Title: A Randomized, Double-Blind, Double-Dummy Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily administration of TAK-438 20 mg compared to Lansoprazole 30 mg in the Treatment of Subjects with Erosive Esophagitis

NCT Number: NCT02388724

Protocol Approve Date: 01-September-2016

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

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

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

PROTOCOL AMENDMENT

A Randomized, Double-Blind, Double-Dummy Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily administration of TAK-438 20 mg compared to Lansoprazole 30 mg in the Treatment of Subjects with Erosive Esophagitis

Sponsor:	Takeda Development Center Asia, Pte. Ltd. 21 Biopolis Road, Nucleos North Tower, Level 4, Singapore 138567		
Study Number:	TAK-438_303		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Compound:	TAK-438		
Date:	01-September-2016	**Amendment Number:**	05

Amendment History

Date	Amendment Number	Amendment Type	Region
08 Aug 2012	Initial Protocol	Not applicable	Asia Pacific
31 Oct 2014	01	Non-substantial	Asia Pacific
26 Jan 2015	02	Non-substantial	Asia Pacific
11 May 2015	03	Substantial	Asia Pacific
14 Dec 2015	04	Substantial	Asia Pacific
01 Sept 2016	05	Non-substantial	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	PPD
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

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

The signature of the responsible Takeda medical officer and other signatories can be found on the signature page.

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

PPD ate

PPD Date

PPD Date

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 05 Summary of Changes

1. The contacts (Section 1.1) have been updated.
2. The protocol approvers (Section 1.2) have been updated.
3. Inclusion criterion #3 (Section 7.1) has been revised to extend the window period for the number of days before randomization for endoscopy to 14 days.
4. Main exclusion criteria have been supplemented with hypersensitivity to lansoprazole, in Study Summary (Section 2.0) and Section 7.2, and to exclude subjects with liver function test (LFT) > upper limit of normal (ULN), in Study Summary (Section 2.0).
5. Information on phase 3 clinical data for TAK-438 has been added to the Background (Section 4.1).
6. LA classification grading O has been included in Section 9.1.16 (Endoscopy), due to routine clinical practice.
7. Section 9.3.1 (Screening Phase procedures) has been revised to include updated wording regarding the window period for the number of days before randomization for ECG, Hepatitis B and C, and endoscopy, which has been extended to 14 days. Additionally, the process of dispensing the Medical Emergency card has been added.
8. For study procedures (Appendix A), the window period for the number of days before randomization for ECG, Hepatitis B and C, and endoscopy has been extended to 14 days. Additionally, the process of dispensing the Medical Emergency card has been added.

Typographical errors and points for clarification have also been added. A full description and supporting rationale for each of the changes implemented in this Protocol Amendment is provided in Appendix G.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Asia Pte. Ltd.</td><td colspan="2">Compound:
TAK-438 / Vonoprazan</td></tr>
<tr><td colspan="2">Title of Protocol: A Randomized, Double-Blind, Double-Dummy Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily administration of TAK-438 20 mg compared to Lansoprazole 30 mg in the Treatment of Subjects with Erosive Esophagitis</td><td>IND No.:
Not applicable</td><td>EudraCT No.:
Not applicable</td></tr>
<tr><td colspan="2">Study Number: TAK-438_303</td><td colspan="2">Phase: 3</td></tr>
<tr><td colspan="4">Study Design:
A phase 3, multicenter, double-blind, non-inferiority study of TAK-438 20 mg versus Lansoprazole 30 mg given once daily (OD) for up to 8 weeks in subjects with erosive esophagitis, with the LA classification grade A/B or C/D serving as the stratification factors at randomization, where all subjects with endoscopic healing of erosive esophagitis 2, 4, or 8 weeks after the start of the study will be construed as “completed cases” who then may be invited to participate with further informed consent in the planned, ensuing, maintenance trial (TAK-438_305).</td></tr>
<tr><td colspan="4">Primary Objectives:
To demonstrate the non-inferior efficacy of TAK-438 versus Lansoprazole in the healing of subjects with erosive esophagitis classified as LA classification grades A to D during the 8-week treatment.</td></tr>
<tr><td colspan="4">Secondary Objectives:
To compare the efficacy of TAK-438 versus Lansoprazole in the healing of subjects with erosive esophagitis classified as LA classification grades A to D during the 2-week treatment.
To compare the efficacy of TAK-438 versus Lansoprazole in the healing of subjects with erosive esophagitis classified as LA classification grades A to D during the 4-week treatment.
To compare the safety of TAK-438 versus Lansoprazole in subjects with erosive esophagitis classified as LA classification grades A to D.
Additional Objectives:
To compare the difference of TAK-438 versus Lansoprazole in the subjective symptoms of erosive esophagitis and health-related quality of life measures.
To compare the difference of TAK-438 versus Lansoprazole in the percentage of days without rescue medication during the treatment phase.</td></tr>
<tr><td colspan="4">Subject Population: Subjects aged ≥18 years (and at least the local age of consent) inclusive with erosive esophagitis who were diagnosed as LA Classification grades A to D.</td></tr>
<tr><td colspan="2">Number of Subjects:
TAK-438 20 mg group: approximately 240
Lansoprazole 30 mg group: approximately 240
Estimated total: approximately 480 at randomization</td><td colspan="2">Number of Sites:
Estimated total: Approximately 50 sites in multiple countries</td></tr>
<tr><td colspan="2">Dose Level(s):
<u>TAK-438 20 mg group</u>: TAK-438 (one 20 mg tablet) + Lansoprazole placebo (matching 30 mg capsule) given once daily after breakfast
<u>Lansoprazole 30 mg group</u>: TAK-438 placebo (matching 20 mg tablet) + Lansoprazole (one 30 mg capsule) given once daily after breakfast</td><td colspan="2">Route of Administration:
Oral</td></tr>
</table>

Duration of Treatment:	**Period of Evaluation:**
2, 4, or 8 weeks	1-28 days (Screening Phase) including 3-7 days of Observation Phase 2, 4, 6 or 8 weeks (Treatment Phase) 7-14 days (Follow-up Phase)

Main Criteria for Inclusion:

All subjects are to be evaluated for eligibility for entry in the study based on the following criteria.

Subjects who have endoscopically confirmed (Los Angeles classification grade A-D) erosive esophagitis. 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.

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, or 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 of this study is the rate of endoscopic healing of erosive esophagitis during the 8-week treatment phase.

The secondary efficacy endpoints of this study are

- the rate of endoscopic healing of erosive esophagitis during the 2-week treatment.
- the rate of endoscopic healing of erosive esophagitis during the 4-week treatment.

Other efficacy endpoints include subjective symptoms of erosive esophagitis as recorded in subject diaries (e.g. heartburn, gastric acid regurgitation), health-related quality of life measures and percentage of days without using rescue medication.

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 Week 8 healing rate of erosive esophagitis, a 2-sided 95% confidence interval (CI) will be constructed for the difference between TAK-438 and Lansoprazole treatment groups and its lower bound will be compared to the non-inferiority margin of -10%.

