Title: A Randomized Double-Blind, Double-Dummy, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-438 20 mg Compared to Lansoprazole 30 mg Once- or Twice-Daily in the Treatment of Endoscopically Confirmed Duodenal Ulcer Subjects With or Without Helicobacter pylori Infection

NCT Number: NCT03050359

Protocol Approve Date: 30 August 2018

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 (PPD) or company confidential information (CCI).

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 TAK-438 20 mg Compared to Lansoprazole 30 mg Once- or Twice-Daily in the Treatment of Endoscopically Confirmed Duodenal Ulcer Subjects With or Without *Helicobacter pylori* Infection

## Comparison of TAK-438 (Vonoprazan) to Lansoprazole in the Treatment of Duodenal Ulcer Subjects With or Without *Helicobacter pylori* Infection

| | | | |
|---|---|---|---|
| **Sponsor:** | Takeda Development Center Asia Pte Ltd<br>21 Biopolis Road, Nucleos North Tower, Level 4, Singapore 138567 | | |
| **Study Number:** | TAK-438_304 | | |
| **IND Number:** | Not Applicable | **EudraCT Number:** | Not Applicable |
| **Compound:** | TAK-438 | | |
| **Date:** | 30 August 2018 | **Amendment Number:** | 03 |

**Amendment History**

| Date | Amendment Number | Amendment Type | Region |
|---|---|---|---|
| 21 Nov 2012 | Initial Protocol | Not applicable | Asia Pacific |
| 27 Sep 2016 | 01 | Substantial | Asia Pacific |
| 21 Dec 2016 | 02 | Substantial | Asia Pacific |
| 30 Aug 2018 | 03 | 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 investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

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

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

## 1.2 Approval

**REPRESENTATIVES OF TAKEDA**

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

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

**SIGNATURES**

PPD

## 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 03 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reason for this amendment is to reduce the sample sizes of the overall population and Chinese subpopulation due to reduction in the dropout rate and change in the proportion of the Chinese subpopulation.

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

For specific descriptions of text changes and where the changes are located, see Appendix E.

**Changes in Amendment 03**

1. Removal of reference to Study TAK-438_115 as part of rationale for study design.
2. Subjects with no ulcer healing at Week 6 could be treated with another course of PPI or other anti-acid secretory agents or antibiotics, at the discretion of the investigator.
3. Exclusion criterion 10 concerning subjects participating in another clinical study within 30 days of Visit 1, is deleted.
4. Exclusion criterion 12 is deleted to allow subjects with ulcer size >2 cm in any diameter and those with >3 separate duodenal ulcers to enter the study.
5. A footnote is added to Table 9.b to clarify that subjects with negative hepatitis C virus antibody test results may be randomized before hepatitis C-viral load-RNA test results are available.
6. Procedure for retesting of abnormal liver function tests, and a clarification concerning elevated serum gastrin and pepsinogen I and II levels, which are physiological responses to increased gastric pH and the suppression of gastric acid secretion.
7. The liver function test at Visit 3 is clarified as a fasting clinical laboratory test.
8. The sample sizes for the overall study population and the Chinese subpopulation have been recalculated on the basis of an estimated dropout rate of 10% (previously 20%), resulting in sample size re-estimation.
9. *H pylori* eradication data from this study (TAK-438_304) will be pooled with data from TAK-438_302.
10. Study-specific endoscopy may be waived at the investigator's discretion if endoscopy with associated images has been performed within 14 days before Day 1.
11. Time of dosing of TAK-438 amended to after breakfast or dinner (previously after breakfast only).
12. Clarification of follow-up guidance on excluded medications and treatments in Table 7.a, amended for proton pump inhibitors, histamine $H_2$ receptor antagonists, insulin, antidiabetic agents, and antibiotics.

13. Provision has been made for the use of premedication for endoscopy to be provided at investigator's discretion.
14. Formulation of bismuth for use in Korean sites is specified in relevant sections of the protocol.
15. Provision for serum gastrin follow-up for all subjects.

## TABLE OF CONTENTS

## LIST OF IN-TEXT TABLES



## LIST OF IN-TEXT FIGURES



## LIST OF APPENDICES

## 2.0 STUDY SUMMARY

| | | |
|---|---|---|
| **Name of Sponsor(s):**<br>Takeda Development Center Asia Pte. Ltd. | **Compound:**<br>TAK-438 (vonoprazan) | |
| **Title of Protocol:** A Randomized Double-Blind, Double-Dummy, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-438 20 mg Compared to Lansoprazole 30 mg Once- or Twice-Daily in the Treatment of Endoscopically confirmed Duodenal Ulcer Subjects with or without *Helicobacter pylori* infection | **IND No.:**<br>Not applicable | **EudraCT No.:**<br>Not applicable |
| **Study Number:** TAK-438_304 | **Phase:** 3 | |

**Study Design:**

This is a phase 3, multicenter, randomized, double-blind, double-dummy, parallel-group, noninferiority study of TAK-438 versus lansoprazole in subjects who have endoscopic evidence of duodenal ulcer with or without *Helicobacter pylori* (*H pylori*) infection. Randomization will be stratified by *H pylori* infection status.

Subjects whose eligibility is confirmed during the 28-day screening period will complete Visit 2/ Day 1 procedures performed as listed in Appendix A to ensure continued eligibility. Dosing will begin after randomization on Day 1 and continue for up to 6 weeks. Study drug administration will depend on the *H pylori* infection status of the subject, and include quadruple therapy for the first 2 weeks in *H pylori* infected (HP+) subjects.

Treatment Period – Dose and Regimen:

- HP+ subjects will take TAK-438 20 mg or lansoprazole 30 mg (blinded with matching placebo) twice daily (BID) in conjunction with bismuth-containing quadruple therapy for 2 weeks (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg [equivalent to 220 mg bismuth], BID). After 2 weeks of eradication therapy, subjects will be required to take only TAK-438 or lansoprazole once daily (QD) for up to 4 weeks (ie, up to a total of 6 weeks treatment). The subjects will remain in the same treatment arm throughout the study duration.
- Non-*H pylori* infected *(HP-)* subjects will take TAK-438 20 mg or lansoprazole 30 mg (blinded with matching placebo) QD for up to 6 weeks.

For all subjects, ulcer healing rates will be assessed by endoscopy at Weeks 4 and 6 of treatment. With or without endoscopic evidence of duodenal ulcer healing, the treatment duration of the study is no more than 6 weeks.

Subjects (HP+ or HP-) with endoscopic healing of duodenal ulcer(s) at Week 4 or Week 6 will discontinue treatment at that time, and subjects without ulcer healing by Week 6 of treatment period will discontinue treatment at Week 6. All subjects will participate in a gastrin recovery and safety follow-up.

Follow-up Period:

The subjects to be followed up will include both HP+ and HP- subjects, with or without confirmed ulcer healing during the treatment period.

The monitoring of the recovery of serum gastrin-17 level and pepsinogen I/II ratio in the follow-up period will be for a maximum of 4 weeks. The follow-up period ends when the recovery of serum gastrin-17 level and pepsinogen I/II ratio is confirmed or at the end of the 4-week follow-up period.

All HP+ subjects will provide a follow-up $^{13}$C-UBT at the F-2 visit to ascertain HP eradication status.

For subjects with no ulcer healing at Week 6 of treatment, the investigator may follow local clinical practice and these subjects may be treated with another course of PPI or other anti-acid secretory agents or antibiotics, during the safety follow-up period

**Primary Objective:**

To demonstrate the noninferior efficacy of TAK-438 versus lansoprazole in the treatment of subjects with duodenal ulcer.

**Secondary Objectives:**

To demonstrate the noninferiority of *H pylori* eradication with TAK-438 versus lansoprazole.
To compare the safety of TAK-438 versus lansoprazole in subjects with duodenal ulcer.

**Subject Population:** Male and nonpregnant, nonlactating female subjects at least 18 years of age (or the minimum legal age of consent, if that is >18 years), with duodenal ulcer(s).

| **Number of Subjects:** | **Number of Sites:** |
|---|---|
| Per treatment group: 265<br>TAK-438 group: approximately 265 randomized<br>Lansoprazole group: approximately 265 randomized<br>Estimated total: 530 randomized subjects | Estimated total: approximately 60 in Asia |
| **Dose Levels:**<br><u>TAK-438 group:</u><br>*HP+ subjects*<br>(Day 1 to Day 14): TAK-438 20 mg + lansoprazole placebo BID for 2 weeks, given in conjunction with bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg BID) for 2 weeks<br>(Day 15 to Day 42): TAK-438 20 mg + lansoprazole placebo QD for up to 4 weeks<br>*HP- subjects*<br>(Day 1 to Day 42): TAK-438 20 mg + lansoprazole placebo QD for up to 6 treatment weeks<br><u>Lansoprazole group:</u><br>*HP+ subjects*<br>(Day 1 to Day 14): lansoprazole 30 mg + TAK-438 placebo BID for 2 weeks given in conjunction with bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg BID) for 2 weeks<br>(Day 15 to Day 42): lansoprazole 30 mg + TAK-438 placebo QD for up to 4 weeks<br>*HP- subjects*<br>(Day 1 to Day 42): lansoprazole 30 mg + TAK-438 placebo QD for up to 6 treatment weeks | **Route of Administration:**<br>Oral |
| **Duration of Treatment:**<br>Up to 6 weeks | **Period of Evaluation:**<br>Up to 14 weeks<br>Screening: up to 4 weeks<br>Treatment period: up to 6 weeks<br>Follow-up period: up to 4 weeks |

**Main Criteria for Inclusion:**

Subjects with endoscopic evidence of one or more active duodenal ulcer(s) (ie, mucosal defects with white coating [including cases associated with blood coagula]) measuring 5 mm or larger in longest diameter within 14 days prior to randomization, who have provided (or when applicable their legally acceptable representative has provided) informed consent, who are capable of understanding and complying with the study procedures and who agree to use appropriate contraception.

