appendix A3](#).

All assessments should be completed at the designated visit/time point(s).

9.3.1 Visit 1: Screening Phase (Day -28 to Day -1)

Prior to any assessments being performed, all subjects will sign the ICF. The first procedure will be to access IWRS to obtain the subject number. Section 9.1.12 documents the procedures for screening failures, Healing Phase Failures, or randomization failures.

Subjects With Ongoing Erosive Esophagitis: All subjects with ongoing erosive esophagitis will undergo assessments for the Screening Phase within 28 days before the initiation of study medication as outlined in [Appendix A1](#).

- Subjects will need to be in a fasted state for the Screening Visit. If fasting is not the routine clinical practice of the site, informed consent should be obtained prior to the request for fasting for the Screening Visit. If the subject comes to the site in an unfasted state, the following procedures will be performed at a second (fasting) Screening Visit.
 - Eligibility assessment (review inclusion/exclusion criteria).
 - Demographics, vital signs, medical and medication history.
 - Height and weight. BMI will be calculated during data analysis.
 - Physical examination including concurrent medical conditions and medications.
 - Concomitant medications assessment.
 - Hepatitis B and C analysis at the local laboratory (reliable, documented Hepatitis B and C results performed in a routine clinical setting within 14 days prior to signing the informed consent will be accepted).
 - ECG procedure (reliable, documented results available from an ECG performed in a routine clinical setting within 14 days prior to signing the informed consent will be accepted).
 - Fasting clinical laboratory tests: hematology, serum chemistry (*excluding* serum gastrin and pepsinogen I/II), urinalysis.
 - Urine pregnancy test (in females of childbearing potential only).
 - FSH (when menopause is suspected).

- Guidance on the avoidance of pregnancy and ova donation.
- Endoscopy.
- Pretreatment events assessment.

Subjects Entering the Current Study on the Same Day as Completing Study TAK-438_303 Treatment: Screening procedures for these are outlined in [Appendix A2](#). If the final study visit in the TAK-438_303 study coincides with the randomization visit (Visit 2) of the current study, these 2 visits can be combined such that all of the overlapped examinations will be exempt from the screening and Day 1 procedures for the TAK-438_305 study. The overlapping examinations are comprised of clinical laboratory tests (hematology, serum chemistry, and urinalysis), serum gastrin and pepsinogen I/II levels, urine hCG, FSH, endoscopy, ECG, the subject diary, EQ-5D-5L, vital signs, and the physical examination.

Laboratory test results from the TAK-438_303 study can be used for eligibility confirmation in the TAK-438_305 study, as long as they are within 28 days prior to randomization in the TAK-438_305 study. For these subjects, data obtained in the week when subjects were confirmed as healed in the TAK-438_303 study will be used as the baseline data for the current study, and data should be transcribed from the last visit in the TAK-438_303 study into the Visit 1 pages in the eCRF for the current study.

Subjects Entering the Current Study Within 7 Days of Completing Study TAK-438_303 Treatment: Screening procedures for these subjects are outlined in [Appendix A2](#). If the subjects are planned to be randomized into the current study within 7 days after completing the last visit in the TAK-438_303 study, Visit 1 and Visit 2 of the current study can be combined. Any overlapped procedures will be exempt from the screening procedures in the TAK-438_305 study. The overlapping examinations are comprised of clinical laboratory tests (hematology, serum chemistry, and urinalysis), serum gastrin and pepsinogen I/II levels, urine hCG, FSH, endoscopy, ECG, and the subject diary. However, EQ-5D-5L, vital signs, and the physical examination will have to be performed.

For these subjects, data obtained in the week when subjects were confirmed as healed in the TAK-438_303 study will be used as the baseline data in the current study, and data should be transcribed from the last visit in the TAK-438_303 study into the Visit 1 pages in the eCRF for the current study.

Subjects Entering the Current Study More Than 7 Days After Completing Study TAK-438_303: Subjects planned to be randomized in to the current study more than 7 days after completing the last visit in the TAK-438_303 study, will follow screening period procedures outlined in [Appendix A3](#).

9.3.2 Visit 2_{HP}: Healing Phase (Week -8)

This visit is only applicable for subjects undergoing the Healing Phase. Procedures to be completed at this visit include:

- Dispense Healing Phase study medication (Lansoprazole 30 mg QD) and record number of cartons/wallets of study medication in the IWRS.
- Guidance on the avoidance of pregnancy and ova donation.
- AE/ Pretreatment Event assessment.
- Concomitant medications assessment.

9.3.3 Visit 3_{HP}: Healing Phase (Week -4)

This visit is only applicable for subjects undergoing the Healing Phase. Procedures to be completed at this visit include:

- Physical examination.
- Vital signs.
- Fasting clinical laboratory tests: hematology, serum chemistry (including serum gastrin and pepsinogen I/II), urinalysis.
- Urine pregnancy test (in females of childbearing potential only).
- ECG procedure.
- Endoscopy. This is an optional procedure based on the investigator's clinical judgment of a subject's symptoms of healing. If the subject's is endoscopically confirmed as healed, and the result of clinical laboratory tests at this visit from central laboratory re-confirms the subject's eligibility, the subjects can be randomized within 14 days of this endoscopy date. During this period of waiting for randomization, subjects shall continue to take the newly dispensed Lansoprazole 30 mg QD. Subjects who do not show endoscopic healing at Visit 3_{HP} may continue in the Healing Phase and undergo endoscopy at Day 1 (Visit 2).
- Guidance on the avoidance of pregnancy and ova donation.
- Study drug accountability and check treatment compliance, re-instruct the subject if necessary, dispense additional Healing Phase study medication (Lansoprazole 30 mg QD) and record the number of cartons/wallets of study medication in the IWRS.
- AE assessment.
- Concomitant medications assessment.

9.3.4 Visit 2: Randomization (Day 1)

Randomization will take place on Day 1 (Visit 2). The procedures followed during Visit 2 vary depending on the route of entry in to the Maintenance Phase. Individual schedule of study-related procedures are presented separately for subjects entering the current study at the Healing Phase ([Appendix A1](#)), subjects entering the current study within 7 days of completing treatment in antecedent Study TAK-438_303 ([Appendix A2](#)), and subjects entering the current study more

than 7 days of completing Study TAK-438_303 ([Appendix A3](#)). *De novo* subjects (an eligible route of entry prior to protocol amendment 6), should follow the schedules outlined in [Appendix A3](#).

In all cases, the EQ-5D-5L questionnaire is the first priority of all procedures in this visit.

- EQ-5D-5L.
- Endoscopy (if the subject has not been confirmed healed after entering the Healing Phase).
- Physical examination.
- Vital signs.
- AE/ Pretreatment Event assessment.
- Concomitant medications assessment.
- Urine pregnancy test (in females of childbearing potential only). This test is applicable only to subjects who are to be randomized more than 7 days after completing the Healing Phase Week -4 [Visit 3_{HP}], or who are randomized more than 7 days after completing TAK-438_303 study treatment, or subjects who are not healed at Week -4 [Visit 3_{HP}].
- Eligibility assessment (review inclusion/ exclusion criteria)
- Collect study medication. This procedure is only applicable to subjects who have participated in the Healing Phase.
- If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IWRS system, as described in [Section 8.2](#). For eligible subjects the following should be completed:
 - Randomization via IWRS.
 - Fasting clinical laboratory tests: hematology, serum chemistry (including serum gastrin and pepsinogen I/II), urinalysis. This test is applicable only to subjects who are to be randomized more than 7 days after completing the Healing Phase Week -4 [Visit 3_{HP}], or who are randomized more than 7 days after completing TAK-438_303 study treatment, or subjects who are not healed at Week -4 [Visit 3_{HP}].
 - Guidance on the avoidance of pregnancy and ova donation.
 - Dispense Maintenance Phase study medication (first daily dose to be taken before subject leaves the study site) and instruct the subject on correct self-administration for subsequent daily doses.
 - Dispense new subject diary for symptom and treatment compliance collection.

For ineligible subjects, the procedure for documenting Screening failures is provided in [Section 9.1.12](#).

9.3.5 Visit 3: Maintenance Phase (Day 15 / Week 2)

- This visit is only applicable for subjects who have completed the Healing Phase, or for subjects who have rolled-over from the TAK-438_303 study and were confirmed as healed erosive esophagitis in the TAK-438_303 study at 2 or 4 weeks.

Procedures to be completed at this visit include:

- Fasting liver function tests: ALT, AST, total bilirubin and direct bilirubin.
- Guidance on the avoidance of pregnancy and ova donation.
- AE assessment.
- Concomitant medications assessment.