The secondary endpoints of Week 2 and Week 4 healing rates of erosive esophagitis will be compared between TAK-438 and Lansoprazole treatment groups by constructing a 2-sided 95% CI for the healing rate difference.

The additional endpoints related to GERD symptoms and the use of rescue medication during treatment 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.

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. No statistical testing or inferential statistics will be generated.

Sample Size Justification:

Assuming that the true Week 8 healing rate is 94.7% for both TAK-438 and Lansoprazole, and assuming that the dropout rate is up to 20%, a sample size of 160 subjects per group will provide 90% power to establish non-inferiority using a 2-sided 95% CI with a -10% non-inferiority margin. A sample size of 240 subjects per group is planned in order to provide more subjects with healed EE to the subsequent maintenance study TAK-438_305 and to provide adequate subjects for regulatory requirements in various countries.

The assumption of the 94.7% true healing rate is based on Phase 2 studies TAK-438/CCT-001 and TAK-390MR/CCT-001.

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.

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
Cmax	maximum observed plasma concentration
CNS	central nerve system
eCRF	electronic case report form
CRO	contract research organization
CYP	cytochrome P450 enzyme
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EE	erosive esophagitis
EDC	electronic data capture
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
TBC	to be confirmed
TBil	total bilirubin
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 Heath-Related Quality of Life (HRQoL).

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 and is water-soluble, requires no particular pharmacological preparations, such as an enteric coating, suggesting that TAK-438 may likely vary less in time for onset of action than the PPIs among those receiving the drug. 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 I 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) (e.g., 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 plasma concentration of TAK-438F increased by 1.35-fold for Cmax 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 non-inferiority 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 ulcer/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 this study was to be implemented to prove the non-inferiority of TAK-438 20 mg to Lansoprazole 30 mg in efficacy for erosive esophagitis. This study will further examine the effectiveness and safety of TAK-438 in Asian subjects outside of Japan with erosive esophagitis.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

The primary objective is to demonstrate the non-inferior efficacy of TAK-438 versus Lansoprazole in the treatment of subjects with erosive esophagitis classified as LA classification grades A to D during the 8–week treatment.

5.1.2 Secondary Objectives

To compare the efficacy of TAK-438 versus Lansoprazole in the healing of subjects with erosive esophagitis classified as LA classification grades A to D during the 2-week treatment.

To compare the efficacy of TAK-438 versus Lansoprazole in the healing of subjects with erosive esophagitis classified as LA classification grades A to D during the 4-week treatment.

To compare the safety of TAK-438 versus Lansoprazole in subjects with erosive esophagitis classified as LA classification grades A to D.

5.1.3 Additional Objectives

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary efficacy endpoint of this study is the rate of endoscopic healing* of erosive esophagitis during the 8-week treatment.

**Endoscopic healing: defined as subjects endoscopically diagnosed as LA classification grade O during the treatment phase.*

5.2.2 Secondary Endpoints

The secondary efficacy endpoints of this study are

- the rate of endoscopic healing of erosive esophagitis during the 2-week treatment,
- the rate of endoscopic healing of erosive esophagitis during the 4-week treatment.

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

5.2.3 Additional Endpoints

CCI

[redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

A phase 3, multi-center, double-blind, non-inferiority study of TAK-438 20 mg versus Lansoprazole 30 mg given once daily for up to 8 weeks in subjects with erosive esophagitis, with the LA classification grade A/B or C/D serving as the stratification factors at randomization, where all subjects with endoscopic healing of erosive esophagitis 2, 4, or 8 weeks after the start of the study will be construed as "completed cases" who then may be invited to participate with further informed consent in the planned, ensuing, maintenance trial (TAK-438_305).

Upon randomization subjects will be assigned (at a 1:1 ratio) to receive either oral TAK-438 20 mg or Lansoprazole 30 mg all study medication will once daily after breakfast except on Day 1 when it will be administered at the study site before the subject's visit is concluded.

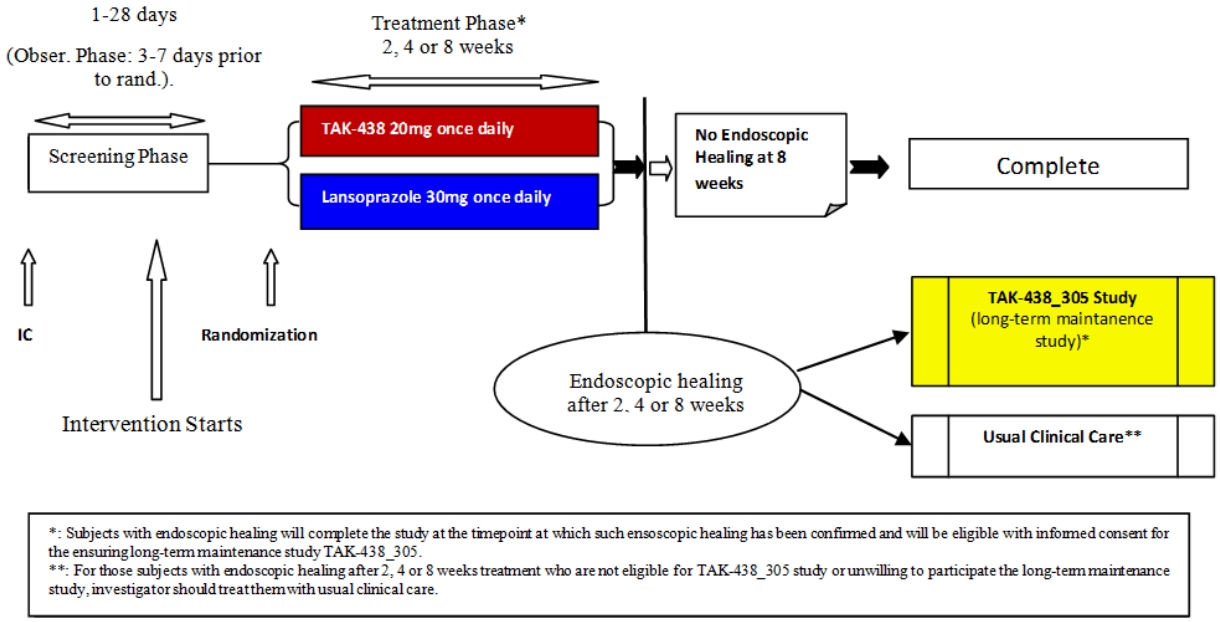
This study will be conducted at a total of around 50 sites across Asia with an estimated total of 240 subjects randomized to each treatment group totaling 480 for the study.