**Main Criteria for Exclusion:**

Subjects who have hypersensitivity to TAK-438, or related compounds or to proton pump inhibitors (PPIs), clarithromycin, amoxicillin, bismuth or lansoprazole; or who have a significant history of CNS, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine or hematological disease; or subjects with a liver function test > upper limit of normal; or who have any significant results from physical examinations, or clinical laboratory results as deemed by the investigator. Subjects that have received HP eradication therapy 30 days prior to visit 2 or endoscopic therapy within 30 days prior to visit 1 or also have active gastric ulcer(s) are also excluded.

**Main Criteria for Evaluation and Analyses:**

**1. Primary Endpoint:**

- The primary endpoint for this study is the percentage of subjects with endoscopically confirmed healing* of duodenal ulcer(s) at Week 4 or 6*.

*Rate of endoscopic healing: defined as the proportion of subjects in whom the disappearance of all white coats associated with duodenal ulcers has been endoscopically confirmed.

**2. Secondary Endpoints:**

- Percentage of HP+ subjects with successful *H pylori* eradication after 4 or 6 weeks of treatment, as determined by $^{13}$C-UBT at F-2.
- Percentage of subjects with endoscopic healing of duodenal ulcer at Week 4.
- Percentage of subjects with posttreatment resolution of gastrointestinal symptoms associated with duodenal ulcer (epigastric pain [postprandial, fasting, nocturnal], abdominal bloating, nausea/vomiting, heartburn, lack of appetite) at Weeks 2 through 6.

**3. Additional Endpoints:**

Other efficacy endpoints include:

- Quality of Life measurements - Euro Quality of Life-5D-5L (EQ-5D-5L).
- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at either Week 4 or Week 6 based on their Baseline *H pylori* status.
- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 based on their Baseline *H pylori* status.
- Percentage of subjects with *H pylori* infection at Baseline who achieve endoscopically confirmed healing of duodenal ulcer either at Week 4 or Week 6 based on their *H pylori* status at follow-up visit F-2.
- Percentage of subjects with *H pylori* infection at Baseline who achieve endoscopically confirmed healing of duodenal ulcer at Week 4 based on their *H pylori* status at follow-up visit F-2.

The safety endpoints of this study include adverse events (AEs), laboratory test values, electrocardiogram (ECG), vital signs, serum gastrin-17, and pepsinogen I/II values (total and ratio).

**Statistical Considerations:**

**Efficacy Analysis**

For the primary efficacy endpoint of Week 4 or 6 healing rate of duodenal ulcer, a 2-sided 95% confidence interval will be constructed for the difference between TAK-438 and lansoprazole treatment groups and its lower bound will be compared to the noninferiority margin of -6%.

For the secondary efficacy endpoint of eradication rate of *H pylori*, a 2-sided 95% CI will be constructed for the difference between TAK-438 and lansoprazole treatment groups in subjects who were HP+ at Baseline, and its lower bound will be compared to the noninferiority margin of -10%.

The secondary endpoint of healing rate of duodenal ulcer at Week 4 will be compared between TAK-438 and lansoprazole treatment groups by constructing a 2-sided 95% CI for the rate difference. The additional secondary

endpoints related to gastrointestinal symptoms during treatment will be compared between treatment groups using Wilcoxon rank-sum tests.

Analysis of additional endpoints includes hierarchical tests for noninferiority and superiority of the primary endpoint and the 1st secondary endpoint. Additionally, Quality-of-Life endpoints will be conducted with an Analysis of Covariance model with treatment and baseline *H pylori* status as factors and baseline as a covariate.

Statistical inference will be performed at 2-sided 0.05 level of significance or via 2-sided 95% CIs.

**Safety Analysis**

Safety analysis will be performed by summarizing the incidence of AEs, clinical laboratory tests, vital signs, and ECGs. No statistical testing or inferential statistics will be generated.

**Sample Size Justification:**

Assuming that the true Week 4 or 6 duodenal ulcer healing rate is 95.5% for both TAK-438 and lansoprazole, and assuming that the dropout rate is up to 10%, a sample size of 265 subjects per group in the overall population, including no fewer than 238 Chinese subjects per group, will provide at least 80% power to establish noninferiority in the Chinese population using a 2-sided 95% CI with a -6% noninferiority margin. This sample size will also provide 83.9% power to establish noninferiority in the overall population.

# 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 Coordinating Investigator

TDC 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 drugs, 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

| | |
|---|---|
| $^{13}$C-UBT | $^{13}$Carbon Urea Breath Test |
| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under curve |
| BID | twice daily |
| C difficile | Clostridium difficile |
| $C_{max}$ | Maximum concentration |
| CYP | cytochrome P-450 |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EQ-5D-5L | Euro Quality of Life-5D-5L |
| F-1 | Follow-up 2 weeks posttreatment |
| F-2 | Follow-up 4 weeks posttreatment |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |
| HP+ | Helicobacter pylori infected |
| HP- | non-Helicobacter pylori infected |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| IUD | intrauterine device |
| IWRS | interactive web response system |
| LA | Los Angeles |
| LFT | liver function test |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Med ID | medication identification |
| NSAID | nonsteroidal anti-inflammatory drug |
| pH4 HTR | pH 4 holding time ratio |
| PPI | proton pump inhibitor |
| PPS | per-protocol analysis set |
| PTE | pretreatment event |
| QD | once daily |
| QOL | quality of life |
| SAE | serious adverse event |

| | |
|---|---|
| SAP | statistical analysis plan |
| TEAE | treatment emergent adverse event |
| ULN | upper limit of normal |

## 3.4 Corporate Identification

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

# 4.0 INTRODUCTION

## 4.1 Background

Peptic ulcers (gastric and duodenal ulcers) are among major acid-related disorders and are accounted for in large part by *Helicobacter pylori* (*H pylori*) infection and use of nonsteroidal anti-inflammatory drugs (NSAIDs) including low-dose aspirin.

Due to the increased use of NSAIDs including low-dose aspirin in recent years, gastric and duodenal ulcers remain a major concern in Asian countries.

The proton pump inhibitors (PPIs), such as lansoprazole, represent the drugs of first choice for gastric and duodenal ulcers and are being widely used.

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 reasons 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 versus poor metabolizers.

Developed at Takeda Pharmaceutical Company Ltd, TAK-438 belongs to a new class of acid-inhibitory agents called "potassium-competitive acid blockers." 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, and 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 1mg and 120 mg in a phase 1 study (TAK-438/CPH-001) as well as for safety, pharmacokinetics, and acid-inhibitory effects in a 7-day repeated-dose study (TAK-438/CPH-002) at the doses ranging between 10 mg and 40 mg. TAK-438 has been found to be well tolerated

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

Studies of single-dose (TAK-438_101) and repeated-dose (TAK-438_107) TAK-438 were conducted in the UK as well, where TAK-438 was evaluated for its safety, pharmacokinetics and acid-inhibitory effects in the 7-day repeated-dose study at the doses ranging between 10 mg and 40 mg. TAK-438 was shown to be well tolerated at the dose of 40 mg in the repeated-dose study, with the pH4 HTR on day 7 shown to be similar to that in the repeated-dose study conducted in Japan at either of the doses examined, supporting the potent and sustained acid-inhibitory effects of TAK-438. Again, in a study evaluating interactions between TAK-438 and clarithromycin conducted in the UK (TAK-438_110), repeated-dose clarithromycin was examined for its influence on the pharmacokinetics of TAK-438, where, while the plasma concentration of TAK-438F increased by 1.35-fold for the maximum concentration ($C_{max}$) and by 1.58-fold for area under curve (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 (QD) 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 AG-1749 (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 AG-1749, showing the noninferiority of TAK-438 to lansoprazole 30 mg at the doses examined. No particular safety concerns were identified with TAK-438 at the doses examined.

A phase 3 randomized, double-blind, multicenter parallel group comparison study (TAK-438/CCT-101) in subjects with gastric ulcer was conducted to evaluate the efficacy and safety of TAK-438 20 mg QD compared with lansoprazole 30 mg QD. The noninferiority of TAK-438 20 mg treatment to lansoprazole 30 mg treatment was verified. Resolution rate of heartburn was higher in the TAK-438 20 mg group (96.5%) than in the lansoprazole 30 mg group (82.0%). The resolution rate of all other symptoms related to gastric ulcer other than epigastric pain was higher in the TAK-438 20 mg group compared with the lansoprazole 30 mg group.

A phase 3 randomized, double-blind, multicenter parallel group comparison study in subjects with duodenal ulcer (TAK-438/CCT-102) was conducted to evaluate the efficacy and safety of TAK-438 20 mg QD compared with lansoprazole 30 mg QD. For the per-protocol analysis set

(PPS) and for all full analysis set (FAS) subjects who completed the study drug, the noninferiority of TAK-438 20 mg treatment to lansoprazole 30 mg treatment was indicated with respect to the endoscopic healing rate during the 6-week treatment period. Both treatments had favorable effects on the resolution rates (>80%) of duodenal ulcer.

Of note, in a phase 3 *H pylori* eradication study, 7-day treatment with TAK-438 20 mg (n=329) or lansoprazole 30 mg (n=321) in combination with amoxicillin 750 mg plus clarithromycin 200 or 400 mg, *H pylori* eradication rates were 92.6% and 75.9%, respectively. Furthermore, the first 50 treatment failures with good compliance received second-line triple-therapy with TAK-438 20 mg (in combination with amoxicillin 750 mg and metronidazole 250 mg) in an open-label manner and an eradication rate of 98% was observed. All treatments were well-tolerated.

Other phase 3 studies have shown that for the treatment and maintenance of GERD and ulcer prevention in subjects receiving concomitant medications, TAK-438 demonstrated clinical efficacy that was comparable with that of lansoprazole.