9.3.6 Visit 4: Maintenance Phase (Day 29 / Week 4)

Procedures to be completed at Visit 4 include:

- EQ-5D-5L questionnaire. This shall be the first priority of all procedures in this visit.
- Physical examination.
- Vital signs.
- Fasting clinical laboratory tests: hematology, serum chemistry (including serum gastrin and pepsinogen I/II), urinalysis.
- Urine pregnancy test (in females of childbearing potential only).
- Collect completed diary since Visit 2, review completion compliance, and dispense new subject diary. On study visit days, allow the subject to record the administration of study medication for that day before the diary is returned.
- Guidance on the avoidance of pregnancy and ova donation.
- Review treatment compliance, re-instruct the subject if necessary and dispense Maintenance Phase investigational drugs via the IWRS.
- AE assessment.
- Concomitant medications assessment.

9.3.7 Visit 5: Maintenance Phase (Day 43 / Week 6)

- This visit is only applicable for subjects who have completed the Healing Phase, or for subjects who have rolled-over from the TAK-438_303 study and confirmed as healed erosive esophagitis in the TAK-438_303 study at 2 weeks.

Procedures to be completed at this visit include:

- Fasting liver function tests: ALT, AST, total bilirubin and direct bilirubin.

- Guidance on the avoidance of pregnancy and ova donation.
- AE assessment.
- Concomitant medications assessment.

9.3.8 Visit 6: Maintenance Phase (Day 57/ Week 8)

- This visit is only applicable for subjects who have completed the Healing Phase and *de novo* subjects (an eligible route of entry prior to protocol amendment 6). Procedures to be completed at this visit include:
 - Fasting liver function tests: ALT, AST, total bilirubin and direct bilirubin.
 - Guidance on the avoidance of pregnancy and ova donation.
 - AE assessment.
 - Concomitant medications assessment.

9.3.9 Visit 7: Maintenance Phase (Day 85 / Week 12)

Procedures to be completed at Visit 7 include:

- EQ-5D-5L questionnaire. This shall be the first priority of all procedures in this visit.
- Physical examination.
- Vital signs.
- Collect completed diary since visit 4, review completion compliance, and dispense new subject diary (only if the subject's EE has not relapsed).
- Fasting clinical laboratory tests (hematology, chemistry including gastrin & pepsinogen I/II levels, urinalysis).
- ECG procedure.
- Endoscopy (Optional. Only if relapse of erosive esophagitis is suspected due to subjective symptoms or changes in clinical laboratory values).
- Urine pregnancy test (in females of childbearing potential only).
- Guidance on the avoidance of pregnancy and ova donation.
- Review treatment compliance, re-instruct the subject if necessary.
- AE assessment.
- Concomitant medications assessment.
- Dispense additional Maintenance Phase drug via the IWRS, or register as study completion if relapse is confirmed by endoscopy.

- If relapse of erosive esophagitis has been endoscopically confirmed at this visit or any other time, the subject will complete the study at that time point and be considered as a completed case in the Maintenance Phase, regardless of the time point when relapse of disease is confirmed.
- During the 12 weeks between Visit 7 and Visit 8, the site staff will follow their routine clinical practice to follow up with those subjects and make sure the subjects are in compliance of the study treatment and diary recording.

9.3.10 Visit 8: End of Treatment (Day 169 / Week 24) or Study Early Discontinuation Visit (within 14 days after final dose)

The following procedures should be performed and documented at the End of Treatment Visit (Visit 8: Day 169 / Week 24), or at the Study discontinuation visit:

- EQ-5D-5L questionnaire. This shall be the first priority of all procedures in this visit.
- Physical examination.
- Vital signs.
- Collect completed diary since Visit 7, review completion compliance.
- Fasting clinical laboratory tests (hematology, chemistry including gastrin & pepsinogen I/II levels, urinalysis).
- ECG procedure.
- Endoscopy.
- Urine pregnancy test (in females of childbearing potential only).
- Guidance on the avoidance of pregnancy and ova donation.
- Collect study medication and review treatment compliance.
- AE assessment.
- Concomitant medications assessment.
- Register the subject study discontinuation or completion via IWRS.
- For all randomized subjects, the investigator must complete the End of Study eCRF page.

9.3.11 Follow-up

The study site staff will follow up with a phone call between 7 and 14 days after the final dose of study medication. Any new AEs will be recorded in the eCRFs and subject's source documents. Follow-up will begin the first day after the Final Visit/Early Termination and will continue until 14 days post treatment.

9.3.12 Post Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

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10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A pretreatment event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

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

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the

worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The principal 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. Is a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
 - May require intervention to prevent items 1 through 5 above.
 - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
 - Includes any event or synonym described in the Takeda Medically Significant AE List ([Table 10.a](#)).

Table 10.a Takeda Medically Significant AE List

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

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

10.1.5 Special Interest AEs

A Special Interest Adverse Event (serious or non-serious) 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 AEs of Special Interest.

10.1.6 Severity of PTEs and AEs

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

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

10.1.7 Causality of AEs

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

- Yes: 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 can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
- No: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

10.1.8 Relationship to Study Procedures

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

The relationship should be assessed as Yes 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 No.

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 physician.

10.1.10 Stop Date

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

10.1.11 Frequency

Episodic AEs/serious 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 Medication

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

- Dose Interrupted - The study medication was temporarily interrupted (discontinued) (including voluntary drug interruption by the subject) due to the particular AE, and resumed at a later date.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/serious PTE.
- Recovering/Resolving – the intensity is lowered by one 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/serious 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/serious PTE state remaining “Not recovered/not resolved”.
- Resolved with sequelae – the subject recovered from an acute AE/serious PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/serious PTEs which are considered as the cause of death.
- Unknown – the course of the AE/serious 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 – Subjects that did not participate in TAK-438_303

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Visit 2) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Visit 2). Routine collection of AEs will continue until the Final Visit or Early Termination. A follow-up phase will be made to each subject 7-14 days following the last dose of study drug to collect any AEs that may have occurred. The stop date of the AE/serious PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.1.2 AE Collection Period – Subjects that did participate in TAK-438_303

Collection of AEs will commence from the time the subject is first administered study medication for this study and continue until the Final Visit or Early Termination. A follow-up phase will be made to each subject 7-14 days following the last dose of study drug to collect any AEs that may have occurred. The stop date of the AE/serious AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.2.1.3 PTE and AE Reporting

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

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

- Event term.
- Start and stop date.
- Severity.
- Investigator’s opinion of the causal relationship between the event and administration of study medication(s) (yes or no) (not completed for PTEs).
- Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medication (not applicable for PTEs).
- Outcome of event.
- Seriousness.
- Subject diary and questionnaire will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of SAEs

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

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

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

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 Liver Function Tests

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

If subjects experience an increase in any one of ALT, AST or total bilirubin $>2 \times$ ULN, the study medication shall be stopped according to the discontinuation criteria. Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) to monitor recovery should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was found (see Section 9.1.8).

10.3 Follow-up of SAEs

If information not available at the time of the first report 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 will be 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 within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

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11.0 STUDY-SPECIFIC COMMITTEES

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

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12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 eCRFs

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

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

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

Corrections 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.

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 should be copied and certified, 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. 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) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to un-blinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database.

13.1.1 Analysis Sets

Analysis of efficacy variables will be conducted in the Full Analysis Set defined as all randomized subjects who receive at least 1 dose of the Maintenance Phase drug and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment. The primary efficacy endpoint and the secondary efficacy endpoint will also be analyzed in the Per Protocol Set; subject evaluability criteria for the Per Protocol Set will be specified in the SAP. Analysis of safety variables will be conducted in the Safety Analysis Set defined as all subjects who take at least 1 dose of the Maintenance Phase drug and will be based on the treatment received in the Maintenance Phase.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline and demographic information will be listed and summarized by treatment group and overall. For continuous variables, the summary will consist of descriptive statistics (number of subjects, mean, standard deviation, minimum, median, and maximum). For categorical variables, the summary will consist of number and percentage of subjects in each category.

13.1.3 Efficacy Analysis

The following analyses will be provided using the Full Analysis Set.

For the primary efficacy endpoint of rate of endoscopic recurrence of erosive esophagitis during the 24-week Maintenance Phase, a 2-sided 95% confidence interval (CI) will be constructed for the difference between each TAK-438 group and Lansoprazole. The upper bound of this CI will be compared to 10%, the non-inferiority margin for TAK-438 relative to Lansoprazole. Rate of endoscopic recurrence of erosive esophagitis during the 24-week Maintenance Phase will also be analyzed in subgroups defined by LA classification grades A/B vs C/D at the time of erosive esophagitis diagnosis.