The study will consist of a Screening Phase of up to 28 days, including an Observation Phase of 3-7 days prior to the randomization visit (Day 1), during which a baseline observation of EE symptoms will be completed, and then a Treatment Phase of up to 8 weeks. There will be 6 subject visits scheduled: the start of the Observation Phase (Visit 1), the start of the Treatment Phase (Visit 2), after 2 weeks of treatment (Visit 3), after 4 weeks of treatment (Visit 4), after 6 weeks of treatment (Visit 5), after 8 weeks of treatment (Visit 6), and a phone call during the Follow-up phase (only for those not participating in TAK-438_305 study).

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.

Figure 6.a Schematic of Study Design



6.2 Justification for Study Design, Dose, and Endpoints

For the patient population studied

With the westernization of lifestyle and the aging of society, erosive esophagitis has been steadily increasing over the years. In the diagnosis of erosive esophagitis, the LA classification, first introduced in 1994 at the World Congress of Gastroenterology, has been widely used ever since. A phase 2 dose-ranging study of TAK-438 (TAK-438/CCT-001) was conducted earlier using the LA classification. In this trial of TAK-438 in erosive esophagitis, subjects with mucosal breaks diagnosed as the LA classification grades A to D were enrolled, to the exclusion of those with co-morbidities or a history of these conditions that could influence the efficacy evaluation of TAK-438.

For study design and sample size used

1. Study design

This study was designed as a randomized, double-blind, parallel-group comparison of TAK-438 versus the PPI Lansoprazole, a first drug of choice for erosive esophagitis, as control to demonstrate the non-inferiority of TAK-438.

In light of the results of a phase 2 dose-ranging study of TAK-438 (TAK-438/CCT-001) demonstrating a lower rate of endoscopic healing in subjects with the baseline LA classification grades C/D than those with grades A/B, at the start of treatment (visit 1), the present study was planned to stratify the subjects by baseline endoscopic findings (grades A/B or C/D) at randomization.

2. Sample size

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

For the 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 non-inferiority 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 dose of Lansoprazole was determined as 30 mg, which represents its therapeutic dose for erosive esophagitis.

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 $AUC_{0\text{-}48}$ 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. It is of note here that the control agent Lansoprazole 30 mg has been approved for erosive esophagitis as a once-daily regimen.

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

The primary endpoint of the phase 2 dose-ranging study of TAK-438 was defined as the rate of endoscopic healing of erosive esophagitis after 4 weeks of treatment with the study medications, based on the assumption that TAK-438 is expected to have a faster onset of action than the PPIs such as Lansoprazole. However, given that the PPIs have been approved for 8-week dosing as the drugs of first choice for erosive esophagitis, the primary endpoint of this study was defined as the rate of endoscopic healing after 8 weeks of treatment with TAK-438. Therefore, the study was designed to allow the subjects to complete the study at the time point at which endoscopic healing of erosive esophagitis has been confirmed 2, 4, or 8 weeks of treatment to move on to the maintenance study (TAK-438_305).

For the Observation Phase incorporated in the study

Subjects with erosive esophagitis are not only afflicted with esophageal mucosal breaks but also suffer from unpleasant subjective symptoms associated with gastric acid reflux, often leading to a worsening of their HRQoL. Major subjective symptoms associated with acid reflux include heartburn and gastric acid regurgitations and relieving these symptoms as a step toward improving their HRQoL represents an important component of the treatment for subjects with erosive esophagitis.

Thus, it was decided that an observation phase would be included to establish an appropriate baseline for evaluation of the effect of TAK-438 on these major symptoms, i.e., heartburn and gastric acid regurgitations, associated with acid reflux.

For the endpoints used

1. Primary endpoint

Endoscopic healing of esophageal mucosal breaks represents the goal of treatment for erosive esophagitis, in which Lansoprazole 30 mg has been approved for use once daily for up to 8 weeks.

As it is the aim of this study to prove the non-inferior efficacy of TAK-438 versus Lansoprazole in subjects diagnosed as the LA classification grades A to D, the primary endpoint was defined as the rate of endoscopic healing during an 8-week treatment phase.

2. Secondary endpoints

As TAK-438 is expected to produce more sustained, potent acid-inhibitory effects and earlier healing of erosive esophagitis than Lansoprazole 30 mg, the above-mentioned phase 2 dose-ranging study (TAK-438/CCT-001) was conducted with the primary endpoint defined as the rate of endoscopic healing after 4 weeks of treatment, which demonstrated the non-inferiority of TAK-438 versus Lansoprazole. In the approved Japan package insert for TAK-438, it claims that the usual administration should be limited up to 4 weeks. However, when the effect is insufficient, the drug may be administered up to 8 weeks. Furthermore, it is thought likely that TAK-438 produces endoscopic healing of erosive esophagitis as early as after 2 weeks of treatment, given its sustained, potent acid-inhibitory effects. Thus, the secondary endpoint of this study was defined as the rate of endoscopic healing of erosive esophagitis after 2 and 4 weeks of treatment with the study medications.

A dose-dependent elevated serum gastrin was observed in TAK-438 subjects from a completed Phase 2 study so to proactively address safety concerns it is appropriate to monitor serum gastrin level. Thus the serum gastrin and pepsinogen I/II will be collected from baseline to study completed.

3. Additional endpoints

CCI [redacted]

CCI

[redacted]

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 in an endoscopy to have erosive esophagitis, i.e. the LA classification grades A to D within 14 days of the start of the Day 1 (Visit 2).

   Note: The recruitment goal is to ensure that those with LA classification grade C/D will account for more than 30% of all subjects enrolled (144/480), with no further recruitment of those with grade A/B considered when they account for more than 70% (336/480) of all subjects.
4. 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 admitted temporarily for examination.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and 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 within 84 days prior to the start of the Observation phase.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (e.g., 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 serious 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 (including its excipients*) or to proton pump inhibitors (PPIs).

   *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 Observation Phase (Visit 1).
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 within the past 30 days from Visit 1.
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 Observation 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 Observation 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 positive 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 at the start of the Early Observation Phase (visit 1) revealed any of the following abnormalities in the subject:
    a) Creatinine levels: > 2 mg/dL (>177 μmol/L).
    b) ALT, AST or total bilirubin levels: > the upper limit of normal (ULN).
19. Subject is active in the Screening Period after the closure of enrollment identified by the Sponsor or the number of subjects randomized with LA classification A/B or C/D have reached the required sample size.

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 84 days prior to treatment to completion of the study	From 30 days prior to treatment through study completion	From 14 days prior to the screening endoscopy procedure through study completion	From 14 days prior to $^{13}C/^{14}C$ Urea Breath test	From 7 days prior to the start of the Observation Period through study completion	From start of the Observation Period to completion of the study
Other investigational drugs or drugs administered due to participation in another clinical trial	H. pylori eradication therapy (ie, PPI + 2 antibiotics)	PPIs (interfere with gastric acid secretion)	Metronidazole, Bismuth preparations, Ecabet sodium hydrate (interfere with $^{13}C/^{14}C$ Urea breath test)	H_2 antagonists (interfere with gastric acid secretion)	Other agents affecting digestive organs including: muscarinic M_3 receptor antagonists, prokinetics, anticholinergic agents, prostaglandins, anti-gastrin agents or mucosal-protective agents.
	Hormonal contraceptives				Atazanavir sulfates; Rilpivirine hydrochloride (contraindicated with TAK-438)
	Antibiotics($) (interfere with ^{13}C or ^{14}C Urea Breath test (a)				Surgical procedures that could affect gastric acid secretion (e.g. upper gastrointestinal surgery, vagotomy) or for treatment of EE (fundoplication)
					Bisphosphonates (b)

Footnotes are on the following page.