In the completed phase 3 studies to date, 3397 subjects were exposed to TAK-438 10 to 40 mg QD for up to 104 weeks. TAK-438 treatment was generally well tolerated, with a similar safety profile to that of lansoprazole. Incidences of drug-related treatment-emergent adverse events (TEAEs) were low and similar between the TAK-438 and lansoprazole treatment groups. The safety of TAK-438 has been demonstrated in a number of clinical studies across several indications including the treatment of erosive esophagitis healing, gastric ulcer, duodenal ulcer, *H pylori,* and nonerosive esophageal reflux disease. No significant changes in other laboratory test values, vital signs, or electrocardiogram (ECG) findings were observed during the studies.

Potential pharmacological class effects of acid-blocking treatments include hepatic function abnormal, bone fracture, *Clostridium difficile* (*C difficile*) enteric infection, pneumonia neuroendocrine tumors, hypomagnesemia, Vitamin B-12 deficiency, iron deficiency, acute interstitial nephritis, and drug interaction affected by gastric pH. Although no clear evidence has been identified linking them to TAK-438 treatment, hepatic function abnormal, bone fracture, *C difficile* enteric infection, and drug interaction affected by gastric pH are now considered as important potential risks based on the safety profile of drugs with a similar mode of action.

## 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 with TAK-438, demonstrating that TAK-438 is noninferior to lansoprazole at the doses tested (5 mg, 10 mg, 20 mg, and 40 mg), with no particular safety concerns identified. The rate of endoscopic healing of erosive esophagitis in subjects with more severe disease (Los Angeles [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 results of this study indicated TAK-438 20 mg could produce more potent and sustained acid-inhibitory effects than lansoprazole 30 mg, with no safety concerns. Given the disease similarities, TAK-438 20 mg was expected to be at least as effective as lansoprazole 30 mg for the treatment of duodenal ulcer as it was for erosive esophagitis.

Thus, it was decided that a phase 3 multicenter, randomized, double-blind study of TAK-438 20 mg versus lansoprazole 30 mg QD (or double these doses in HP+ subjects as part of an eradication regimen) would be implemented to demonstrate the noninferior efficacy of TAK-438 20 mg in subjects with duodenal ulcer.

# 5.0 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objective

To demonstrate the noninferior efficacy of TAK-438 versus lansoprazole in the treatment of subjects with duodenal ulcer.

### 5.1.2 Secondary Objectives

To demonstrate the noninferiority of HP eradication with TAK-438 versus lansoprazole.

To compare the safety of TAK-438 versus lansoprazole in subjects with duodenal ulcer.

## 5.2 Endpoints

### 5.2.1 Primary Endpoint

The primary endpoint for this study is the percentage of subjects with endoscopically confirmed healing* of duodenal ulcer(s) at Week 4 or 6*.

*Rate of endoscopic healing: defined as the proportion of subjects in whom the disappearance of all white coats associated with duodenal ulcers has been endoscopically confirmed.

### 5.2.2 Secondary Endpoints

Secondary endpoints for this study are:

- Percentage of HP+ subjects with successful *H pylori* eradication after 4 or 6 weeks of treatment, as determined by $^{13}$C Urea Breath Test ($^{13}$C-UBT) at F-2 (follow-up 4 weeks posttreatment).
- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4.
- Percentage of subjects with posttreatment resolution of gastrointestinal symptoms associated with duodenal ulcer (epigastric pain [postprandial, fasting, nocturnal], abdominal bloating, nausea/vomiting, heartburn, lack of appetite) at Weeks 2 through 6.

### 5.2.3 Additional Endpoints

Additional efficacy endpoints include:

- Quality of life (QOL) measurement Euro Quality of Life-5D-5L (EQ-5D-5L).
- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at either Week 4 or Week 6 based on their baseline *H pylori* status.
- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 based on their baseline *H pylori* status.

- Percentage of subjects with *H pylori* infection at Baseline who achieve endoscopically confirmed healing of duodenal ulcer either at Week 4 or Week 6 based on their *H pylori* status at Follow-up visit F-2.
- Percentage of subjects with *H pylori* infection at Baseline who achieve endoscopically confirmed healing of duodenal ulcer at Week 4 based on their *H pylori* status at Follow-up visit F-2.

Safety endpoints include adverse events (AEs), laboratory test values, ECG, vital signs, serum gastrin-17, and pepsinogen I/II values (total and ratio).

# 6.0 STUDY DESIGN AND DESCRIPTION

## 6.1 Study Design

This is a phase 3, multicenter, randomized, double-blind, double-dummy, parallel-group, noninferiority study of TAK-438 versus lansoprazole in subjects who have endoscopic evidence of duodenal ulcer with or without *H pylori* infection.

Approximately 530 subjects across approximately 60 sites in Asia will be randomized in a 1:1 ratio to either TAK-438 20 mg or to lansoprazole 30 mg (265 subjects per treatment arm). The randomization will be stratified by HP status:

- TAK-438: 265 subjects.
- Lansoprazole: 265 subjects.

*Treatment Period:*

A schematic of the study design is included as Figure 6.a. A schedule of assessments is listed in Appendix A.

Dosing will begin on Day 1 after randomization (Visit 2) and last for up to 6 weeks. Study drug administration will depend on the *H pylori* infection status of the subject.

Administration of the 2 treatments will be according to the following regimens:

- *H pylori* infected (HP+) subjects will take TAK-438 20 mg or lansoprazole 30 mg (blinded with matching placebo) twice daily (BID) in addition to bismuth-containing quadruple therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg [equivalent to 220 mg bismuth] BID) for 2 weeks. After 2 weeks of eradication therapy, subjects will be required to take only the TAK-438 or lansoprazole once a day (QD) for up to 4 weeks (ie, up to a total of 6 weeks of treatment). The subject remains in the same treatment arm throughout the study duration.
- Non-*H pylori* infected (HP-) subjects will take TAK-438 or lansoprazole (blinded with matching placebo) QD for up to 6 weeks.

For all subjects, ulcer healing rates will be assessed by endoscopy at Weeks 4 and 6 of treatment. With or without endoscopic evidence of duodenal ulcer healing, the treatment duration of the study is no more than 6 weeks.

Subjects (HP+ or HP-) with endoscopic healing of duodenal ulcer(s) at Week 4 or Week 6 will discontinue treatment at that time, and enter into the Follow-up period.

Subjects (HP+ or HP-) without ulcer healing by Week 6 of treatment period will discontinue treatment at Week 6 and enter into the Follow-up period.

*Follow-up Period:*

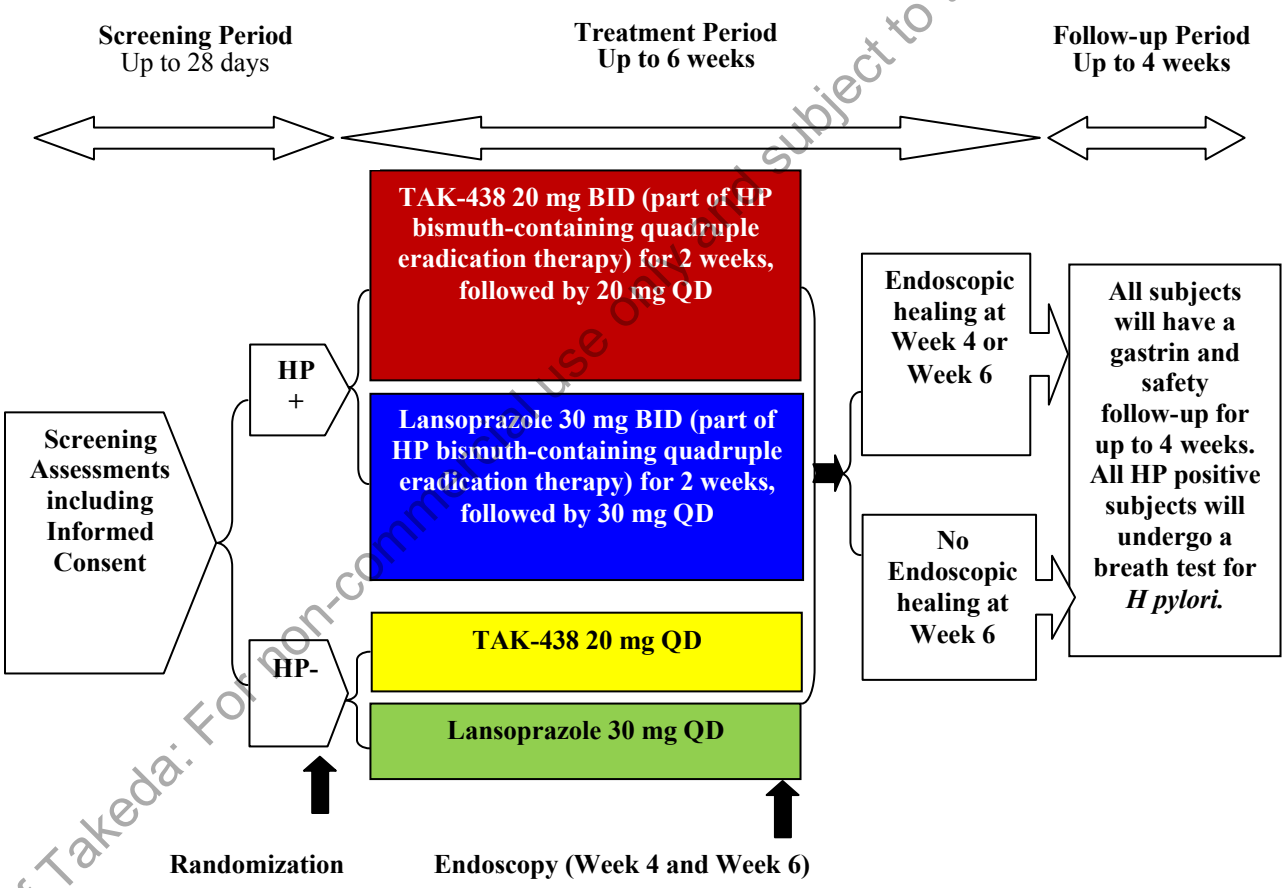
The subjects to be followed up will include both HP+ and HP- subjects, with or without confirmed ulcer healing during the treatment period.