The secondary endpoint of rate of endoscopic recurrence of erosive esophagitis during the first 12 weeks of treatment in the Maintenance Phase will be compared between each TAK-438 group and Lansoprazole by constructing a 2-sided 95% CI for the healing rate difference.

The additional endpoints related to GERD symptoms that occur during treatment in the Maintenance Phase will be compared between treatment groups using Wilcoxon rank-sum tests,

with treatment effects presented using Hodges-Lehmann estimator and 95% Moses CI. Analysis of HRQoL endpoints will be conducted with an Analysis of Covariance model with treatment and baseline EE grade (A/B vs C/D) as factors and baseline as a covariate.

Statistical inference will be performed at 2-sided 0.05 level of significance or via 2-sided 95% CIs. Adjustment for multiplicity will be performed for the primary and secondary efficacy endpoints in the following order under the closed testing procedure:

- The primary endpoint will be tested for non-inferiority between the TAK-438 20 mg group and Lansoprazole.
- If the previous test is successful, the primary endpoint will be tested for non-inferiority between the TAK-438 10 mg group and Lansoprazole.
- If the previous test is successful, the primary endpoint will be tested for superiority between the TAK-438 20 mg group and Lansoprazole. The upper bound of the CI of the difference between the TAK-438 20 mg group and Lansoprazole will be compared to 0%.
- If the previous test is successful, the primary endpoint will be tested for superiority between the TAK-438 10 mg group and Lansoprazole.
- If the previous test is successful, the secondary endpoint will be tested for superiority between the TAK-438 20 mg group and Lansoprazole.
- If the previous test is successful, the secondary endpoint will be tested for superiority between the TAK-438 10 mg group and Lansoprazole.

13.1.4 Handling of Missing Data

For the primary efficacy endpoint of rate of endoscopic recurrence of erosive esophagitis during the 24-week Maintenance Phase, FAS subjects who have no endoscopy data obtained on Day 2 or after (where Day 1 is the date of first dose of the Maintenance Phase drug) and within 14 days after the date of last dose will be excluded from the analysis. FAS subjects assessed as LA classification of Grade A to D based on the endoscopy data obtained on Day 2 or after and within 14 days after the date of last dose will be considered as relapsed subjects. Other FAS subjects will be considered as 'not relapsed'.

For the secondary endpoint of rate of endoscopic recurrence of erosive esophagitis during the first 12 weeks of treatment in the Maintenance Phase, FAS subjects who have no endoscopy data during Day 2 to Day 127 and within 14 days after the date of last dose of the Maintenance Phase will be excluded from the analysis. FAS subjects assessed as LA classification of Grade A to D based on the endoscopy data obtained between Day 2 and Day 127 and within 14 days after the date of last dose will be considered relapsed subjects. Other FAS subjects will be considered 'not relapsed'.

Further details will be described in the Statistical Analysis Plan.

13.1.5 Safety Analysis

Safety analysis will be performed for the Maintenance Phase using the safety analysis set.

The number and percentage of subjects with treatment-emergent AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related AEs overall and by severity. Change from baseline in clinical laboratory tests (including serum gastrin and pepsinogen I/II), 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

No interim analysis is planned.

13.3 Determination of Sample Size

Assuming that the true Week 24 recurrence rate is 30.4% for Lansoprazole, 22.0% for TAK-438 10 mg, and 13.6% for TAK-438 20 mg, and assuming that the dropout rate is approximately 30%, a sample size of 208 subjects per group will provide an overall power of 90% to establish noninferiority using a 2-sided 95% CI with a 10% noninferiority margin. 231 subjects per group will be included to allow adequate numbers for the regulatory requirements of various countries.

The assumption of the true recurrence rate is based on a phase 3 study that showed a Week 24 recurrence rate of 30.4% for Lansoprazole 15 mg and 13.6% for Lansoprazole 30 mg.

Based on results from an earlier study of Lansoprazole as maintenance therapy for erosive esophagitis (AG-1747/CCT-202), the point estimate for the difference (Lansoprazole 15 mg group – famotidine group) was calculated as -57.6% with the upper limit of the confidence interval being -30.7%. Therefore, the noninferiority margin is specified as 10%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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 FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

Appendix A1 For Subjects With Ongoing Erosive Esophagitis Entering the Healing Phase.

Study Day/ Week	Screening Phase	Healing Phase			Maintenance Phase							Follow-up Phase
	Weeks -12 to -8	Week -8	Week -4	Day 1**	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 12 (Day 85)	Week 24 (Day 169)	Early Discontinuation Visit	Follow-up phone call
Visit Windows (Days):	-	±3	±3	-	±3	±3	±3	±3	±3	±3	Within 14 days after final dose	7-14 days after final dose
Visit Number	1	2 _{HP}	3 _{HP}	2	3 (1)	4	5	6	7	8	-	
Informed Consent	X											
Inclusion/exclusion criteria	X			X								
Concurrent medical conditions, medication and medical history	X											
Demographics	X											
Physical examination	X		X	X		X			X	X	X	
Vital signs	X		X	X		X			X	X	X	
Height, weight and BMI	X											
Concomitant medications	X	←									→X	
Fasting Clinical laboratory tests (a)	X		X	X*		X			X	X	X	
Liver function test (k)					X		X	X				
Serum gastrin/pepsinogen I/II levels			X	X*		X			X	X	X	
Guidance on avoidance of pregnancy and ova donation(b)	X	X	X	X	X	X	X	X	X	X	X	
FSH (c)	X											
Urine pregnancy test (hCG) (d)	X		X	X*		X			X	X	X	
Electrocardiogram (ECG)	X(o)		X						X	X	X	
Hepatitis B and C tests (e)	X											
Dispense/collect subject diary, review compliance (f)				X		X			X	X	X	
EQ-5D-5L questionnaire				X		X			X	X	X	
Endoscopy (g)	X		X(m)	X(n)					X(i)	X	X	
Obtain subject number via IWRS	X											
Randomization via IWRS				X								
Dispense investigational drug via IWRS				X(h)		X			X			
Record investigational drug in IWRS		X	X									
Collect study medication and review its compliance			X	X		X			X	X	X	
Access IWRS for study screen failure, discontinuation or			X							X	X	

Study Day/ Week	Screening Phase	Healing Phase		Maintenance Phase							Follow-up Phase	
	Weeks -12 to -8	Week -8	Week -4	Day 1**	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 12 (Day 85)	Week 24 (Day 169)	Early Discontinuation Visit	Follow-up phone call
Visit Windows (Days):	-	±3	±3	-	±3	±3	±3	±3	±3	±3	Within 14 days after final dose	7-14 days after final dose
Visit Number	1	2 _{HP}	3 _{HP}	2	3 (l)	4	5	6	7	8	-	
completion(j)												
AE/PTE assessment	X											X
Follow-up Phone call												X

*Only for subjects who are to be randomized more than 7 days after completing the Healing Phase Week -4 [Visit 3_{HP}], or who are not healed at Week -4 [Visit 3_{HP}].

**The date of first investigational drug administration for Maintenance Phase is defined as Day 1.

(a) Hematology, serum chemistry, and urinalysis.

(b) Women of child-bearing potential.

(c) Only if menopause is suspected.

(d) To be performed only in female subjects of childbearing potential.

(e) Hepatitis B and C analysis in accordance with Section 9.1.8 will be conducted either at the local laboratory or at the central laboratory depending on the site capability. However, any reliable, documented Hepatitis B and C results performed in a routine clinical setting within 14 days prior to Healing Phase (before signing of informed consent) will be accepted.

(f) On study visit days, allow the subject to record the administration of study medication for that day before the diary is returned.

(g) The endoscopy taken at Screening must be within 4 weeks prior to receiving open-label Lansoprazole. Considering the invasive nature of the endoscopy, any reliable, documented results available from an endoscopy performed in a routine clinical setting before signing of informed consent will be acceptable instead. Additionally, the endoscopy can be performed anytime during the treatment if recurrence is suspected.

(h) The subjects will be given the first daily dose of the study medication to before leaving the study site after completion visit assessments.

(i) If relapse of erosive esophagitis is suspected in the subject due to subjective symptoms or changes in clinical laboratory values, he/she will undergo confirmatory endoscopy.

(j) At any time during the study, once the relapse is confirmed by endoscopy, the subject is considered "Completed". If the subject is not randomized and withdrawn from the study, eg, failed during Healing Phase, the subject is considered "Screen Failed".

(k) Liver function tests include ALT, AST, total bilirubin and direct bilirubin. All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks (see Section 9.1.8 for further details on the timings of these tests).