(a) Prohibited period is 4 weeks prior to the ^{13}C or ^{14}C Urea breath test or local ^{13}C or ^{14}C Urea breath test kits package insert requirement.
(b) 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 has 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.
- The subject should ensure that all study medications are swallowed with approximately 240 ml water soon after breakfast according to the administration, dose and dosing schedule. Subjects should be instructed according to section 8.1.3.1 (Missed Doses) and 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 night time (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 the use of rescue medication since the start of the Observation Period as well as his/her study medication compliance status during the Treatment Phase.
- 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 and endoscopy will be performed.
- After the start of treatment with the study medication in the Treatment Phase, the subject should present to the clinic in the morning as scheduled during the Treatment Phase.
- 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 the study investigators 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 principal 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 1 month 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 9.1.13.

1. Pretreatment event or adverse event (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 (20 mg tablets and matching placebo tablets) and Lansoprazole (30 mg capsules and matching placebo capsules) defined below. Study medication will be packaged in a blinded fashion.

8.1.1.1 Investigational drug

The chemical name of TAK-438 is:
1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-*1H*-pyrrrol-3-yl]-N-methyl methanamine monofumarate. The code name is TAK-438. The International Nonproprietary Name (INN) is vonoprazan. TAK-438 20 mg and matching placebo investigational drug is manufactured by Takeda Pharmaceutical Company, Osaka, Japan and will be supplied as pale red, 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 30 mg will have a dual supply chain. The Lansoprazole 30 mg for the study conducted in China is manufactured locally by Tianjin Takeda, Tianjin China. Lansoprazole 30 mg for all other countries and matching placebo for Lansoprazole 30 mg is manufactured by Takeda Pharmaceutical Company, Osaka, Japan. All Lansoprazole 30 mg and matching placebo will be supplied as a white colored capsule.

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 20 mg or placebo tablets and 20 Lansoprazole 30 mg or placebo capsules.

Each blister card will be labeled in a blinded fashion with 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
TAK-438 20 mg tablet	Pale red film-coated tablet scored on both sides	Takeda Pharmaceutical Company Ltd, Japan
TAK-438 20 mg matching placebo tablet	Pale red film-coated tablet scored on both sides	Takeda Pharmaceutical Company Ltd, Japan
Lansoprazole 30 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 30 mg matching placebo capsule	White capsule	Takeda Pharmaceutical Company Ltd, Japan

The TAK-438 tablets, the Lansoprazole and each 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.

8.1.1.4 Rescue Medication

During the study period including the screening period, those over-the-counter medication such as Gelusil (main ingredients are aluminum hydroxide, magnesium hydroxide and simethicone) or other bicarbonate based medication if available in the participating countries can be used as the rescue medication if the symptoms caused by acid reflux could not be tolerated by the subjects. The administration of rescue medication shall be in accordance to the package insert approved in the corresponding countries. Subjects shall be instructed to refrain from using rescue medication. Subjects shall contact the investigators if they would like to take the rescue medication at a dose higher than the approved ones in the local insert package.

The use of rescue medication shall be recorded in the subject daily diary.

For detailed rescue medication administration guideline at each country, please refer to the Appendix F.

8.1.2 Storage

TAK-438, Lansoprazole and each matching placebo investigational drug should be stored at 25°C; with excursions permitted 15°C to 30°C. Protect from moisture and humidity. 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

Each subject who meets all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive either once daily TAK-438 or Lansoprazole after breakfast via the IWRS.

Blinding will be achieved using double-dummy, therefore at each dosing time-point subjects will take 1 tablet and 1 capsule, one will be active and the other 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 2-8 weeks of treatment, thereafter those who that do not continue on to the TAK-438-305 study, will move into the follow-up phase 7-14 days after the last dose (with a phone call follow-up completed within 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 Treatment Phase the subject should be instructed to present to the clinic for study visit 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

Treatment Group	Dose	Treatment Description	
		Active	Placebo
A	20 mg TAK-438 QD	One 20 mg TAK-438 tablet	One placebo for 30 mg Lansoprazole capsule
B	30 mg Lansoprazole QD	One 30 mg Lansoprazole capsule	One placebo for 20 mg TAK-438 tablet

8.1.3.1 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 adverse events) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Adverse events 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 Visit 1 after the subject provides informed consent in order to obtain a subject number. When study eligibility is confirmed (ie, 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 20 mg tablet or matching placebo tablet, Lansoprazole 30 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.

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 1 Med ID number for dispensing to subjects for a 2 week visit and 2 Med ID numbers for a 4 week visit.

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 study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

Subjects will be assigned in a 1:1 ratio to TAK-438 and Lansoprazole treatment groups. Subject randomization will be stratified by baseline endoscopic findings (LA classification grades A/B vs C/D).

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 are 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 20 mg, Lansoprazole 30 mg, or their 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 TAK-438 20 mg, Lansoprazole 30 mg and their matching placebo 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 to be obtained will include date of birth, sex, race as described by the subject, smoking status, history of use alcohol and history of caffeine-containing drinks, history of H. pylori eradication therapy (e.g., triple therapy with PPI + amoxycillin + clarithromycin) and date of completion of such therapy (within the past 1 year/more than 1 year) of the subject at Observation Phase.

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 of the informed consent form. Medication history will include the following:

- PPIs.
- Histamine H_2 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.

BMI = weight (kg)/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 Trial 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/baseline examination. The condition (ie, diagnosis) should be described.

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. 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 3.5-19.5 mL (Visit1, Visit 2, Visit 3, Visit 4, Visit 5 or Visit 6/Early Discontinuation). Additionally, the volume of blood to be collected for Hepatitis B and C tests at the Screening visit is up to 10 mL. The approximate total volume of blood to be collected for the study is 43 ml to 83 mL depending on the time point of completing the study. 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	Urine sugar (qualitative)
Hemoglobin	AST(*)	
Hematocrit	GGT Gastrin(*) Pepsinogen I/II(*) ($)	
Platelets	Total bilirubin(*)	**Hepatitis B and C Analysis(#)**
White blood cell fractions (neutrophils, eosinophils, basophils, monocytes, lymphocytes)	Direct bilirubin(*) LDH CK (CPK) Albumin Total protein Creatinine BUN Uric acid Total cholesterol Triglycerides(*) Glucose(*) Potassium Sodium Magnesium Calcium Inorganic phosphorus Chloride Serum iron Vitamin B_{12}	HBsAg HCV-antibody HCV-antigen(+) HCV-RNA(+)

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.