The recovery of serum gastrin-17 level and pepsinogen I/II ratio in the Follow-up period will be monitored for a maximum of 4 weeks. The Follow-up period ends when the recovery of serum gastrin-17 level and pepsinogen I/II ratio are confirmed or at the end of the 4-week Follow-up.

All HP+ subjects will provide a follow-up $^{13}$C-UBT at the F-2 visit to ascertain HP eradication status.

For subjects with no ulcer healing at Week 6 of treatment, the investigator may follow local clinical practice and these subjects may be treated with another course of PPI or other anti-acid secretory agents or antibiotics, during the safety follow-up period (please see Table 7.a). This should be documented during the F-2 visit.

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




## 6.2 Justification for Study Design, Dose, and Endpoints

For the subject population studied

Subjects will be included in the study if they are diagnosed as having duodenal ulcer (ie, mucosal defects with white coat [including the case associated with blood coagula]) and having one or more duodenal ulcers associated with a white coat measuring 5 mm or larger in longest diameter.

For study design and sample size used

(1) Study design

This study is designed as a randomized, double-blind, parallel-group comparison of TAK-438 20 mg versus the PPI lansoprazole 30 mg, a first drug of choice for duodenal ulcer as control to demonstrate the noninferiority of TAK-438. Subjects with HP+ disease will receive double these doses as part of a BID *H pylori* eradication regimen for 2 weeks.

For all subjects, serum gastrin-17 and pepsinogen I/II recovery status will be monitored during the Follow-up period (Visits F-1 [follow-up 2 weeks posttreatment] and F-2), which is planned to last up to 4 weeks but to be completed at the time point at which serum gastrin-17 level and pepsinogen I/II ratio recovery has been confirmed in these subjects. This is to monitor the dose-dependent elevated serum gastrin levels observed in TAK-438 subjects. The 4-week duration of monitoring was selected so that subjects who remain HP+ at F-2 may be further treated with alternative HP eradication regimens. Data arising from these alternative regimens will not be included in the study data.

(2) Sample size

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

For doses of the study drugs used

In a phase 2 dose-ranging study of TAK-438 in subjects with erosive esophagitis (TAK-438/CCT-001), TAK-438 exhibited a dose-response efficacy at doses 5 mg, 10 mg, 20 mg, and 40 mg, and demonstrated its noninferiority to lansoprazole 30 mg at either of the doses examined after 4 weeks of treatment, 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. As the clinically recommended dose of lansoprazole for duodenal ulcer is the same as that for erosive esophagitis (30 mg), the clinically recommended dose of lansoprazole for duodenal ulcer was determined as 30 mg.

The quadruple therapy is a well-established treatment regimen in conjunction with a PPI for the treatment of *H pylori* infection.

For timing of administration

In a phase 1 single-dose study of TAK-438 in healthy male volunteers conducted in Japan (TAK-438 CPH-001 study), 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 as a once-daily regimen.

It was thus decided that TAK-438 would be given after breakfast or dinner as a once-daily regimen. The preference is for the dose to be given after breakfast; however, if the first randomization visit was scheduled in the late afternoon, it is acceptable for the dose to be taken after dinner.

<u>For duration of treatment used</u>

The PPIs, the first drug of choice for duodenal ulcer, have been approved for use for 6 weeks. Thus, the study was so designed to allow the study medication to be given for up to 6 weeks but to be completed if endoscopic healing of duodenal ulcer has been confirmed in the subjects after 4 weeks of treatment.

<u>For endpoints used</u>

1) Primary endpoint

Endoscopic healing of duodenal ulcer represents the goal of treatment for duodenal ulcer, for which lansoprazole 30 mg has been approved for use QD for up to 6 weeks.

Thus, the primary endpoint was defined as the rate of endoscopic healing of duodenal ulcer during the 6-week treatment period.

2) Secondary endpoints

As eradication of *H pylori* is standard of care in HP+ subjects, eradication of *H pylori* has been included as the main secondary endpoint.

As TAK-438 is expected to produce more sustained, potent acid-inhibitory effects and earlier healing of duodenal ulcer than the PPIs such as lansoprazole 30 mg, before 6 weeks of treatment, ie, the duration of treatment approved for the PPIs, the rate of endoscopic healing of duodenal ulcer after 4 weeks of treatment was included as a secondary endpoint.

Additionally, as duodenal ulcer may be associated with gastrointestinal symptoms, the occurrence of duodenal ulcer-associated symptoms (epigastric pain [postprandial, fasting, nocturnal], abdominal bloating, nausea/vomiting, heartburn, lack of appetite) is also included as secondary endpoints.

3) Additional Endpoints

Additional endpoints include measurement of QOL, and other endpoints designed to minimize the potentially confounding impact of *H pylori* eradication.

4) Safety Endpoints

Safety endpoints include AEs, SAEs, laboratory test values, ECG, vital signs, serum gastrin-17 and pepsinogen I/II values.

## 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 drug 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 Sites

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. Subjects with endoscopic evidence of active duodenal ulcer(s) (ie, mucosal defects with white coating [including cases associated with blood coagula as long as there is no active bleeding]) measuring 5 mm or larger in longest diameter within 14 days prior to randomization.
4. The subject is male or female, at least 18 years of age (or at least the minimum legal age of consent, if that is >18 years), with duodenal ulcer(s) at the time of signing informed consent.
5. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and 4 weeks after last dose of study drug.

> *Definitions and 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 90 days prior to the treatment period.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling), or who may have consented under duress.
4. The subject has, in the judgment of the investigator, clinically significant abnormal physical examinations, hematological parameters of hemoglobin, hematocrit, or erythrocytes at Screening**.**
5. The subject has a history or clinical manifestations of significant CNS, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine or hematological disease that, in the opinion of the investigator, would confound the study results or compromise subject safety.

6. The subject has a history of hypersensitivity or allergies to TAK-438 or lansoprazole, including any associated excipients. The subject has a known hypersensitivity to any component of the formulation of TAK-438 or lansoprazole, for example, D-mannitol, crystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, yellow iron sesquioxide, and iron sesquioxide.
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the treatment period.
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 4 weeks after participating in this study; or intending to donate ova during such time period.
10. Previous exclusion criterion 10 in Amendment No. 02 has been deleted.
11. Subjects who have been treated with *H pylori* eradication therapy within 30 days prior to study treatment.
12. Previous exclusion criterion 12 in Amendment No. 02 has been deleted.
13. Subjects with a diagnosis of duodenal malignancy or a duodenal ulcer whose morphology suggested malignancy as evident by endoscopy within 14 days prior to randomization.
14. Subjects suspected of having acute gastro-duodenal mucosal lesions (AGDML) as evident by endoscopy within 14 days prior to randomization.
15. Subjects in whom a linear ulcer (including a linear ulcer scar) is confirmed by endoscopy within 14 days prior to randomization.
16. Subjects with active postoperative (eg, endoscopic mucosal resection/endoscopic submucosal dissection) ulcer(s) as confirmed by endoscopy within 14 days prior to randomization.
17. Subjects in whom gastric ulcer is confirmed by endoscopy within 14 days prior to randomization.
18. Subjects with ulcers for which medical therapy alone is not indicated (eg, perforation, pyloric stenosis, duodenal stenosis, major bleeding).
19. Subjects who have undergone therapeutic upper GI endoscopic therapy (eg, endoscopic hemostasis, excision biopsy) within 30 days prior to visit 1. Biopsy done for diagnostic purposes may be permitted.
20. Subjects with Zollinger-Ellison syndrome or gastric acid hypersecretion or those with a history of gastric acid hypersecretion.
21. Subjects who have undergone major surgical procedures within 30 days prior to Visit 1 or are scheduled to undergo surgical procedures that may affect gastric acid secretion (eg, abdominal surgery, vagotomy or craniotomy).

22. The subject has a history of malignancy or was treated for malignancy within 5 years before the start of the visit 1 (the subject may be included in the study if he/she has cured cutaneous basal cell carcinoma or cervical carcinoma in situ).
23. The subject has a known acquired immunodeficiency syndrome or hepatitis infection, including hepatitis virus carriers (hepatitis B surface antigen [HBsAg] or hepatitis C virus [HCV]-antibody-positive) (the subject may be included in the study if he/she is HCV-viral load-RNA-negative).
24. Subjects for whom laboratory tests performed prior to randomization revealed any of the following abnormalities:
    a) Creatinine levels: >2 mg/dL (>177 μmol/L).
    b) Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin levels: > the upper limit of normal (ULN).
    (Note: 1 retest is allowed; if still >ULN, subject should be excluded.)
25. Subjects with hypersensitivity to PPIs, bismuth, clarithromycin, or amoxicillin. Skin testing may be performed according to local standard practice (for HP+ subjects only).

### 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. The investigator should review any additions or changes in medications. All medications should be recorded in the source documents or equivalent and then transcribed onto the appropriate electronic case report forms (eCRFs).