(l) This visit is only applicable for subjects who have completed the Healing Phase.

(m) Optional. If EE healing is suspected at the investigators' judgment, the endoscopy may be performed. Once the healing is endoscopically confirmed and eligibility re-confirmed including clinical laboratory test results, the subject may be randomized providing this occurs within 14 days of the endoscopy. The study medication Lansoprazole 30 mg QD shall be continued until the randomization.

(n) Endoscopy is applicable only to those subjects who were not confirmed as healed at Week-4.

(o) Any reliable, documented results available from an ECG performed in a routine clinical setting within 14 days prior to Healing Phase (before signing of informed consent) will be accepted.

**Appendix A2 For Subjects Entering the Current Study Within 7 Days of Completing Study
 TAK-438_303 Treatment**

Study Day/ Week	Maintenance Phase								Follow-up Phase
	Screening/Day 1**	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 12 (Day 85)	Week 24 (Day 169)	Early Discontinuation Visit Within 14 days after final dose	Follow-up phone call 7-14 days after final dose
Visit Windows (Days):		±3	±3	±3	±3	±3	±3		
Visit Number	Visit 2	Visit 3 (l)	Visit 4	Visit 5 (m)	Visit 6 (n)	Visit 7	Visit 8	-	
Informed Consent	X								
Inclusion/exclusion criteria	X								
Concurrent medical conditions, medication and medical history	X								
Demographics	X								
Physical examination	X*		X			X	X	X	
Vital signs	X*		X			X	X	X	
Height, weight and BMI	X								
Concomitant medications	X							X	
Clinical laboratory tests (a)			X			X	X	X	
Liver function test (k)		X		X					
Serum gastrin/ pepsinogen I/II levels			X			X	X	X	
Guidance on avoidance of pregnancy and ova donation(b)	X	X	X	X		X	X	X	
FSH (c)									
Urine pregnancy test (hCG) (d)			X			X	X	X	
Electrocardiogram (ECG)						X	X	X	
Hepatitis B and C tests (e)									
Dispense/collect subject diary, review compliance (f)	X		X			X	X	X	
EQ-5D-5L questionnaire	X*		X			X	X	X	
Endoscopy (g)						X (i)	X	X	
Obtain subject number via IWRS	X								
Randomization via IWRS	X								
Dispense investigational drug via IWRS	X (h)		X			X			
Collect study medication and review its compliance			X			X	X	X	

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Study Day/ Week	Maintenance Phase								Follow-up Phase
	Screening/Day 1**	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 12 (Day 85)	Week 24 (Day 169)	Early Discontinuation Visit	Follow-up phone call
Visit Windows (Days):		±3	±3	±3	±3	±3	±3	Within 14 days after final dose	7-14 days after final dose
Visit Number	Visit 2	Visit 3 (l)	Visit 4	Visit 5 (m)	Visit 6 (n)	Visit 7	Visit 8		
Access IWRS for study discontinuation or completion(j)							X	X	
AE/PTE assessment	X ←								→ X
Follow-up Phone call									X

* Only for the subject that his/her randomization visit in this study is not the same visit as the completion visit in the TAK-438_303 study.

**The date of first investigational drug administration for the Maintenance Phase is defined as Day 1. All the procedures at the last visit of TAK-438_303 should be performed according to TAK-438_303 protocol. Additional procedures at the Day 1 visit in TAK-438_305 should also be performed.

(a) Hematology, serum chemistry, and urinalysis.

(b) Women of child-bearing potential.

(c) Not required in this scenario.

(d) To be performed only in female subjects of childbearing potential.

(e) Not required in this scenario.

(f) The diary shall be dispensed to subjects for completion at least 3 days prior to randomization in order to provide baseline data. However, completion of the diary is not an inclusion/exclusion criterion. On study visit days, allow the subject to record the administration of study medication for that day before the diary is returned.

(g) Endoscopy confirmed healed in TAK-438_303 is considered the baseline endoscopy in this study. Additionally, the endoscopy can be performed anytime during the treatment if the recurrence is suspected.

(h) The subjects will be given the first daily dose of the study medication to be taken before leaving the study site after completion visit assessments.

(i) If relapse of erosive esophagitis is suspected in the subject due to subjective symptoms or changes in clinical laboratory values, he/she will undergo confirmatory endoscopy.

(j) At any time during the study, once the relapse is confirmed by endoscopy, the subject is considered "Completed".

(k) Liver function tests include ALT, AST, total bilirubin and direct bilirubin. All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks (see Section 9.1.8 for further details on the timings of these tests).

(l) This visit is only applicable for subjects who have rolled-over from the TAK-438_303 study and confirmed as healed erosive esophagitis in the TAK-438_303 study at 2 or 4 weeks.

(m) This visit is only applicable for subjects who have rolled-over from the TAK-438_303 study and confirmed as healed erosive esophagitis in the TAK-438_303 study at 2 weeks.

(n) This visit is NOT applicable for roll-over subjects from TAK-438_303 study.

Appendix A3 For Subjects Entering the Current Study More Than 7 Days After Completing Study TAK-438_303 and *de Novo* Subjects (where *de novo* was an eligible route of entry prior to Protocol Amendment 06).

Study Day/ Week	Screening Phase	Maintenance Phase								Follow-up Phase
	Day -28 to Day -1	Day 1**	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 12 (Day 85)	Week 24 (Day 169)	Early Discontinuation Visit	Follow-up phone call
Visit Windows (Days):	-	-	±3	±3	±3	±3	±3	±3	Within 14 days after final dose	7-14 days after final dose
Visit Number	Visit 1	Visit 2	Visit 3 (l)	Visit 4	Visit 5 (m)	Visit 6 (n)	Visit 7	Visit 8	-	
Informed Consent	X									
Inclusion/exclusion criteria	X	X								
Concurrent medical conditions, medication and medical history	X									
Demographics	X									
Physical examination	X	X		X			X	X	X	
Vital signs	X	X		X			X	X	X	
Height, weight and BMI	X									
Concomitant medications	X								X	
Clinical laboratory tests (a)	X	X*		X			X	X	X	
Liver function test (k)			X		X	X				
Serum gastrin/pepsinogen I/II levels		X		X			X	X	X	
Guidance on avoidance of pregnancy and ova donation(b)	X	X	X	X	X	X	X	X	X	
FSH (c)	X									
Urine pregnancy test (hCG) (d)	X	X*		X			X	X	X	
Electrocardiogram (ECG)	X						X	X	X	
Hepatitis B and C tests (e)	X									
Dispense/collect subject diary, review compliance (f)	X	X		X			X	X	X	
EQ-5D-5L questionnaire	X	X		X			X	X	X	
Endoscopy (g)	X						X (i)	X	X	
Obtain subject number via IWRS	X									

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Study Day/ Week	Screening Phase	Maintenance Phase								Follow-up Phase	
	Day -28 to Day -1	Day 1**	Week 2 (Day 15)	Week 4 (Day 29)	Week 6 (Day 43)	Week 8 (Day 57)	Week 12 (Day 85)	Week 24 (Day 169)	Early Discontinuation Visit	Follow-up phone call	
Visit Windows (Days):	-	-	±3	±3	±3	±3	±3	±3	±3	Within 14 days after final dose	7-14 days after final dose
Visit Number	Visit 1	Visit 2	Visit 3 (l)	Visit 4	Visit 5 (m)	Visit 6 (n)	Visit 7	Visit 8	-		
Randomization via IWRS		X									
Dispense investigational drug via IWRS		X (h)		X			X				
Collect study medication and review its compliance				X			X	X	X		
Access IWRS for study discontinuation or completion(j)								X	X		
AE/PTE assessment	X									X	
Follow-up Phone call										X	

* Only for subjects that had more than 7 days between Visit 1 and Visit 2.

**The date of first investigational drug administration for Maintenance Phase is defined as day 1.

(a) Hematology, serum chemistry, and urinalysis.

(b) Women of child-bearing potential.

(c) Only if menopause is suspected.

(d) To be performed only in female subjects of childbearing potential.

(e) Hepatitis B and C analysis in accordance with Section 9.1.8 will be conducted either at the local laboratory or at the central laboratory depending on the site capability.

(f) The diary shall be dispensed to subjects for completion at least 3 days prior to randomization in order to provide baseline data. But completeness of the diary is not an inclusion/exclusion criteria. On study visit days, allow the subject to record the administration of study medication for that day before the diary is returned.