If subjects 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. 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 during the Treatment Phase.

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*:

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

Intrauterine devices (IUDs):

- 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 and matching placebo) 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 Determination of H. pylori infection status using breath test

To obtain information on H. pylori infection that reportedly could affect the onset of erosive esophagitis, H.pylori infection status will be measured. To establish H. pylori infection status a ^{13}C urea breath test or ^{14}C urea breath test will be performed. Exhaled air samples will be taken in accordance with instructions for use of locally available testing kits for H. pylori infection status determination.

9.1.13 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:

- 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.

9.1.14 Documentation of Randomization

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

If the subject is found to be not eligible for randomization/treatment 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 20 mg or Lansoprazole 30 mg 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 via the IWRS should be documented in the subject's medical record and/or eCRF.

9.1.15 CCI

CCI

CCI

CCI

Table 9.c Severity of Subjective Symptoms

CCI

9.1.16 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 the current esophageal erosions 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 subject's lesion (erosive esophagitis) should be classified based on the LA classification (Table 9.d).

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

Mucosal break meaning: 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

Classification of Barrett's mucosa should be in accordance with the following criteria:

- At Visit 1 (within 14 days of Visit 2 [Day 1]): present (3 cm or greater), present (less than 3 cm), absent, unknown.
- Other time points for endoscopy: increased, unchanged, reduced, disappeared, unknown.

Classification of esophageal hiatal hernia should be in accordance with the following criteria:

- At Visit 1 (within 14 days of Visit 2 [Day 1]): present (2 cm or greater), present (less than 2 cm), absent, unknown.

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

To ensure the accuracy of the EE evaluation according to LA grading, a 2nd review process of the endoscopy images will be established at each site. The 1st reviewer i.e. the endoscopist should take sufficient images or videotape the process at each endoscopic examination. The 2nd reviewer will evaluate the EE LA grading according to the endoscopic images.

- Preferably, the principal investigator performs as the 2nd reviewer and conducts the 2nd review in a timely manner after the endoscopy is performed by the 1st reviewer who is a sub-investigator in this study.
- In cases where the principal investigator is the 1st reviewer, a sub-investigator at the same site can be delegated as the 2nd reviewer and conducts the 2nd review in a timely manner.
- Only investigators (either principal investigators or sub-investigators) can be delegated as the 2nd 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

9.2 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 (TAK-438 20 mg, Lansoprazole 30 mg and matching placeboes) (e.g. 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 reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

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

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

All subjects will be assessed for the following from the informed consent before the start of the study medication for the Treatment Phase (Visit 2). All subjects will be examined for eligibility for entry in the study in accordance with the primary inclusion and exclusion criteria as per Sections 7.1 and 7.2. See Section 9.1.13 for procedures for documenting screening or randomization failures.

Informed consent could be obtained from the subjects within 28 days before the start of the Treatment Phase (Visit 2). And once the ICF is signed, registration in IWRS and collection of PTE/AE shall be started. Endoscopy, Hepatitis B and C tests, and ECG shall be performed within 14 days prior to randomization visit. However, all the other procedures for eligibility check must be completed within Observation Phase which is **3 to 7 days before randomization day** (Visit 2) in order to obtain a baseline data for the subject including the EE symptoms recorded in patient diaries.

If fasting is not the routine clinical practice of the site, the procedures requiring fasting will be performed at another visit.

Procedures to be completed at Visit 1 include:

- Informed consent obtained.
- Access IWRS to obtain subject number.

- EQ-5D-5L questionnaire. In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures after the subject provides Informed Consent and are registered in the IWRS.
- Eligibility assessment (review Inclusion/exclusion criteria).
- Demographics, vital signs, medical and medication history and concurrent medical conditions.
- Concomitant medication assessment.
- Height and weight. BMI will be calculated during data analysis.
- Physical examination.
- ECG procedure.
- Fasting clinical laboratory examination (urinalysis, hematology, serum chemistry *excluding* gastrin & pepsinogen I/II).
- Urine pregnancy test (in females of childbearing potential only).
- FSH (when menopause is suspected).
- Hepatitis B and C analysis at the local laboratory or the central laboratory depending on the site capability.
- Guidance on the avoidance of pregnancy and ova donation.
- Endoscopy.
- Instructions on how to make entries in the subject diary, provision of the diary, and commencement of diary entry.
- Pretreatment events assessment.
- Prescribe rescue medication.
- Dispense Medical Emergency Card.

9.3.2 Visit 2: Treatment Phase (Randomization, Day1)

Randomization will take place on Day 1. The following procedures will be performed and documented during Study Randomization:

- EQ-5D-5L questionnaire. In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Eligibility assessment (review Inclusion/exclusion criteria).
- Physical examination.
- Vital signs.
- Urine pregnancy test (in females of childbearing potential only).

- ^{13}C or ^{14}C Urea Breath test for H. pylori.
- Fasting clinical laboratory examination (Serum gastrin, pepsinogen I, II and I/II ratio).
- Concomitant medications assessment.
- Collect daily subject diary since Visit 1 and review.
- Adverse Event/ Pretreatment Event assessment.

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.
- Dispense study medication (first daily dose to be taken after completion of scheduled study assessments and before subject leaves the study site) and instruct the subject on correct self-administration for subsequent daily doses as described in Section 6.1.
- Dispense new diary and re-instruct on completion and compliance if needed.
- Prescribe rescue medication if needed.
- Guidance on the avoidance of pregnancy and ova donation.

For ineligible subjects, the procedure for documenting Screening failures is provided in Section 9.1.13.

9.3.3 Visit 3: Treatment Phase (Day 15 / Week 2)

Procedures to be completed at Visit 3 include:

- EQ-5D-5L questionnaire. In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Physical examination.
- Vital signs.
- Fasting clinical laboratory tests (hematology, chemistry including gastrin & pepsinogen I/II, urinalysis).
- Urine pregnancy test (in females of childbearing potential only).
- ECG procedure (to be performed in those in whom endoscopic healing has been confirmed during visits involving endoscopy).
- Endoscopy.
- Review treatment compliance, re-instruct the subject if appropriate.
- Collect subject diary since visit 2 and review, dispense new diary and re-instruct the subject if appropriate.

- Guidance on the avoidance of pregnancy and ova donation.
- Adverse Event assessment.
- Concomitant medications assessment.
- Register the subject study completion in the IWRS if endoscopic healing of erosive esophagitis has been confirmed after 2 weeks of treatment.
- Initiate informed consent process for TAK-438_305 (only if endoscopic healing is confirmed and if the TAK-438_305 study has not been completed).
- Collect the study drugs dispensed at the last visit including the used packages and dispense additional Treatment Phase drug via the IWRS (only if endoscopic healing of erosive esophagitis has not been confirmed after 2 weeks of treatment).
- Prescribe rescue medication if needed.