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

## Table 7.a Excluded Medications and Treatments

| Excluded Medication/Treatment | Beginning of Exclusion | End of Exclusion |
|---|---|---|
| Other investigational drugs or drugs administered due to participation in another clinical trial | 90 days prior to study treatment | End of Follow-up |
| Medications that may interfere with $^{13}$C-UBT (metronidazole, bismuth preparations, ecabet sodium hydrate) (a) | At least 14 days prior to $^{13}$C-UBT (at Screening), and through to end of $^{13}$C-UBT testing at F-2 visit | End of $^{13}$C-UBT (HP+ subjects only) |
| Antibiotics | 30 days prior to $^{13}$C-UBT (at Screening) and through to end of $^{13}$C-UBT testing at F-2 visit, with the exception of subjects with non-healed ulcer who received further treatment at the end of study treatment period | End of Follow-up |
| Antiprotozoals | 30 days prior to study treatment | End of Follow-up |
| Non–study-related *H pylori* eradication therapy | 30 days prior to study treatment | End of Follow-up |
| Medications contraindicated with clarithromycin: pimozide, ergot derivatives, tadalafil, terfenadine, astemizole, cisapride simvastatin, lovastatin, atorvastatin etc.<br>Note: other statins such as fluvastatin, pravastatin, and rosuvastatin may be allowed but used with caution | 30 days prior to study treatment (applies to HP+ subjects only) | End of HP eradication therapy (HP+ subjects only) |
| Strong inhibitors or inducers of CYP3A4 (eg, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin) | 30 days prior to study treatment | End of HP eradication therapy (HP+ subjects only) |
| Non–study-related PPIs and $H_2$ receptor antagonists. | 14 days prior to study treatment and at least 14 days prior to $^{13}$C-UBT (at Screening), with the exception of subjects with non-healed ulcer who received further treatment at the end of study treatment period | End of Follow-up |
| Surgical procedures that could affect gastric acid secretion (eg, upper gastrointestinal surgery, vagotomy) | Start of study treatment | End of Follow-up |
| NSAIDs (c) | Start of study treatment | End of Follow-up |
| Agents affecting digestive organs, including muscarinic M3 antagonists, prokinetics, anticholinergic agents, prostaglandins, anti-gastrin agents or mucosal-protective agents. (b) | Start of study treatment | End of Follow-up |
| Atazanavir sulfates; rilpivirine hydrochloride (contraindicated with TAK-438) | Start of study treatment | End of Follow-up |

| | | |
|---|---|---|
| Corticosteroids (c), anti-platelets (includes low-dose aspirin) (c), anticoagulants (c), psychotropics (c), antidepressants (c), bisphosphonates (c, d), methotrexate and probenecid* (contraindicated with bismuth). | Start of study treatment | End of Follow-up<br>* For probenecid - End of HP eradication therapy |

Footnotes are on the following page.

(a) Prohibited period is 14 days prior to any $^{13}$C-UBT or as otherwise stated in package insert for $^{13}$C urea breath testing kit package to be used.
(b) The use of gastric mucosal protective agents may be allowed during the Follow-up period.
(c) Except subjects that were using these agents before signing the informed consent form at visit 1 and the dose and administration will not be changed during the study.
(d) Switching between once-daily and weekly regimens is allowed for drugs containing the same active ingredients. Also allowed are compliant subjects on a stable dose (in accordance with the package insert) at the time of signing consent who have no GI inflammation or history of such.

## 7.4 Diet, Fluid, Activity Control

Subjects should be instructed as follows:

- To adhere closely to the scheduled visits, seek medical consultation, and undergo predetermined laboratory tests.
- To take study drug(s) after breakfast or dinner at about the same time as he/she usually does with approximately 240 ml water (for HP- subjects and for HP+ after the 2-week eradication therapy period). For the HP+ subjects in first 2 weeks of HP eradication therapy period, to ensure that bismuth and TAK-438/lansoprazole are to be taken 0.5 hour before breakfast and dinner. Breakfast and dinner should be completed within 0.5 hour before taking clarithromycin and amoxicillin, ie, 1 hour after bismuth and TAK-438/lansoprazole dosing.
- To present to the clinic in a fasting state when he/she is scheduled for laboratory tests and/ or endoscopy. On such study visit days, subjects will be instructed to take their dose of study drug(s) (if appropriate) after study procedures are completed.
- Subjects should be instructed according to Section 8.1.3.1 (Missed Doses) and Section 9.2 (Compliance) at every study visit. Details of any missed or forgotten doses should be reported to the Investigator or designee at the subsequent study visit.
- To store all medications in a cool, dry, safe place which is out of reach of children and to bring all study supplies (empty / used / unused drug packets) to each study visit.
- If during study participation the subject is prescribed medication by a nonstudy physician or other healthcare professional, he/she should consult the investigator beforehand. Such treatment or consultation, or the use of over-the-counter medicine should be reported at the next study visit.
- To report on all subjective or objective symptoms experienced with regard to their details, day of onset, severity, outcome, and day of outcome at every visit. In case of emergency, such as occurrence of an SAE, the subject or his/her family should contact the investigator as soon as possible.

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

### 7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.12.

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

- Liver Function Test (LFT) 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 × ULN.

2. Significant protocol deviation. The discovery after 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: noncompliance.

### 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 study material.

## 8.1 Study Drug and Materials

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term "study drug" refers to any and all of the drugs administered as part of the study, including TAK-438 or lansoprazole (and their matching placebo) as well as the companion drugs given for *H pylori* infection eradication in HP+ subjects. The properties of TAK-438 (20 mg tablets and matching placebo tablets) and lansoprazole (30 mg capsules and matching placebo capsules) are detailed in Table 8.a. These drugs will be packaged in a blinded fashion. The companion drugs refer to amoxicillin (500 mg tablets/capsules), clarithromycin (500 mg tablets) and bismuth potassium citrate/bismuth tripotassium dicitrate (300 mg tablets/capsules) which will be packaged in an open fashion.

#### *8.1.1.1 TAK-438 and Lansoprazole*

TAK-438 and lansoprazole will be foil/foil blistered packaged into child-resistant blister cards. Each blister card will contain 20 tablets (containing either TAK-438 or placebo) and 20 capsules (containing either lansoprazole or placebo).

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.

TAK-438 20 mg Active and Placebo Tablets

The chemical name of TAK-438 is:
1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-*1H*-pyrrrol-3-yl]-*N*-methyl methanamine monofumarate. The generic name for TAK-438 is vonoprazan. The active study drug, TAK-438 (vonoprazan) 20 mg and matching placebo are provided as pink, film-coated tablets manufactured by Takeda Pharmaceutical Company, Osaka, Japan.

Lansoprazole 30 mg Active and Placebo Capsules

The chemical name of lansoprazole (AG-1749) is:
2-[(*RS*)-[[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl]sulfinyl]-1*H*-benzimidazole. Lansoprazole 30 mg will have a dual supply chain. Lansoprazole 30 mg will be manufactured by Tianjin Takeda, Tianjin, China, and matching placebo will be manufactured by Takeda Pharmaceutical Company, Osaka, Japan, and will be supplied to all investigational sites in China. Takeda Pharmaceutical Company, Osaka, Japan, will manufacture lansoprazole 30 mg and matching placebo for all other countries. All lansoprazole 30 mg and matching placebo will be supplied as a white colored capsule.

**Table 8.a TAK-438 and Lansoprazole Properties**

| Study medication form | Description | Manufacturer and Location |
|---|---|---|
| TAK-438 20 mg tablet | Pale red film-coated tablet scored on both sides | Takeda Pharmaceutical Company Limited, Osaka, Japan |
| TAK-438 20 mg matching placebo tablet | Pale red film-coated tablet scored on both sides | Takeda Pharmaceutical Company Limited, Osaka, Japan |
| Lansoprazole 30 mg capsule | White capsule | Tianjin Takeda Pharmaceuticals Co., Ltd, China (will be supplied to China) / Takeda Pharmaceutical Company Limited, Osaka, Japan (will be supplied to countries except for China) |
| Lansoprazole 30 mg matching placebo capsule | White capsule | Takeda Pharmaceutical Company Limited, Osaka, Japan |

The TAK-438 tablets and the lansoprazole capsules are difficult to distinguish from their matching placebos by their appearance.

#### *8.1.1.2 Companion Drugs (for H pylori Positive Subjects Only)*

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

#### *8.1.1.3 Sponsor-Supplied Study Drugs*

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

#### *8.1.1.4 Rescue Medication*

During the study period including the screening period, those over-the-counter medications 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 duodenal ulcer 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.

### 8.1.2 Storage

TAK-438, lansoprazole and matching placebo should be stored at 25°C; with excursions permitted 15°C to 30°C. Protect from moisture and humidity. These drugs are to remain in their blister cards until time of dosing. Companion drugs should be stored according to the storage conditions on each label.

All sponsor-supplied study drugs 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 study 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 excursions must be reported to the sponsor or designee.

### 8.1.3 Dose and Regimen

Subjects who qualify for the study will be randomly assigned to receive either TAK-438 or lansoprazole.

At the randomization visit/ Visit 2, *H pylori* positive subjects will receive 2 blister cards, each card containing 20 tablets of TAK-438 (or placebo tablets) and 20 capsules of lansoprazole (or placebo capsules). Subjects will be required to take 1 tablet (containing either TAK-438 or placebo) and 1 capsule (containing either lansoprazole or placebo) twice daily (BID) for 2 weeks. HP+ subjects will also receive a 2-week supply of companion drugs (amoxicillin 1 g, clarithromycin 500 mg, and bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg), to be taken twice a day BID for 2 weeks. Subjects will be instructed to take bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg and 1 dose of TAK-438 or lansoprazole BID, 0.5 hours before taking breakfast and dinner. Subjects will be advised to complete their meals (breakfast and dinner) within 0.5 hours. Clarithromycin 500 mg and amoxicillin 1 g are to be taken BID after meals, ie, 1 hour after bismuth and study drug dosing. After completing 2 weeks of HP eradication therapy, subjects will follow the same dosing regimen as *H pylori* negative subjects (1 dose daily, described below) until the end of treatment period.

*H pylori* negative subjects will be dispensed 1 blister card containing TAK-438 or lansoprazole (with appropriate placebo) after randomization at Visit 2 and at subsequent visits as required. HP- subjects will be required to take 1 tablet (containing either TAK-438 or placebo) and 1 capsule (containing either lansoprazole or placebo) daily (QD) after breakfast or dinner at about the same time as he/she usually does, with approximately 240 mL water. The preference is for the dose to be given after breakfast; however, if the first randomization visit was scheduled in the late afternoon, it is acceptable for the dose to be taken after dinner.

Subjects should be fasted for laboratory tests and/ or endoscopy. On such study visit days, subjects will be instructed to take their dose of study drugs (if appropriate) after study procedures are completed.

Table 8.b describes the dose and tablet/capsule count that will be provided to each group.