(g) Endoscopy must be within 7 days prior to the randomization. Considering the invasive nature of the endoscopy, any reliable, documented results available from an endoscopy performed in a routine clinical setting within 7 days prior to randomization (Day 1) before signing of informed consent) will be acceptable instead. Additionally, the endoscopy can be performed anytime during the treatment if the recurrence is suspected.

(h) The subjects will be given the first daily dose of the study medication to before leaving the study site after completion visit assessments.

(i) If relapse of erosive esophagitis is suspected in the subject due to subjective symptoms or changes in clinical laboratory values, he/she will undergo confirmatory endoscopy.

(j) At any time during the study, once the relapse is confirmed by endoscopy, the subject is considered "Completed".

(k) Liver function tests include ALT, AST, total bilirubin and direct bilirubin. All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks (see Section 9.1.8 for further details on the timings of these tests).

(l) This visit is only applicable for de-novo subjects, and subjects who have rolled-over from the TAK-438_303 study and confirmed as healed erosive esophagitis in the TAK-438_303 study at 2 or 4 weeks.

(m) This visit is only applicable for de-novo subjects, and subjects who have rolled-over from the TAK-438_303 study and confirmed as healed erosive esophagitis in the TAK-438_303 study at 2 weeks.

(n) This visit is only applicable for de-novo subjects.

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities

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

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

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Appendix C Elements of the Subject Informed Consent

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

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

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
 - a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
 - b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
 - c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
 - d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
 - e) that the subject's identity will remain confidential in the event that study results are published.

24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening and 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 medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
25. 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 medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

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

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

Appendix E Definition of Heartburn/ Regurgitation Severity

Definitions of Heartburn/Regurgitation Severity

None	No symptoms
Mild	Occasional symptoms, can be ignored, does not influence daily routine
Moderate	Symptoms cannot be ignored and/ or occasionally influence daily routine
Severe	Symptoms present most of the day and/ or regularly influence daily routine

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Appendix F Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 06 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Updated study team contacts and approvers.

The primary change occurs in Section 1.1 (Contacts) and Section 1.2 (Approval):

Description of change: In Section 1.1, Asia Pacific contact details have been updated for :

- Serious adverse event, pregnancy, and special interest adverse event reporting.
- Medical Monitor.

In Section 1.2, the approver VP Head of Clinical Science GI TAU has been removed

Rationale for Change:

Updates made for alignment with template and standard operating process.

Change 2: Information from phase 3 clinical studies of TAK-438 has been added.

The primary change occurs in Section 4.1 Background:

Added text: **TAK-438 has been studied in a number of acid-related diseases and noninferiority with Lansoprazole has been confirmed in several phase 3 studies including reflux esophagitis healing and prevention of recurrence studies, gastric/duodenal ulcer healing and for the prevention of recurrence of a gastric or duodenal ulcer during NSAID or aspirin administration and has subsequently been launched in Japan for these indications. All treatments were well-tolerated.**

Rationale for Change:

New information describing the efficacy and safety of TAK-438 is available.

Change 3: Added a 4- or 8-week, open-label single-arm Lansoprazole 30 mg treatment period (the Healing Phase); new language to distinguish between the open-label Healing Phase and randomized, double-blind Maintenance Phase; defined Healing Phase Failures, and qualified that de novo subjects are no longer eligible to enroll.

The primary change occurs in Section 6.1.1 Study Description:

Initial wording: ~~All subjects who have been confirmed on endoscopy to have healing of erosive esophagitis will be randomized at a 1:1:1 ratio to oral TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily given in the Maintenance Phase lasting 24 weeks.~~

If relapse of erosive esophagitis has been endoscopically confirmed in any subject, the subject will complete the study at that time point (to be construed as “complete cases in the Maintenance Phase”, regardless of the time point where relapse of disease is confirmed).

This study will be conducted at a total of around 60 sites across Asia with an estimated total of 231 subjects randomized to each treatment group totaling 693 for the study.

The study will consist of a Screening Phase of up to 28 days followed by a Treatment Phase of up to 24 weeks. There will be 8 subject visits scheduled: the start of the Screening Phase (Visit 1), the start of the Treatment Phase (Visit 2), 2 weeks after treatment (Visit 3), 4 weeks after of treatment (Visit 4), 6 weeks after treatment (Visit 5), 8 weeks after treatment (Visit 6), 12 weeks after treatment (Visit 7), and 24 weeks after treatment (Visit 8), and a Follow-up phase. The LFT monitoring visits at Week 2, 6 and 8 depend on whether the subjects have completed TAK-438_303 treatment or how long they have been in TAK-438_303 study. The biweekly LFT monitoring visits for blood draws is required for 8 weeks after subjects starts the study medication at TAK-438_303.

Dosing will commence on Day 1 after randomization at Visit 2 (after completion of all required assessments scheduled on the day 1).

A schematic of the study design is included as

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

Amended
or new
wording:

This study is comprised of 2 treatment periods: An open-label, single-arm period in which subjects receive Lansoprazole 30 mg for up to 8 weeks (Healing Phase), and a double-blind, parallel-group period in which subjects are randomized at a 1:1:1 ratio to TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily for up to 24 weeks (Maintenance Phase). To enroll in the study subjects must have ongoing erosive esophagitis or have completed Study TAK-438_303. Subjects with ongoing erosive esophagitis are required to undergo the Healing Phase. Once erosive esophagitis healing is confirmed by endoscopy, these subjects may be randomized to 1 of 3 treatments in the Maintenance Phase. Subjects with endoscopic-confirmed healing of erosive esophagitis following the completion of Study TAK-438_303 will be randomized into the Maintenance Phase without carrying out the open-label Healing Phase. Subjects who previously entered the study (prior to Protocol Amendment 06) after confirmation of healed erosive esophagitis following treatment with a proton pump inhibitor (termed “*de novo*” subjects) are no longer eligible to enter the study; any ongoing subjects may continue being treated in the Maintenance Phase. A schematic of the study design is included in [Figure 6.a](#). A schedule of assessments is listed in [Appendix A](#).

If relapse of erosive esophagitis has been endoscopically confirmed in any subject, the

subject will complete the study at that time point (to be construed as “complete cases in the Maintenance Phase”), regardless of the time point where relapse of disease is confirmed.

This study will be conducted at a total of around 70 sites across Asia with an estimated total of 231 subjects randomized to each treatment group during the Maintenance Phase (totaling 693 subjects entering the Maintenance Phase for the study).

The study will consist of a Screening Phase of up to 28 days duration (Visit 1), a Healing Phase (for those subjects with ongoing erosive esophagitis only) of 4 or 8 weeks duration (Visits 2_{HP} and 3_{HP}), followed by a Maintenance Phase of up to 24 weeks (Visits 2-8), and a Follow-up Period of up to 14 days duration. With the exception of the Follow-up (which will be carried out by phone), all visits will occur at the clinic. The total duration of treatment is up to 6 months (24 weeks) in subjects entering from Study TAK-438_303, and up to 8 months (32 weeks) in subjects entering the study with ongoing erosive esophagitis.

Subjects with ongoing erosive esophagitis: Subjects who have ongoing erosive esophagitis will enter the Healing Phase and administration of Lansoprazole 30 mg once daily will commence following the completion of all required assessments at Visit 2_{HP}. Subjects will then undergo a visit at Week -4 (Visit 3_{HP}), where the subject may undergo endoscopy to confirm healing of erosive esophagitis. This is an optional procedure where the decision to perform endoscopy is based on the investigator’s clinical judgment of a subject’s symptoms of healing. Subjects who do not show endoscopic healing at Visit 3_{HP} may continue in the Healing Phase and undergo endoscopy at Day 1 (Visit 2). Subjects with endoscopically confirmed healing of erosive esophagitis at Week -4 or Day 1 will be eligible to enter the Maintenance Phase. Where the results from clinical laboratory tests confirming eligibility for the Maintenance Phase at Week -4 are not immediately available, subjects should continue to receive Lansoprazole 30 mg for up to 14 days. Subjects healed at Day 1 should be immediately randomized. Subjects who do not have endoscopic-confirmed healed erosive esophagitis after 8 weeks treatment (Healing Phase Failures) will not be randomized into the Maintenance Phase and should be treated using routine clinical care.

Subjects with healed erosive esophagitis: Subjects with healed erosive esophagitis will undergo a randomization visit (Visit 2), and dosing for the Maintenance Phase will commence following the completion of all required assessments on Day 1. Visits will then occur at 2 week intervals after the initiation of treatment in the Maintenance Phase. As a result of Protocol Amendment 06, subjects with healed erosive esophagitis following treatment with a proton pump inhibitor (*de novo* subjects) are no longer eligible to enter the study; any ongoing subjects

may continue to be treated in the Maintenance Phase.