9.3.4 Visit 4: Treatment Phase (Day 29 / Week 4)

Procedures to be completed at Visit 4 include:

- EQ-5D-5L questionnaire. In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Physical examination.
- Vital signs.
- Fasting clinical laboratory tests (hematology, chemistry including gastrin & pepsinogen I/II, urinalysis).
- Urine pregnancy test (in females of childbearing potential only).
- Endoscopy.
- ECG procedure (to be performed in those in whom endoscopic healing has been confirmed during visits involving endoscopy).
- Guidance on the avoidance of pregnancy and ova donation.
- Review treatment compliance, re-instruct the subject if necessary and dispense investigational drugs.
- Collect completed diary since Visit 3, review completion compliance, and dispense new daily diary.
- Adverse Event assessment.
- Concomitant medications assessment.
- Register the subject study completion in the IWRS if endoscopic healing of erosive esophagitis has been confirmed after 4 weeks of treatment.

- Initiate informed consent process for TAK-438_305 (only if endoscopic healing is confirmed and if the TAK-438_305 study has not been completed).
- Collect the study drugs dispensed at the last visit including the used packages and dispense additional Treatment Phase drug via the IWRS (only if endoscopic healing of erosive esophagitis has not been confirmed after 4 weeks of treatment).
- Prescribe rescue medication if needed.

9.3.5 Visit 5: Treatment Phase (Day 43 / Week 6)

Procedures to be completed at Visit 5 include:

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

9.3.6 Visit 6: End of Treatment (Day 57 / Week 8) or Study Early Discontinuation (within 14 days after last dose)

The Final Visit will be performed on Visit 6 (Day 57), or at the Study early discontinuation visit. The following procedures will be performed and documented:

- EQ-5D-5L questionnaire. In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Physical examination.
- Vital signs.
- Collect completed diary since visit 4, review completion compliance.
- Fasting clinical laboratory tests (hematology, chemistry including gastrin & pepsinogen I/II, urinalysis).
- ECG procedure.
- Urine pregnancy test (in females of childbearing potential only).
- Endoscopy.
- Review treatment compliance.
- Adverse Event assessment.
- Concomitant medications assessment.
- Guidance on the avoidance of pregnancy and ova donation.

- Initiate informed consent process for TAK-438_305 (only endoscopic healing is confirmed and if the TAK-438_305 study has not been completed).
- Register the subject study discontinuation or completion via IWRS.
- Collect the study drugs dispensed at the last visit including the used packages.

For all randomized subjects, the investigator must complete the End of Study eCRF page.

9.3.7 Follow-up

The study site staff will follow up with a phone call (only for subjects that do not continue on to the TAK-438_305 study) between 7 and 14 days after the last dose of study medication. Any new AEs will be recorded in the eCRFs and subject's medical record. Follow-up will begin the first day after the Final Visit/Early Termination and will continue until 14 days post treatment.

9.3.8 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.

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 (i.e. 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 (e.g. 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 (e.g. 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 (e.g. "worsening of…").
- If a subject has a pre-existing episodic condition (e.g. 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 (e.g. "worsening of…").
- If a subject has a degenerative concurrent condition (e.g. 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 (e.g. "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 (e.g. "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 (e.g. "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 (e.g. 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 adverse events.

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 adverse events.

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 (e.g. 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 Interrupt–d - 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 (e.g. 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

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 phone call will be made to each subject 7 to 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 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 as an SAE

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

10.3 Follow-up of SAEs

If information 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.

11.0 STUDY-SPECIFIC COMMITTEES

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

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (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 unblinding 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 study medication and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment. The primary efficacy endpoint and the secondary efficacy endpoints 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 study medication and will be based on the treatment received.

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, and 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 Week 8 healing rate of erosive esophagitis, a 2-sided 95% confidence interval (CI) will be constructed for the difference between TAK-438 and Lansoprazole treatment groups. If the lower bound of this CI is $\geq$-10%, non-inferiority for TAK-438 relative to Lansoprazole will be declared. Week 8 healing rate of erosive esophagitis will also be analyzed in subgroups defined by baseline LA classification grades A/B vs C/D.

The secondary endpoints of the Week 2 healing rate of erosive esophagitis and the Week 4 healing rate of erosive esophagitis will be compared between TAK-438 and Lansoprazole treatment groups by constructing a 2-sided 95% CI for the healing rate difference.

The additional endpoints related to GERD symptoms during treatment 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.

Another additional endpoint of percentage of days without rescue medication during the treatment phase will be compared between treatment groups using Wilcoxon rank-sum test.

Statistical inference will be performed at a 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 fashion: The primary endpoint of Week 8 healing rate will be first tested for non-inferiority; if non-inferiority with regard to the primary endpoint is established, then the secondary endpoint of Week 2 healing rate will be tested for superiority.

13.1.4 Handling of Missing Data

For the primary efficacy endpoint of Week 8 healing rate of erosive esophagitis, FAS subjects assessed as LA classification of Grade O based on the endoscopy data obtained on Day 2 or after (where Day 1 is the date of first dose of study medication) will be considered as healed subjects. Other FAS subjects will be considered as 'not healed'. Missing data will not occur in the analysis of the primary endpoint.

For the secondary endpoint of Week 2 healing rate of erosive esophagitis, FAS subjects who have no endoscopy data during Day 2 to Day 21 will be excluded from the analysis. FAS subjects assessed as LA classification of Grade O based on the endoscopy data obtained between Day 2 and Day 21 will be considered as healed subjects. Other FAS subjects will be considered as 'not healed'.

For the secondary endpoint of Week 4 healing rate of erosive esophagitis, FAS subjects who have no endoscopy data during Day 2 to Day 42 will be excluded from the analysis. FAS subjects assessed as LA classification of Grade O based on the endoscopy data obtained between Day 2 and Day 42 will be considered as healed subjects. Other FAS subjects will be considered as 'not healed'.

Further details will be described in the Statistical Analysis Plan.

13.1.5 Safety Analysis

Safety analysis will be performed using the safety analysis set.

The number and percentage of subjects with treatment-emergent adverse events 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 adverse events 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 8 healing rate is 94.7% for both TAK-438 and Lansoprazole, and assuming that the dropout rate is up to 20%, a sample size of 160 subjects per group will provide 90% power to establish non-inferiority using a 2-sided 95% CI with a -10% non-inferiority margin. A sample size of 240 subjects per group is planned in order to provide more subjects with healed EE to the subsequent maintenance study TAK-438_305 and to provide adequate subjects for regulatory requirements in various countries.

The assumption of the 94.7% true healing rate is based on Phase 2 studies TAK-438/CCT-001 and TAK-390MR/CCT-001.