**Table 8.b Dose Regimen of Sponsor-Supplied Drugs**

| Treatment | Group Description | Dose | Treatment Description | |
|---|---|---|---|---|
| | | | **Active** | **Placebo** |
| A1 | **TAK-438** (**HP-** subjects for 6 weeks) | TAK-438 20 mg QD | 1 TAK-438 20 mg tablet QD | 1 placebo matching lansoprazole 30 mg capsule QD |
| A2 | **TAK-438** (**HP+** subjects in first 2 weeks) | TAK-438 20 mg BID | 1 TAK-438 20 mg tablet BID, with amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg, BID | 1 placebo matching lansoprazole 30 mg capsule BID |
| | (**HP+** subjects in Weeks 3-6) | TAK-438 20 mg QD | 1 TAK-438 20 mg tablet QD | 1 placebo matching lansoprazole 30 mg capsule QD |
| B1 | **Lansoprazole** (**HP-** subjects for 6 weeks) | Lansoprazole 30 mg QD | 1 lansoprazole 30 mg capsule QD | 1 placebo matching TAK-438 20 mg tablet QD |
| B2 | **Lansoprazole** (**HP+** subjects in first 2 weeks) | Lansoprazole 30 mg BID | 1 lansoprazole 30 mg capsule BID with amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg, BID | 1 placebo matching TAK-438 20 mg tablet BID |
| | (**HP+** subjects in Weeks 3-6) | Lansoprazole 30 mg QD | 1 lansoprazole 30 mg capsule QD | 1 placebo matching TAK-438 20 mg tablet QD |

#### *8.1.3.1 Missed Doses*

Subjects should be instructed that all doses of TAK-438 or lansoprazole and companion drugs should be taken on time. If any dose is missed inadvertently it is acceptable for that dose to be taken within 6 hours of the time that it was due. If more than 6 hours have passed since the dose was due, it should not be taken.

### 8.1.4 Overdose

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

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

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

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

## 8.2 Study Drug Assignment and Dispensing Procedures

An interactive web response system (IWRS) 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 study drugs after study completion.

The investigator or investigator's designee will access the IWRS at Screening visit 1 to obtain the subject study number. The investigator or the investigator's designee will utilize the IWRS to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number that was assigned at screening. The medication identification (Med ID) number of the study drugs to be dispensed will then be provided via the IWRS.

If sponsor-supplied drugs are lost or damaged, the site can request a replacement from IWRS. (Refer to IWRS manual provided separately.) At subsequent drug-dispensing visits, the investigator or designee will again contact the IWRS to request additional study drug(s) for a subject.

Please refer to the IWRS user guide for the details of the Med ID number assignments for the study drugs.

## 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, stratified by HP status using IWRS.

## 8.4 Investigational Drug Blind Maintenance

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

## 8.5 Unblinding Procedure

The blinding for TAK-438 and lansoprazole 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, the investigator will be able to access IWRS to determine subject's treatment group assignment. The investigator will, whenever possible, discuss options with the medical monitor before unblinding.

The sponsor must be notified as soon as possible if the drug blinding 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, drug treatment 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 drugs are used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drugs, 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 drugs, 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 or designee must record the current inventory of all sponsor-supplied drugs on a 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 drug accountability log will include all required information as a separate entry for each subject to whom sponsor-supplied drugs are dispensed.

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

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

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

# 9.0 STUDY PLAN

## 9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

### 9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed.

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

### 9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth (or age in countries where collection of birth date is not allowed), sex, race as described by the subject, and smoking status, drinking status, history of consumption of caffeine-containing drinks, history of *H pylori* eradication therapy (eg, triple therapy with PPI + amoxicillin + clarithromycin) at Screening. Additionally, characteristics of the current duodenal ulcers should be captured as shown in Table 9.a.

**Table 9.a Characteristics of Current Duodenal Ulcers**

| Evaluation | Finding |
|---|---|
| Location (a) | Superior part (including bulb), descending part |
| Number of ulcers found | *<enter number>* |
| Morphology (a) | Circular, ellipsoidal, other |
| Size (a) | Minuscule, <5 mm; minor, ≥5 mm/<10 mm; intermediate, ≥10 mm/≤20 mm; large, >20 mm/<30 mm; giant ≥30 mm |

(a) In case of multiple lesions, information needs to be obtained on the largest of the lesions.

#### *9.1.2.1 History of Duodenal Ulcers*

Information needs to be obtained on the following:

- Date of onset of current ulcers.
- Use of NSAIDs or low-dose aspirin (except topical preparations) at the time of ulcer onset. If any of these agents was being used by the subject at the time of ulcer onset, the principal or co-investigator should record the agent(s) used in the medication history and/or as concomitant medications (see Section 9.1.6) in the eCRF.

- Primary/recurrent ulcers (if recurrent, obtain information on the date of onset of previous ulcers).

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).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 30 days prior to signing of informed consent.

Medication history will include the following medications if stopped within 30 days prior to visit 1, note that information on the NSAID(s) and low-dose aspirin used should also be obtained between onset of current ulcers and signing of informed consent:

- Agents affecting the digestive organs (PPIs, Histamine $H_2$ receptor antagonists, muscarinic $M_3$ receptor antagonists, gastrointestinal prokinetic agents, anti-cholinergic agents, prostaglandins, anti-gastrin agents, gastric mucosal protective agents).
- *H pylori* eradication therapy (eg, triple therapy with PPI + 2 antibiotics).
- Atazanavir sulfates.
- Corticosteroids.
- Anti-platelet agents (including low-dose aspirin).
- Anticoagulants.
- Psychotropics.
- Antidepressants.
- NSAIDs.
- Bisphosphonates.

### 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 Schedule of Study Procedures (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 drug. 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 drug (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, ECG, or physical examination abnormalities noted at the Screening examination. The condition (ie, diagnosis) should be described.

### 9.1.8 Procedures for Clinical Laboratory Samples

Clinical laboratory tests are shown in Table 9.b. All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 25 mL, and the approximate total volume of blood for the study is 93 mL, depending on the subject's number of follow-up visits. Details of these procedures and required safety monitoring will be given in the laboratory manual.

**Table 9.b Clinical Laboratory Tests**

| Hematology | Serum Chemistry | Urinalysis |
|---|---|---|
| Red blood cells<br>White blood cells<br>Hemoglobin<br>Hematocrit<br>Platelets<br>White blood cell fractions (neutrophils, eosinophils, basophils, monocytes, lymphocytes) | ALT (fasting)<br>Albumin<br>Alkaline phosphatase (ALP) (fasting)<br>AST (fasting)<br>Total bilirubin (fasting)<br>Direct bilirubin (fasting)<br>Total cholesterol (fasting)<br>Triglycerides (fasting)<br>Calcium<br>Chloride<br>Creatinine<br>Creatine kinase<br>Blood urea nitrogen (BUN)<br>γ-Glutamyl transferase (GGT)<br>Serum gastrin-17 (fasting)<br>Glucose (fasting)<br>Inorganic phosphate<br>Serum iron<br>Lactate dehydrogenase (LDH)<br>Magnesium<br>Pepsinogen I/II (fasting) (a)<br>Potassium<br>Total protein<br>Sodium<br>Uric acid (fasting)<br>Vitamin B12<br>**Hepatitis B & C Analysis**<br>HBsAg<br>HCV antibody<br>HCV-viral load-RNA (b) | Appearance<br>Color<br>pH<br>Specific gravity<br>Ketones<br>Protein<br>Glucose<br>Nitrite<br>Urobilinogen<br>Blood |

**Other:**
$^{13}$C-UBT

| Serum | Urine |
|---|---|
| Female subjects if menopause is suspected only<br>– Follicle-stimulating hormone (FSH) | Female subjects of child-bearing potential only<br>– hCG (for pregnancy) |

(a) This includes pepsinogen I, pepsinogen II and pepsinogen I/II ratio.
(b) Subjects with negative HCV antibody test results may be randomized before HCV-viral load-RNA test results are available. If the HCV-viral load-RNA test result is positive, the subject will be withdrawn from the study.

The central laboratory will perform laboratory tests for hematology, serum chemistries, hepatitis and urinalysis. The results of the laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. Refer to Appendix A for the laboratory test schedule at each study visit.

If subjects experience an increase in any one of ALT, AST or total bilirubin >2 × ULN, the study drug shall be stopped due to the discontinuation criteria having been met (Section 7.5). Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found.

(Note for ALT/AST and total bilirubin: >ULN to ≤2 × ULN. Kindly re-test LFT in 2 weeks to monitor abnormal LFT. This abnormal LFT value should not be reported as AE unless is clinically significant. An unscheduled visit may be performed if necessary.)

TAK-438 or lansoprazole may be associated with increases in serum gastrin-17 and pepsinogen I/II levels. Thus, all subjects will be examined for gastrin-17 and pepsinogen I/II levels (total and ratio) to investigate the magnitude of these increases during the Treatment and Follow-up periods. Increases in serum gastrin and pepsinogen I/II levels are physiological responses to gastric acid suppression and elevation in gastric content pH, due to the pharmacological action of the study drugs.

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

Additional blood may be collected per the investigator's discretion.

Local laboratories may be used to perform laboratory tests for HBV, HCV and LFT tests, etc, only under special circumstances, on case by case basis with sponsor's agreement. The Investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Please refer to Section 10.2.3 for the appropriate guidance on Reporting of Abnormal LFTs as SAEs.

### 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 (a):** | **Intrauterine devices (IUDs):** |
|---|---|
| • Cap (plus spermicidal cream or jelly) PLUS male condom | • Copper T |
| • Diaphragm (plus spermicidal cream or jelly) PLUS male condom | |

(a) Barrier methods are only applicable in countries where spermicide is available.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

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

### 9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drugs should be immediately discontinued.

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

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

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.

If a routine ECG is done within 14 days prior to randomization, it can be used as study data.

### 9.1.12 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

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

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

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

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

### 9.1.13 Documentation of Randomization

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

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

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.

### 9.1.14 Endoscopy

Endoscopy should be performed while subjects are fasted and according to the usual practice of the institution. Use of pre-medications for endoscopy (e.g. analgesics, local anesthetics, anticholinergic agents, sedatives, anticholinergics/antispasmodics, antifoaming agents) may be allowed at the discretion of the Investigator as per local standard practice.