All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks. For subjects entering the Maintenance Phase of the current study within 7 days of completing Study TAK-438_303, the requirement for 8 weeks of monitoring can be totalled across the 2 studies. Further detail on the LFT monitoring requirements is available in Section 9.1.8.

Rationale for Change:

To improve subject recruitment to the study, subjects with ongoing erosive esophagitis are permitted to enroll and first receive Lansoprazole 30 mg once daily for 4 or 8 weeks. To reduce the complexity of the study, subjects previously known as de novo subjects (subjects with healed erosive esophagitis following treatment with a proton pump inhibitor as per standard clinical practice) are no longer eligible to enter the study.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
 - Section 4.2 Rationale for the Proposed Study
 - Section 6.2 Justification for Study Design, Dose, and Endpoints.
 - Section 9.1.12 Documentation of Screen Failure
 - Section 9.3.1 Visit 1: Screening Phase (Day -28 to Day -1).
-

Change 4: Added the Healing Phase to the Study Design Schematic.

The primary change occurs in [Figure 6.a Schematic of Study Design](#)

Amended **Figure 6.a Schematic of Study Design**

or new wording: [Figure changed to indicate that subjects with ongoing erosive esophagitis may enter the study and undergo a 4- or 8-week open-label Healing Phase.]

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

Change 5: Clarified the primary and secondary objectives.

The primary change occurs in Section 5.1 Objectives

Initial wording: **Primary Objective(s)**

To demonstrate the non-inferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI, as well as to determine the clinically recommended dose of TAK-438 for maintenance therapy in erosive esophagitis.

Secondary Objectives

To evaluate the efficacy of TAK-438 during the 12-week treatment and the safety of TAK-438 versus Lansoprazole in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.

Amended or new wording: **Primary Objectives**

- To demonstrate the noninferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.
- To determine the clinically recommended dose of TAK-438 for maintenance therapy in erosive esophagitis **in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.**

Secondary Objectives

- To evaluate the efficacy of TAK-438 during the **first** 12-weeks of treatment in the Maintenance Phase in subjects with endoscopically confirmed healed erosive esophagitis receiving TAK-438 or a PPI.
 - **To evaluate** the safety of TAK-438 versus Lansoprazole in subjects in the Maintenance Phase (24 weeks) **in whom endoscopic healing of erosive esophagitis has been confirmed after treatment with TAK-438 or a PPI.**
-

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
-

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

Change 6: Changed the inclusion criteria.

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

Initial wording:

- ~~The subject has undergone PPI treatment if he/she is not rolled over from TAK-438_303 study. PPI treatment is defined as the treatment with at least 2 weeks on a registered dose of a PPI combined with an endoscopy within 1 week of randomization confirming healing of the erosive esophagitis.~~
- The subject has been confirmed on endoscopy to have healing of erosive esophagitis. This endoscopy, if not part of the TAK-438_303 study, must have been within the last 4 week prior to randomization, otherwise the endoscopy must be repeated to confirm healing before randomization in the TAK-438_305 study.

Amended or new wording:

- If the subject is not rolled over from TAK-438_303 study, he/she has undergone an open-label PPI treatment (Lansoprazole 30 mg, once daily) of 4 or 8 weeks within the TAK-438_305 protocol.**
- The subject has been confirmed on endoscopy to have healing of erosive esophagitis. This endoscopy, if not part of the TAK-438_303 study, must have been within the last **14 days** prior to randomization, otherwise the endoscopy must be repeated to confirm healing before randomization in the TAK-438_305 study.

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

The following sections also contain this change:

- Section [2.0 STUDY SUMMARY](#)
-

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Change 7: Updated the timings relating to excluded medications and treatments.

The primary change occurs in [Table 7.a Excluded Medications and Treatments:](#)

Initial wording:	From 84 days prior to treatment to completion of the study	From 30 days prior to treatment through study completion	From 7 days prior to treatment through study completion	From start of treatment to completion of the study
Amended or new wording:	From the start of From 12 weeks prior to randomization to study completion		From 7 days prior to randomization	From start of randomization to study completion

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

Change 8: Stated the dosing instructions for Lansoprazole 30 mg.

The primary change occurs in [Section 7.4 Diet, Fluid, Activity Control:](#)

Amended or new wording:	With the exception of Lansoprazole 30 mg during the Healing Phase (where applicable), which should be administered according to the approved local package insert , the subject should ensure that all study medications are swallowed with 240 ml water soon after breakfast according to the administration, dose and dosing schedule. Subjects should be instructed according to Section 8.1.3.3 (Missed Doses) and Section 9.2 (Compliance). Details of any missed or forgotten doses should be reported to the Investigator or designee at the subsequent study visit.
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Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

The following sections also contain this change:

- [Section 2.0 STUDY SUMMARY](#)
 - [Section 8.1.3.1 Healing Phase.](#)
-

Change 9: Stated dosage form, manufacturing, packaging, and labeling for Lansoprazole 30 mg.

The primary change occurs in Section 8.1.1.1 Investigational Drug:

Amended or new wording: The chemical name of Lansoprazole (AG-1749) is: (RS)-2-({[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridylmethyl]sulfinyl}benzimidazole. Lansoprazole 15 mg will have a dual supply chain. The Lansoprazole 15 mg **and 30 mg** for the study conducted in China is manufactured locally by Tianjin Takeda, Tianjin China. Lansoprazole 15 mg **and 30 mg** for all other countries and matching placebo for Lansoprazole 15 mg is manufactured by Takeda Pharmaceutical Company, Osaka, Japan. All Lansoprazole 15 mg and matching placebo will be supplied as a white colored capsule. **Lansoprazole 30 mg will be supplied as a white colored capsule with the exception of the Malaysia marketed version where Lansoprazole 30 mg will be supplied as a white-to-yellowish white uncoated tablet with orange-to-dark brown speckles.**

For the Healing Phase, Lansoprazole 30 mg will be foil/foil blistered packaged into 35-day (4 weeks plus 7 extra days) child-resistant blister cards for sites in Korea and Taiwan. The daily dose will be 1 capsule. The country-specific marketed version of Lansoprazole 30 mg will be supplied for sites in China and Malaysia respectively. These products will be labelled in an open fashion.

For the Maintenance Phase, TAK-438 and Lansoprazole investigational drug will be foil/foil blistered packaged into 20-day (2 weeks plus 6 extra days) child-resistant blister cards. Each blister card will include 20 TAK-438 10 mg or placebo tablets; 20 TAK-438 20 mg or placebo tablets and 20 Lansoprazole 15 mg or placebo capsules. The daily dose will be 2 tablets and 1 capsule. **Each blister card will be labeled in a blinded fashion. For all investigational treatments,** each blister card will be accompanied by a single panel or multi language booklet label appropriate to the countries in which it will be used. The labels will include pertinent study information and country-specific regulatory caution statement.

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
-

Change 10: Clarified dispensing procedures during the Healing Phase.

The primary change occurs in Section 8.2 Investigational Drug Assignment and Dispensing Procedures:

Amended or new wording: The investigator or investigator's designee will access the IWRS at the Screening Visit after the subject provides informed consent in order to obtain a subject number.

Healing Phase: The investigator or investigator's designee will access IWRS in order to record the number of Lansoprazole cartons/ wallet cards that will be dispensed at Week -8 and Week -4 in order to provide enough study medication to cover the duration until the next visit. Lansoprazole 30 mg provided for Healing Phase has a different count of capsules/tablets in a carton/wallet card depending on the country. Please refer to the IWRS manual on how many cartons/wallet cards will need to be dispensed.

Maintenance Phase: Following confirmation of healed erosive esophagitis and study eligibility at Visit 2, 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 Med ID number of the investigational drug to be dispensed will then be provided by the IWRS.

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

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Change 11: Clarified the total volume of blood collected.

The primary change occurs in Section 9.1.8: Procedures for Clinical Laboratory Samples

Initial wording The maximum volume of blood to be collected at any single visit for central laboratory analysis is approximately 3.5 - 19.5 mL (~~Visit 1, Visit 2, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8/Early Discontinuation Visit~~). Additionally, the volume of blood to be collected for Hepatitis B and C tests at the Screening visit is up to 10 mL and the approximate total volume of blood to be collected for the study is 79.5~96.0 mL. Details of these procedures and required safety monitoring will be given in the central laboratory manual.