In a randomized, double-blind study in US (M87-092), the difference in Week 8 EE healing rate between lansoprazole 30 mg and placebo groups was 42.9% with a lower limit of 27.8% for the 2-sided 95% confidence interval. Based on this study, the non-inferiority 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 (i.e. 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 (i.e. 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 (e.g. 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 (e.g. 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 (i.e. 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

	Screening Phase	Treatment Phase						Follow-up Phase
Timing	**At start of Signing ICF**	**At start of study drug**	**After 2 weeks**	**After 4 weeks**	**After 6 weeks**	**After 8 weeks**		
Study Day:	**Days –28 to –1 (Observation Period: Day -7 to -3)**	**Day 1*** **(e)**	**Week 2 (Day 15) (e)**	**Week 4 (Day 29) (e)**	**Week 6 (Day 43)**	**Week 8 (Day 57) (e)**	**At study early discontinuation**	**Follow-Up phone call (k)**
Visit Windows (Days)			**±3**	**±3**	**±3**	**±3**	**Within 14 days after the last dose**	**7 – 14 days after the last dose**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**		
Informed consent	X		X(j)	X(j)		X(j)		
Inclusion/exclusion criteria	X(a)	X						
Demographics/medical history	X(a)							
Medication history	X(a)							
Physical examination	X(a)	X	X	X		X	X	
Vital signs	X(a)	X	X	X		X	X	
Weight, height and BMI	X(a)							
Concomitant medications	X(a) ←						→ X	
Concurrent medical conditions	X(a)							
Clinical laboratory tests (b)	X (a)		X	X		X	X	
Liver function test (p)					X			
Serum gastrin/ pepsinogen I/II levels		X	X	X		X	X	
H. pylori breath test		X						
Guidance on avoidance of pregnancy and ova donation	X(a)	X	X	X	X	X	X	
FSH	X(c)							
Urine pregnancy test (hCG) (d)	X(a)	X	X	X		X	X	
Electrocardiogram (ECG)	X (f)		X (h)	X (h)		X	X	
Hepatitis B and C tests	X (f, n)							
Dispense / collect / review Daily diary (symptom collection and rescue medication use), and complete EQ-5D-5L questionnaire (m)	X(a)	X	X	X		X	X	
Dispense the Medical Emergency Card	X							
Endoscopy	X (f)		X (l)	X (l)		X (l)	X	
Prescribe rescue medication (o)	X	X	X	X				
Obtain subject number via IWRS	X							
Randomization via accessing IWRS		X(g)	X(l)	X(l)		X(l)		
Dispense investigational drug via IWRS		X (g)	X (i)	X(i)				
Collect the drug dispensed			X	X		X	X	
Review study medication compliance			X	X		X	X	

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

	Screening Phase	Treatment Phase						Follow-up Phase
Timing	**At start of Signing ICF**	**At start of study drug**	**After 2 weeks**	**After 4 weeks**	**After 6 weeks**	**After 8 weeks**		
Study Day:	**Days –28 to –1 (Observation Period: Day -7 to -3)**	**Day 1* (e)**	**Week 2 (Day 15) (e)**	**Week 4 (Day 29) (e)**	**Week 6 (Day 43)**	**Week 8 (Day 57) (e)**	**At study early discontinuation**	**Follow-Up phone call (k)**
Visit Windows (Days)			**±3**	**±3**	**±3**	**±3**	**Within 14 days after the last dose**	**7 – 14 days after the last dose**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**		
Access IWRS for study discontinuation or completion if applicable			X	X		X	X	
AE/PTE assessment	←	—	—	—	—	—	—	→
Follow-up phone call (k)								X

* The day of first investigational drug administration for Treatment period is Day 1. The day before first investigational drug administration for Treatment period is Day -1.
(a) The visit window for those annotated procedures is **3 to 7 days** prior to the start of the study treatment. During this period, the baseline observation of EE symptoms recorded in the patient diary will be completed.
(b) Hematology, serum chemistry, and urinalysis.
(c) Only if menopause is suspected.
(d) Urine HCG test to be performed only in female subjects of childbearing potential.
(e) During the treatment phase, the subject should be instructed to present to the clinic without taking the study medication when instructed (ie, 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). The daily dose of the study medication will be taken by the subject after completion of assessments on the day of study visits.
(f) The visit window for assessment of Hepatitis B and C, and endoscopy is defined as Day -14 to Day -1. However, any reliable, documented results available from an endoscopy performed in a routine clinical setting within 14 days prior to randomization (Day 1) (before signing of informed consent) will be accepted instead, given the invasive nature of the procedure. Additionally, reliable, documented results available from an ECG performed in a routine clinical setting, and tests for Hepatitis B and C, within 14 days prior to randomization (Day 1) (before signing of informed consent) will be accepted.
(g) The first dose of the study medication will be taken by the subject after completion of scheduled study assessments and before subject leaves the study site. Access the IWRS for the randomization before start administration.
(h) To be performed in those in whom endoscopic healing has been confirmed during visits involving endoscopy.
(i) To be performed in those in whom endoscopic healing has not been confirmed.
(j) If appropriate initiate consent process for TAK-438_305 study.
(k) Only for subjects that do not continue on to the TAK-438_305 study.
(l) At the time point where endoscopic healing of erosive esophagitis has been confirmed after 2, 4, or 8 weeks of treatment, the subject will complete the study, and may be eligible for randomization of the long-term EE maintenance study (TAK-438_305) after signing of further informed consent.
(m) EQ-5D-5L questionnaire shall be the first priority in all procedures (except signing the ICF) at each visit.
(n) Hepatitis B and C analysis in accordance with Section 9.1.8 Table 9.a will be conducted at the local laboratory or central laboratory depending on the site capability.
(o) Rescue medication is prescribed by the investigators at the start of the Screening visit and, if needed, at the subsequent visits.
(p) Liver function tests include ALT, AST, total bilirubin and direct bilirubin.

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

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

Appendix C Elements of the Subject Informed Consent

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

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

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

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. 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

Appendix F Rescue Medication Guideline

A guideline of commonly used medications which may be used as rescue medications in each of the 4 countries is presented in the table below. The local insert package will be distributed to sites once sites are activated. If the listed rescue medications are not available, please contact Quintiles/Takeda Medical Advisor for confirmation of available brand. During the rescue medication administration, please note:

1. Subjects should be instructed to take rescue medication only after consultation with the investigator;
2. The administration of rescue medication shall be in accordance to the local package insert;
3. For aluminum based medications, an interval of at least 2 hours must be maintained between administration of study medication (TAK-438 or lansoprazole) and rescue medication;
4. When rescue medication has been taken for more than 7 consecutive days, or more than 25% of the days in whole study period, investigator should discuss with CRO/sponsor and decide whether to withdraw the subject.