During endoscopy the Investigator, or designee, should ensure that the duodenal mucosa is observed for a sufficient duration that the subject's eligibility is confirmed and ensure that any white coat (including the case associated with blood coagulation, with no active bleeding) present in the subject is measured for its longest diameter using the endoscopic clamp or open biopsy forceps as a measure and determine the characteristics of current ulcers in accordance with Section 9.1.2. The Investigator should judge the ulcers as "Healed" or "Unhealed" based on endoscopy findings from Visit 4 onward. Digital images of the current ulcers 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.

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

Preferably, the principal investigator performs as the second reviewer and conducts the second review in a timely manner after the endoscopy is performed by the first reviewer who is a subinvestigator in this study.

In cases where the principal investigator is the first reviewer, a subinvestigator at the same site can be delegated as the second reviewer and conducts the second review in a timely manner.

Only investigators (either principal investigators or subinvestigators) can be delegated as the second reviewer.

If the evaluations of duodenal ulcer by the 2 reviewers are consistent, this result becomes the final report. If not, the 2 reviewers will discuss their findings and reach a consensus, which will then become the final report.

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

Study-specific endoscopy may be waived at the investigator's discretion if endoscopy with associated images has been performed within 14 days before Day 1.

### 9.1.15 Gastrointestinal Symptoms of Duodenal Ulcer and Quality of Life

Any gastrointestinal symptoms related to duodenal ulcer (epigastric pain [postprandial, fasting/nocturnal], abdominal bloating, nausea/vomiting, heartburn, lack of appetite) will be captured at the start of the treatment period (Visit 2). At all visits from Visit 2 through the completion of the study drug administration, symptoms noted at Visit 2 will be followed up. If any symptom resolved during the treatment period, the date of resolution will be recorded in the eCRF.

Additionally, during study visits the EQ-5D-5L will be completed before all other procedures at that study visit. This questionnaire will be available in the local language in a paper format. It should be completed by the subject directly while attending the study visit.

## 9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study drug containers/unused medications to each dispensing site visit. Investigators or designee should perform subject treatment compliance checks by reviewing the returned medications. If a subject is persistently noncompliant with the study drug (eg, at more than 2 consecutive compliance checks to have taken less than 75% or more than 133% of the study drug, including HP eradication therapy), 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 drug 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).

Visit windows should be calculated from the day of randomization. Visit windows are listed in Appendix A. Unscheduled nonstudy visits can be held, if in the opinion of the investigator a closer follow-up regimen is required for the subject.

### 9.3.1 Visit 1 (Screening)

Subjects will be screened within 28 days prior to Randomization/ Visit 2. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See

Section 9.1.12 for procedures for documenting screening failures.

Procedures to be completed during the Screening Period are detailed in Appendix A.

- Informed consent.
- Demographics, vital signs, weight, height, medical and medication history.
- Physical examination including concurrent medical conditions and concomitant medications.
- FSH (when menopause is suspected).
- Urine pregnancy test (for females of child bearing potential).
- Guidance on the avoidance of pregnancy.
- Eligibility review (inclusion and exclusion criteria).
- Access IWRS to obtain subject number.
- Complete QOL questionnaire (EQ-5D-5L). 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.

- Pretreatment event assessment.

The following additional screening assessments have to be completed within 14 days prior to Day 1 and must also be documented in the subject's medical record:

- Fasting clinical laboratory tests (hematology, chemistry, urinalysis, hepatitis B & C screening tests).
- Endoscopy to confirm duodenal ulcer.
- ECG procedure.
- $^{13}$C-UBT.

### 9.3.2 Visit 2 (includes Randomization)

Randomization will take place on Day 1 after the following procedures have been performed and documented:

- Physical examination including concomitant medications.
- Vital signs.
- Gastrointestinal symptoms associated with duodenal ulcer.
- Urine pregnancy test (for females of child bearing potential).
- Fasting clinical laboratory tests for gastrin-17, pepsinogen I/II levels [total and ratio].
- Guidance on the avoidance of pregnancy.
- Eligibility review (inclusion and exclusion criteria).
- Randomization using IWRS and also to obtain Med ID numbers of study drug(s) that should be dispensed.
- Study drug(s) dispensed.
- Pretreatment and AE assessments.

If the subject satisfies all of the inclusion criteria and none of the exclusion criteria for randomization, the subject will be randomized (stratified by HP status) using the IWRS as described in Section 8.2. Subjects will be instructed on when to take the first dose of investigational drug as described in Section 6.1. The procedure for documenting Screening failures is provided in Section 9.1.12. For all randomized subjects, the investigator must also complete the End of Study eCRF page.

### 9.3.3 Treatment Period – Visit 3

At treatment Week 2/Visit 3 the subject should return to the study site to complete the following procedures:

- Physical examination including concomitant medications review.

- Vital signs.
- Collect QOL questionnaire (EQ-5D-5L). In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Fasting clinical laboratory test for liver function.
- Urine pregnancy test (for females of child bearing potential).
- Gastrointestinal symptoms associated with duodenal ulcer.
- Collect study drug card issued at visit 2, review treatment compliance, and access IWRS to obtain Med ID numbers for dispensing of new study drug.
- AE assessment.
- Guidance on the avoidance of pregnancy.

### 9.3.4 Treatment Period – Visit 4

At treatment Week 4/Visit 4 the subject should return to the study site to complete the following procedures:

- Physical examination including concomitant medications review.
- Vital signs.
- Collect QOL questionnaire (EQ-5D-5L). In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Endoscopy (if healing is confirmed subject will move into the follow-up period and subject should be registered complete via IWRS).
- Fasting clinical laboratory tests (hematology, chemistry including gastrin-17, pepsinogen I/II levels [total and ratio], and urinalysis).
- Urine pregnancy test (for females of child bearing potential).
- ECG procedure (only if endoscopic healing is confirmed).
- Gastrointestinal symptoms associated with duodenal ulcer.
- Collect study drug card issued at visit 3 and review treatment compliance, and if endoscopic healing is not confirmed access IWRS to obtain Med ID numbers for dispensing of new study drug.
- AE assessment.
- Guidance on the avoidance of pregnancy.

If endoscopic healing is confirmed the subject is considered to have completed the study. The subject should discontinue study drug therapy and move into the follow-up period directly.

### 9.3.5 End of Treatment Period – Visit 5

At treatment Week 6/Visit 5 the subject should return to the study site to complete the following procedures:

- Physical examination including concomitant medications review.
- Vital signs.
- Collect QOL questionnaire (EQ-5D-5L). In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Endoscopy.
- Fasting clinical laboratory tests (hematology, chemistry including gastrin-17 and pepsinogen I/II levels (total and ratio), urinalysis).
- Urine pregnancy test (for females of child bearing potential).
- ECG procedure.
- Gastrointestinal symptoms associated with duodenal ulcer.
- Collect study drug card issued at visit 4, review treatment compliance.
- AE assessment.
- Guidance on the avoidance of pregnancy.
- Register subjects as completed via IWRS.

If after 6 weeks treatment endoscopic healing is confirmed the subject should move into the follow-up period. If endoscopic healing is not confirmed, the subject should be treated according to the Investigator's judgment. In either case the subject is considered to have completed the study. Follow-up will also be performed for HP+ subjects who do not have endoscopically confirmed healing after 6 weeks treatment.

### 9.3.6 Early Termination

If a subject discontinues study treatment prematurely and does not have endoscopically confirmed healing an Early Termination Visit will be performed within 14 days of the last dose of study drug. The following procedures will be performed and documented:

- Physical examination including concomitant medications review.
- Vital signs.
- Collect QOL questionnaire (EQ-5D-5L). In order to avoid subject's bias, this shall be completed by the subjects as the first priority of all procedures at this visit.
- Endoscopy (if healing is confirmed subject may move into the follow-up period).

- Fasting clinical laboratory tests (hematology, chemistry including gastrin-17, pepsinogen I/II levels [total and ratio], and urinalysis).
- Urine pregnancy test (for females of child bearing potential).
- ECG procedure.
- Gastrointestinal symptoms associated with duodenal ulcer.
- Collect study drug card issued at previous visit, review treatment compliance.
- AE assessment.
- Guidance on the avoidance of pregnancy.
- Register subjects as discontinued (if not healed) or completed (if healed) via IWRS.

### 9.3.7 Follow-up Period – Visits F-1 and F-2

The follow-up period comprises a maximum of 2 subject visits, and will begin the first day after the end of the treatment period. Subjects with endoscopically confirmed healing of ulcer(s) at Week 4 or at Week 6 will discontinue treatment at that time and enter the follow-up period. Subjects without endoscopically confirmed ulcer healing by Week 6 of the treatment period will discontinue treatment at Week 6 and enter the follow-up period.

The following procedures will be performed and documented during each of the 2 Follow-up visits:

- Physical examination including concomitant medications review.
- Fasting blood sampling for serum gastrin-17 and pepsinogen I/II levels (total and ratio).
- $^{13}$C-UBT for subjects treated with HP eradication therapy only (at visit F-2).
- AE assessment.

After completion of the 2 visits, or when serum gastrin-17 levels and the pepsinogen I/II ratio have returned to normal and the subject has provided the $^{13}$C-UBT sample (if applicable), the subject is considered to have completed the follow-up period.

# 10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

## 10.1 Definitions

### 10.1.1 Pretreatment Events

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

### 10.1.2 AEs

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

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory 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 drug, or of a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

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

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

### 10.1.4 SAEs

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

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

**Table 10.a Takeda Medically Significant AE List**

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

PTEs that fulfil 1 or more of the serious criteria above are also to be considered 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 nonserious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

There are no AEs of Special Interest in this study.

### 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 drug(s) will be assessed using the following categories:

Yes: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug can be argued, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.

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

### 10.1.8 Relationship to Study Procedures

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

The relationship should be assessed as Yes if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as No.