Amended or new wording: The maximum volume of blood to be collected at any single visit for central laboratory analysis is approximately 3.5 to 19.5 mL. Additionally, the volume of blood to be collected for Hepatitis B and C tests at the Screening visit is up to 10 mL and the approximate total volume of blood to be collected for the study is 79.5~96.0 mL **for those subjects entering directly in to the Maintenance Period and 96.0~112.5 mL for those subjects entering the Healing Phase and Maintenance Phase**. Details of these procedures and required safety monitoring will be given in the central laboratory manual.

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

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Change 12: Further detailed the site visits for liver function tests.

The primary change occurs in Section 9.1.8 Procedures for Clinical Laboratory Samples:

Amended or new wording: **All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks. For subjects entering the Maintenance Phase of the current study within 7 days of completing Study TAK-438_303, the frequency of the LFT monitoring visits depends on when the subject was healed in Study TAK-438_303. For example, a subject healed at Week 2 of Study TAK-438_303 would complete LFT monitoring visits at Weeks 2, 4, and 6 of the current study, whereas a subject healed at Week 4 of Study TAK-438_303 would complete LFT monitoring visits at Weeks 2 and 4 of the current study. Subjects entering the Maintenance Phase of the current study more than 7 days after completing antecedent study TAK-438_303, as well as subjects entering the Maintenance Phase after completing the Healing Phase, and *de novo* subjects (an eligible route of entry prior to protocol amendment 6), will be required to complete LFT monitoring visits every 2 weeks from Day 1 (at Weeks 2, 4, 6, and 8).**

The following sections also contain this change:

- [Appendix A1](#), [Appendix A2](#), and [Appendix A3](#), footnote K.
-

Rationale for Change:

To clarify the frequency in site visits for liver function tests.

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Change 13: Clarified the classification of endoscopy.

The primary change occurs in Section 9.1.14 Endoscopy:

Amended or new wording: The investigator should classify any lesions seen based on the LA classification (Table 9.b), any Barrett's mucosa in accordance with the following criteria:

- At **Screening Phase (Visit 1), Visit 3_{HP}, and Day 1**: present (3 cm or greater), present (less than 3 cm), absent, unknown.
- Other time points for endoscopy: increased, unchanged, reduced, disappeared, unknown.

And any esophageal hiatal hernia in accordance with the following criteria:

- At **Screening Phase (Visit 1), Visit 3_{HP} and Day 1**: present (2 cm or greater), present (less than 2 cm), absent, unknown.

After the endoscopy the investigator should promptly record any findings or observations in the subject's medical record.

...

The investigator (or designee) will record the results of endoscopy (including results of the LA classification and other gradings) in the subject's medical record. For LA Grade O, the investigator is allowed to record the result as either "No mucosal breaks" and/or Grade O. This reflects the clinical practice of recording 'No mucosal breaks' in medical records, as Grade O is not routinely used.

Rationale for Change:

Addition of endoscopy procedures during the Healing Phase has been included to provide consistency with the revised text supporting the addition of the Healing Phase to the study design.

Addition of LA classification grading O has been included to reflect routine clinical practice.

Change 14: Clarified procedures around diary collection on study visit days.

The primary change occurs in Section 9.1.15 Diary for Gastrointestinal symptoms and Health-Related Quality of Life:

Amended or new wording: The subject must start entering the subject diary in the next morning (upon rising) after the start of the Screening Phase. Any subjective symptoms experienced should be entered on a once daily basis in accordance with the descriptions given in Table 9.c, throughout the study, describing in the diary the severity of all heartburns or acid regurgitations experienced during the previous daytime and nighttime periods (previous 24 hours), in the morning. The subject must also record the study medication taken on a daily basis in the diary during the **Maintenance Phase**. **On study visit days, the administration of study medication for that day should be entered into the diary before the diary is returned.**

The following sections also contain this change:

- Appendix A1, Appendix A2, and Appendix A3, footnote F.
-

Rationale for Change:

To ensure compliance is accurately reported, investigators are requested to ensure the subject has completed the diary for the study visit day indicating that study medication has been taken before the diaries are collected.

Change 15: Updated compliance instructions to include treatment during the Healing Phase.

The primary change occurs in Section 9.2 Monitoring Subject Treatment Compliance:

Amended or new wording: If a subject is persistently noncompliant with the study medication (**Lansoprazole 30 mg during the Healing Phase or** TAK-438 10 mg, 20 mg or Lansoprazole 15 mg and their matching placebos **during the Maintenance Phase**) (eg, at more than 2 consecutive compliance checks to have taken less than 75% or more than 133% of the study medication), it may be appropriate to withdraw the subject from the study.

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

Change 16: Clarified that 3 schedules of study-related procedures are included in Appendix A.

The primary change occurs in Section 9.3 Schedule of Observations and Procedures:

Amended or new wording: The schedule for all study-related procedures for all evaluations is shown in Appendix A. **Individual schedule of study-related procedures are presented separately for subjects entering the current study at the Healing Phase (Appendix A1), subjects entering the current study within 7 days of completing Study TAK-438_303 (Appendix A2), and subjects entering the current study more than 7 days after completing Study TAK-438_303 (Appendix A3). Ongoing de novo subjects (an eligible route of entry prior to protocol amendment 06), should follow the schedules outlined in Appendix A3.**

All assessments should be completed at the designated visit/time point(s).

Rationale for Change:

To provide consistency with the revised text supporting this change to the study design.

The following sections also contain this change:

- Section 9.3.4 Visit 2: Randomization (Day 1).
 - Appendix A1, Appendix A2, and Appendix A3.
-

Change 17: Clarified the study-related procedures to be conducted during the Screening Phase (Visit 1)

The primary change occurs in Section 9.3.1 Visit 1: Screening Phase (Day -28 to Day -1):

Initial wording: All subjects will be assessed for the following within 28 days before the start of the study medication for the Treatment Phase (Visit 2). Only those subjects that did not participate in TAK-438_303 or who had more than 7 days between finishing that study and starting this one will be examined for eligibility. See Section 9.1.12 for procedures for documenting screening or randomization failures.

For subjects who participated in TAK-438_303:

If the final study visit in the 303 study coincides with the first (randomization) visit in the 305 study, these 2 visits can be combined together. All of the overlapped examinations, i.e. laboratory procedures including hematology, urine analysis, serum chemistry, gastrin and pepsinogen I/II levels, urine hCG, FSH, and ECG, endoscopy in the 305 study will be exempted. It is also not required to repeat EQ-5D-5L, vital signs, the physical examination and subject diary completion. The data taken from the last visit in the 303 study can be used as the baseline data for the 305 study. Laboratory test results from the 303 study can be used for eligibility confirmation in the 305 study.

as long as they are within 28 days prior to randomization in the 305 study.

If the subjects are planned to be randomized in the 305 study within 7 days after completing the last visit in the 303 study, Visit 1 and Visit 2 of the 305 study can be combined together. The overlapped procedures, i.e. safety laboratory tests including hematology, urine analysis, serum chemistry, gastrin and pepsinogen I/II levels, urine hCG, FSH, endoscopy, ECG and diary completion in the 305 study will be exempted. However, EQ-5D-5L, vital signs, and the physical examination will have to be performed. The baseline clinical safety data of those subjects in this study will be the same data as obtained when subjects were confirmed healed either at Week 2, Week 4 or Week 8 in the previous TAK-438_303 study.

For the above two cases, the data should be transcribed from the last visit in the 303 study into the Visit 1 pages in the eCRF in the 305 study to comprise the baseline data in this study.

If the subjects are planned to be randomized in the 305 study after 7 days of completing the last visit in the 303 study, these subjects will follow the same procedures as the de novo subjects.

A clear procedure instruction can be found in [Appendix A](#).

Procedures to be completed at Visit 1 include:

- Informed consent (will be obtained from the subjects within 28 days before the start of the Treatment Phase (Visit 2)).
- Access IWRS to obtain subject number.
- If fasting is not normal, routine clinical practice of the site, informed consent should be obtained prior to the request for fasting for the Screening Visit. The following procedures will be performed at a second (fasting) Screening date.
- EQ-5D-5L questionnaire. It shall be completed as the first priority of all procedures except obtaining the ICF and access IWRS.
- Eligibility assessment (review Inclusion/exclusion criteria).
- Demographics, vital signs, medical and medication history.
- Height and weight. BMI will be calculated during data analysis.
- Physical examination including concurrent medical conditions and medications.
- Concomitant medications assessment.
- Hepatitis B and C analysis at the local laboratory*
- ECG procedure*
- Fasting clinical laboratory examination (urinalysis, hematology, serum chemistry

but ~~excluding~~ gastrin & pepsinogen I/II,)*

- ~~Urine pregnancy test (in females of childbearing potential only)*~~
- ~~FSH (when menopause is suspected)*~~
- ~~Guidance on the avoidance of pregnancy and ova donation.~~
- ~~Subject diary dispensed (to collect heartburn and acid reflux symptoms).~~
- ~~Endoscopy *~~
- ~~Pretreatment events assessment.~~

*: Only for subjects that did not participate in TAK-438_303 or who had more than 7 days between finishing that study treatment and starting this one.