Country/Region	Brand Name	Constituents
China	Hydrotalcite Chewable Tablets	Hydrotalcite 0.5g
	Hydrotalcite Talcid	Hydrotalcite 0.5g
	Gaviscon Tablets	Aluminium hydroxide 0.05g, Magnesium trisilicate 0.0125g, Alginic acid 0.25g
Malaysia	Gelusil	$Al(OH)_3$ 250 mg, Mg trisilicate 500 mg
	Eno	Anhydrous citric acid, Na bicarbonate, Na carbonate
	Gaviscon	Na alginate 250mg, Na bicarbonate 133.5mg, Ca carbonate 80mg.
	Noriflux	Na alginate, Na bicarbonate, Ca carbonate
Korea	Amphojel tab	Aluminum hydroxide
	Almagel suspension/tab	Almagate
	Gelfos	Aluminum phosphate colloidal 12.38g /20g
	Lamina-G sol	Sodium alginate 5g/100 ml
Taiwan	Gowell Tablets “WECAM”	Aluminum Dihydroxyal (50.000 mg), Metamagnesium aluminum silicate(450.000 mg)
	Alginos oral suspension	Alginate Sodium 50mg, Sodium Bicarbonate 26.7mg, Calcium Carbonate 16mg
	NACID	Aluminum Magnesium Carbonate Hydroxide Tetrahydrate Synthetic 500mg

Appendix G Detailed Description of Amendments to Text

Page 2, Section 1.1 Contacts

Existing Text

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

Revised Text

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

Rationale for Amendment

To prevent repetitious amendments for staff changes at Quintiles, a generic reference contact has been used. The Responsible Medical Officer has been changed.

Page 3, Section 1.2 Approvals

Existing Text

PPD

Revised Text

PPD

Rationale for Amendment

The Responsible Medical Officer has been changed. The list of approvers has been updated to reflect company procedure.

Page 12, Study Summary: Main Exclusion Criteria

Existing Text

Subjects who have hypersensitivity to TAK-438 or related compounds, 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, 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.

Revised Text

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, **or 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.

Rationale for Amendment

An exclusion criterion for subjects with a hypersensitivity to lansoprazole, administered during the study, has been added to the Study Summary and to Section 7.4 (Exclusion Criteria), and the exclusion of subjects with an LFT > ULN has been added to the Study Summary to align with the current text in Section 7.4.

Page 18, Page 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 ulcer/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 Amendment

To provide further knowledge and data on TAK-438, a summary of phase 3 clinical data has been added to the Background section.

Page 27, Section 7.1 Inclusion Criteria

Existing Text

3. The subject has been confirmed in an endoscopy to have erosive esophagitis, i.e. the LA classification grades A to D within *7* days of the start of the Day 1 (Visit 2).

Revised Text

3. The subject has been confirmed in an endoscopy to have erosive esophagitis, i.e. the LA classification grades A to D within 14 days of the start of the Day 1 (Visit 2).

Rationale for Amendment

The window period before randomization for endoscopic confirmation of erosive esophagitis has been extended to 14 days to reduce screen and prescreen failure.

Page 46, Section 9.1.16 Endoscopy

Existing Text

Classification of Barrett's mucosa should be in accordance with the following criteria:

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

Classification of esophageal hiatal hernia should be in accordance with the following criteria:

- At Visit 1: present (2 cm or greater), present (less than 2 cm), absent, unknown.

The investigator (or designee) will record the results of endoscopy (including results of the LA classification and other gradings) performed promptly in the subject's medical record.

Revised Text

Classification of Barrett's mucosa should be in accordance with the following criteria:

- At Visit 1 **(within 14 days of Visit 2 [Day 1])**: present (3 cm or greater), present (less than 3 cm), absent, unknown.
- Other time points for endoscopy: increased, unchanged, reduced, disappeared, unknown.

Classification of esophageal hiatal hernia should be in accordance with the following criteria:

- At Visit 1 **(within 14 days of Visit 2 [Day 1])**: present (2 cm or greater), present (less than 2 cm), absent, unknown.

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

Rationale for Amendment

Wording has been added to qualify when endoscopy should be performed during the Screening period (Visit 1). Additionally, text has been added to reflect clinical practice in recording 'No mucosal breaks' in medical records, as Grade O is not routinely used.

Page 47, Section 9.3.1 (Screening Phase)

Existing Text

Informed consent could be obtained from the subjects within 28 days before the start of the Treatment Phase (Visit 2). And once the ICF is signed, registration in IWRS and collection of PTE/AE shall be started. However, all the other procedures for eligibility check must be completed within Observation Phase which is **3 to 7 days before randomization day** (Visit 2) in order to obtain a baseline data for the subject including the EE symptoms recorded in patient diaries.

Revised Text

Informed consent could be obtained from the subjects within 28 days before the start of the Treatment Phase (Visit 2). And once the ICF is signed, registration in IWRS and collection of PTE/AE shall be started. **Endoscopy, Hepatitis B and C tests, and ECG shall be performed within 14 days prior to randomization visit.** However, all the other procedures for eligibility check must be completed within Observation Phase which is **3 to 7 days before randomization day** (Visit 2) in order to obtain a baseline data for the subject including the EE symptoms recorded in patient diaries.

Added Text

- **Dispense Medical Emergency Card.**

Rationale for Amendment

The window period before randomization for endoscopic confirmation of erosive esophagitis has been extended to 14 days to reduce screen and prescreen failure. As ECG, and tests for Hepatitis B and C, is performed at the time of endoscopy, this window period has been extended to 14 days, too.

The procedure: Dispense the Medical Emergency Card, in the Screening Visit, has been added to address an audit finding. Many investigators were not clear when the card shall be dispensed to the patients.

Page 75, Appendix A Schedule of Study Procedures

Existing Text

FSH	X(*a*)							

(f) The visit window for assessment of *ECG,* Hepatitis B and C, and endoscopy is defined as Day -7 to Day -1. However, 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 accepted instead, given the invasive nature of the procedure.

Added and Revised Text

FSH	X(**c**)							

Dispense the Medical Emergency Card	**X**							

(f) The visit window for assessment of Hepatitis B and C, and endoscopy is defined as Day **-14** to Day -1. However, any reliable, documented results available from an endoscopy performed in a routine clinical setting within **14** days prior to randomization (Day 1) (before signing of informed consent) will be accepted instead, given the invasive nature of the procedure. **Additionally, reliable, documented results available from an ECG performed in a routine clinical setting, and tests for Hepatitis B and C, within 14 days prior to randomization (Day 1) (before signing of informed consent) will be accepted.**

Rationale for Amendment

The window period before randomization for endoscopic confirmation of erosive esophagitis has been extended to 14 days to reduce screen and prescreen failure. As ECG, and the tests for Hepatitis B and C, is performed at the time of endoscopy, this window period has been extended to 14 days, too. Footnote for FSH assessment has been corrected.

Amendment 05 to A Randomized, Double-Blind, Double-Dummy Phase 3 Study to Evaluate the Efficacy and Safety of Oral Once-Daily administration of TAK-438 20 mg compared to Lansoprazole 30 mg in the Treatment of Subjects with Erosive Esophagitis

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	05-Sep-2016 11:30 UTC
	Medical Monitor Approval	06-Sep-2016 04:38 UTC
	Biostatistics Approval	06-Sep-2016 10:20 UTC