Amended
or new
wording:

Prior to any assessments being performed, all subjects will sign the ICF. The first procedure will be to access IWRS to obtain the subject number. Section 9.1.12 documents the procedures for screening, Healing Phase Failures, or randomization failures.

***Subjects With Ongoing Erosive Esophagitis:* All subjects with ongoing erosive esophagitis will undergo assessments for the Screening Phase within 28 days before the initiation of study medication as outlined in [Appendix A1](#).**

- **Subjects will need to be in a fasted state for the Screening Visit. If fasting is not the routine clinical practice of the site, informed consent should be obtained prior to the request for fasting for the Screening visit. If the subject comes to the site in an unfasted state, the following procedures will be performed at a second (fasting) Screening Visit.**
 - **Eligibility assessment (review inclusion/exclusion criteria).**
 - **Demographics, vital signs, medical and medication history.**
 - **Height and weight. BMI will be calculated during data analysis.**
 - **Physical examination including concurrent medical conditions and medications.**
 - **Concomitant medications assessment.**
 - **Hepatitis B and C analysis at the local laboratory (reliable, documented Hepatitis B and C results performed in a routine clinical setting within 14 days prior to signing the informed consent will be accepted).**
 - **ECG procedure (reliable, documented results available from an ECG performed in a routine clinical setting within 14 days prior to signing the informed consent will be accepted).**
 - **Fasting clinical laboratory tests: hematology, serum chemistry (excluding**

serum gastrin and pepsinogen I/II), urinalysis.

- Urine pregnancy test (in females of childbearing potential only).
- FSH (when menopause is suspected).
- Guidance on the avoidance of pregnancy and ova donation.
- Endoscopy
- Pretreatment events assessment.

Subjects Entering the Current Study on the Same Day as Completing Study

TAK-438_303 Treatment: Screening procedures for these are outlined in **Appendix A2**. If the final study visit in Study TAK-438_303 study coincides with the randomization visit (Visit 2) of the current study, these 2 visits can be combined such that all of the overlapped examinations will be exempt from the screening and Day 1 procedures for the TAK-438_305 study. The overlapping examinations are comprised of clinical laboratory tests (hematology, serum chemistry, and urinalysis), serum gastrin and pepsinogen I/II levels, urine hCG, FSH, endoscopy, ECG, the subject diary, EQ-5D-5L, vital signs, and the physical examination.

Laboratory test results from the TAK-438_303 study can be used for eligibility confirmation in the TAK-438_305 study, as long as they are within 28 days prior to randomization in the TAK-438_305 study. For these subjects, data obtained in the week when subjects were confirmed as healed in the TAK-438_303 study will be used as the baseline data for the current study, and data should be transcribed from the last visit in the TAK-438_303 study into the Visit 1 pages in the eCRF for the current study.

Subjects Entering the Current Study Within 7 Days of Completing Study

TAK-438_303 Treatment: Screening procedures for these subjects are outlined in **Appendix A2**. If the subjects are planned to be randomized into the current study within 7 days after completing the last visit in the TAK-438_303 study, Visit 1 and Visit 2 of the current study can be combined. Any overlapped procedures will be exempt from the screening procedures in the TAK-438_305 study. The overlapping examinations are comprised of clinical laboratory tests (hematology, serum chemistry, and urinalysis), serum gastrin and pepsinogen I/II levels, urine hCG, FSH, endoscopy, ECG, and the subject diary. However, EQ-5D-5L, vital signs, and the physical examination will have to be performed.

For these subjects, data obtained in the week when subjects were confirmed as healed in the TAK-438_303 study will be used as the baseline data in the current study, and data should be transcribed from the last visit in the TAK-438_303 study into the Visit 1 pages in the eCRF for the current study.

Subjects Entering the Current Study More than 7 Days After Completing Study

TAK-438_303: Subjects planned to be randomized in to the current study more than 7 days after completing the last visit in the TAK-438_303 study, will follow screening period procedures outlined in [Appendix A3](#).

Rationale for Change:

To provide consistency with the revised text supporting the addition of a Healing Phase to the study design.

The following sections also contain this change:

[Appendix A](#) Schedule of Study Procedures.

Change 18: Added a description of study procedures during Healing Phase visits.

The primary change occurs in Section 9.3.2 Visit 2HP: Healing Phase (Week -8) and Section 9.3.3 Visit 3HP: Healing Phase (Week -4):

Amended **Section 9.3.2 Visit 2HP: Healing Phase (Week -8)**

or new
wording:

**This visit is only applicable for subjects undergoing the Healing Phase.
Procedures to be completed at this visit include:**

- **Dispense Healing Phase study medication (Lansoprazole 30 mg QD) and record number of cartons/wallets of study medication in the IWRS.**
- **Guidance on the avoidance of pregnancy and ova donation.**
- **AE/ Pretreatment Event assessment.**
- **Concomitant medications assessment.**

Section 9.3.3 Visit 3HP: Healing Phase (Week -4)

**This visit is only applicable for subjects undergoing the Healing Phase.
Procedures to be completed at this visit include:**

- **Physical examination.**
 - **Vital signs.**
 - **Fasting clinical laboratory tests: hematology, serum chemistry (including serum gastrin and pepsinogen I/II), urinalysis.**
 - **Urine pregnancy test (in females of childbearing potential only).**
 - **ECG procedure.**
 - **Endoscopy. This is an optional procedure based on the investigator's clinical judgment of a subject's symptoms of healing. If the subject's is endoscopically confirmed as healed, and the result of clinical laboratory tests at this visit from central laboratory re-confirms the subject's eligibility, the subjects can be randomized within 14 days of this endoscopy date. During this period of waiting for randomization, subjects shall continue to take the newly dispensed Lansoprazole 30 mg QD. Subjects who do not show endoscopic healing at Visit 3HP may continue in the Healing Phase and undergo endoscopy at Day 1 (Visit 2).**
 - **Guidance on the avoidance of pregnancy and ova donation.**
 - **Study drug accountability and check treatment compliance, re-instruct the subject if necessary, dispense additional Healing Phase study medication (Lansoprazole 30 mg QD) and record the number of cartons/wallets of study**
-

medication in the IWRS.

- **AE assessment.**
- **Concomitant medications assessment.**

Rationale for Change:

To provide consistency with the revised text supporting this change to the study design.

Change 19: Repeated the discontinuation criteria for liver function abnormalities.

The primary change occurs in Section 10.2.3 Reporting of Abnormal Liver Function Tests:

Added text: **If subject experience an increase in any one of ALT, AST or total bilirubin >2 ×ULN, the study medication shall be stopped according to the discontinuation criteria. Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) to monitor recovery should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was found (see Section 9.1.8).**

Rationale for Change:

To ensure all information pertaining to liver function abnormalities is consistent throughout the document.

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Change 20: Confirmed that the questionnaires used to rate a subject's symptoms and severity of symptoms are the same as that used in the Japanese clinical development program. Repeated the discontinuation criteria for liver function abnormalities. Information from phase 3 clinical studies of TAK-438 has been added.

The primary change occurs in Section 6.2 Justification for Study Design, Dose, and Endpoints Background:

Added text: 3 Additional endpoints

Heartburn and gastric acid regurgitation are typical symptoms of erosive esophagitis which could impact the subject's Health-Related Quality of Life. The severity and frequency of those symptoms are recorded via the daily diary by the subjects **using the questionnaires outlined in Table 9.c and Table 9.d, which were also implemented in the Japanese clinical development program.** while **The** HRQoL will be assessed by subjects completing validated questionnaires. The EQ-5D-5L index score has been previously used to demonstrate that moderate to severe symptoms of GERD are associated with a significant impairment in HRQoL[2, 3]. Consequently those subjective symptoms and health-related quality of life using EQ-5D-5L are considered as additional endpoints in this study.

Rationale for Change:

Clarification purposes.

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Amendment 6 to A Randomized, Double-Blind, Double-Dummy, Parallel-group Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily Administration of TAK-438 10 or 20 mg Compared to Lansoprazole 15 mg in the Maintenance Treatment of Subjects With Endoscopic Healing of Erosive Esophagitis

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	24-Nov-2016 15:03 UTC
	Clinical Approval	25-Nov-2016 01:22 UTC
	Medical Monitor Approval	25-Nov-2016 03:38 UTC

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