### 10.1.9 Start Date

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

### 10.1.10 Stop Date

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

### 10.1.11 Frequency

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

### 10.1.12 Action Concerning Study Drug(s)

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Reduced – the dose was reduced due to the particular AE
- Dose Interrupted - The study drug was temporarily interrupted (discontinued) (including voluntary drug interruption by the subject) due to the particular AE, and resumed at a later date

### 10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/serious PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/serious PTE with the condition remaining “recovering/resolving”.

- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/serious PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/serious PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/serious PTEs which are considered as the cause of death.
- Unknown – the course of the AE/serious PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

## 10.2 Procedures

### 10.2.1 Collection and Reporting of AEs

*10.2.1.1 PTE and AE Collection Period*

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

Collection of AEs will commence from the time that the subject is first administered study drug (Visit 2, randomization). Routine collection of AEs will continue until the subject's last study visit (ie, Early Termination or Follow-up visit).

*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. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

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

- Event term.
- Start and stop date.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study 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.

### 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 LFTs as SAEs (Medically Significant Event)

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 (medically significant event - Hy's Law) 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 transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, 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 Drug Dictionary.

### 12.1 CRFs

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

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

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

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, subject evaluability, and appropriateness of the planned statistical methods.

### 13.1.1 Analysis Sets

In this study, 3 kinds of analysis sets are defined: FAS, PPS and safety analysis set. The FAS, the main analysis set used for primary efficacy analysis, will be defined as "all subjects who were randomized and received at least 1 dose of the study drug." The definition of each analysis set will be described in the SAP.

### 13.1.2 Analysis of Demographics and Other Baseline Characteristics

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

### 13.1.3 Efficacy Analysis

**(1) Primary endpoint and analytical methods**

Primary endpoint

The primary endpoint for this study is the percentage of subjects with endoscopically confirmed healing of duodenal ulcer(s) at Week 4 or 6.

Primary analysis

The following analyses will be based on the FAS.

The healing rate of duodenal ulcer at Week 4 or Week 6 and the 2-sided 95% CI will be provided by treatment group. The healing rate difference between the TAK-438 treatment group and the lansoprazole treatment group (the TAK-438 treatment group minus the lansoprazole group) at Week 4 or Week 6 and the 2-sided 95% CIs using Newcombe methods will be provided.

Secondary analysis

To check the robustness of the results, the same analyses as the primary analyses will be performed using the PPS.

**(2) Secondary endpoints and analytical methods**

Eradication rate of *H pylori*

The evaluation of the *H pylori* eradication rate will be based on a pooled analysis described in item (7) below, rather than from separate analyses of data from TAK-438_302 or TAK-438_304. Eradication rates and the 2-sided 95% CIs will be provided by treatment group. The eradication rate difference between the TAK-438 treatment group and the lansoprazole group (the TAK-438 treatment group minus the lansoprazole group) and the 2-sided 95% CI will also be provided.

Healing rate of duodenal ulcer during the 4-week treatment

The same analyses as the primary analyses of the primary endpoint will be conducted.

Gastrointestinal symptoms associated with duodenal ulcer

For each symptom (epigastric pain [postprandial, fasting, nocturnal], abdominal bloating, nausea/vomiting, heartburn, lack of appetite), the frequency distribution will be provided by treatment group, and the point estimates and 2-sided 95% CIs will be calculated, and the point estimates and 2-sided 95% CIs of the proportion differences between the treatment groups will be calculated.

**(3) Multiple Comparison/Multiplicity**

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

- The primary endpoint of healing rate of duodenal ulcer during the 6-week treatment will be tested for noninferiority between the TAK-438 group and the lansoprazole group based on the FAS. If the lower bound of the 95% CI is ≥-6%, noninferiority for TAK-438 relative to lansoprazole with regard to duodenal ulcer healing will be declared.
- If the previous test is successful, the secondary endpoint of eradication rate of *H pylori* will be tested for noninferiority between the TAK-438 group and the lansoprazole group based on the FAS. If the lower bound of the 95% CI of the difference is ≥-10%, noninferiority for TAK-438 relative to lansoprazole with regard to *H pylori* eradication will be declared.
- If the previous test is successful, the primary endpoint of healing rate of duodenal ulcer during the 6-week treatment will be tested for superiority between the TAK-438 group and the lansoprazole group based on the FAS. If the lower bound of the 95% CI is ≥0%, superiority for TAK-438 relative to lansoprazole with regard to duodenal ulcer healing will be declared.
- If the previous test is successful, the secondary endpoint of eradication rate of *H pylori* will be tested for superiority between the TAK-438 group and the lansoprazole group based on the FAS. If the lower bound of the 95% CI of the difference is ≥0%, superiority for TAK-438 relative to lansoprazole with regard to *H pylori* eradication will be declared.

The noninferiority margin for *H pylori* eradication is based on literature on omeprazole/amoxicillin/clarithromycin/bismuth quadruple therapy (bismuth-containing).

Limited data are available from clinical trials with PPI/amoxicillin/clarithromycin/bismuth quadruple therapy (bismuth-containing). In previous phase 3 trials, the eradication rate of *H pylori* with PPI-based triple therapy in HP+ subjects with gastric or duodenal ulcers was shown to be 86.4% to 89.2% for lansoprazole/amoxicillin/clarithromycin, 78.8% to 83.0% for omeprazole/amoxicillin/clarithromycin, and 85.7% to 91.4% for rabeprazole/amoxicillin/clarithromycin; the range of these eradication rates (78.8% to 91.4%) corresponds to a difference of ≥10%. Hence the noninferiority margin is specified as -10%.

**(4) Additional efficacy endpoints and methods**

QOL endpoints (EQ-5D-5L)

QOL endpoints will be conducted with an analysis of covariance model with treatment and baseline *H pylori* status as factors and baseline as a covariate.

Confirmed healing of duodenal ulcer

- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at either Week 4 or Week 6 based on their baseline *H pylori* status.
- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 based on their baseline *H pylori* status.

Percentage of subjects with endoscopically confirmed healing of duodenal ulcer and the 2-sided 95% CI will be provided by treatment group and baseline *H pylori* status. Healing percentage difference between the TAK-438 treatment group and the lansoprazole treatment group (the TAK-438 treatment group minus the lansoprazole group) and the 2-sided 95% stratified Newcombe CI with baseline *H pylori* status as a stratified factor will be provided.

- Percentage of subjects with *H pylori* infection at Baseline who achieve endoscopically confirmed healing of duodenal ulcer either at Week 4 or Week 6 based on their *H pylori* status at Follow-up visit F-2.
- Percentage of subjects with *H pylori* infection at Baseline who achieve endoscopically confirmed healing of duodenal ulcer at Week 4 based on their *H pylori* status at Follow-up visit F-2.

With regard to the percentage of subjects with *H pylori* infection at Baseline and endoscopically confirmed healing of duodenal ulcer, a similar approach to the aforementioned will be applied.

**(5) Methods of data transformation and handling of missing data**

Details will be described in the SAP.

**(6) Significance level and confidence coefficient**

- Significance level: 5% (2-sided test)
- Confidence coefficient: 95% (2-sided)

**(7) Pooled analysis for eradication rate of *H pylori***

Eradication rate difference between the TAK-438 treatment group and the lansoprazole group (the TAK-438 treatment group minus the lansoprazole group) and the 2-sided 95% CI will be provided. Eradication rate of *H pylori* and its 2-sided 95% stratified Newcombe CI with study as a stratified factor will be provided by treatment group, using pooled FAS dataset from studies TAK-438_302 and TAK-438_304.

Furthermore, assuming that the true eradication rate of *H pylori* is 90% for both TAK-438 and lansoprazole bismuth-containing quadruple therapies, a sample size of more than 150 HP+ subjects per group across both studies TAK-438_302 and TAK-438_304 will provide over 80% power to establish noninferiority using a 2-sided 95% CI with a -10% noninferiority margin in the Chinese population.

### 13.1.4 Safety Analysis

Safety analysis will be performed using the safety analysis set.

The number and percentage of subjects with TEAEs will be summarized by 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 TEAEs overall and by severity. Change from Baseline in clinical laboratory tests, vital signs and quantitative ECG variables will be summarized by treatment group. For qualitative ECG assessments, postbaseline 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

The protocol for TAK-438_304 study was written in 2012 while the TAK-438 duodenal ulcer pivotal study (CCT-102) was still ongoing in Japan. The sample size of 640 was based on the assumption that the Week 6 duodenal ulcer healing rate would be 97.8% for both TAK-438 and lansoprazole, and assuming a dropout rate of up to 20%. The assumption for the ulcer healing rate was based on historical studies with lansoprazole. In a phase 3 study in Japan to compare the efficacy of lansoprazole and famotidine for healing of duodenal ulcer, the Week 6 healing rate was 97.8% for lansoprazole and 91.5% for famotidine.

TAK-438 CCT-102 study was completed in 2013. The duodenal ulcer healing rate was 95.5% in the TAK 438 treatment arm. The design of TAK-438-304 study is based on TAK-438 CCT-102 study with identical key enrollment criteria. Therefore, the sample size has been recalculated based on a 95.5% healing rate. In addition, since *H pylori* eradication rate is a secondary endpoint, this endpoint has not been used for sample size calculation.

Assuming that the true Week 6 duodenal ulcer healing rate is 95.5% for both TAK-438 and lansoprazole, and assuming that the dropout rate is up to 10%, a sample size of 265 subjects per group in the overall population, including no fewer than 238 Chinese subjects per group, will provide at least 80% power to establish noninferiority in the Chinese population using a 2-sided 95% CI with a -6% noninferiority margin. This sample size will also provide 83.9% power to establish noninferiority in the overall population.

In a phase 3 study in Japan to compare the efficacy of lansoprazole and famotidine for healing of duodenal ulcer, the Week 6 healing rate was 97.8% for lansoprazole and 91.5% for famotidine, corresponding to a difference of 6.3%. Additionally, in studies of lansoprazole versus placebo in US (M87-090), the Week 4 healing rate was 91.7% for lansoprazole 30 mg and 46.1% for placebo in one study, corresponding to a difference of 45.6%, and 80.3% for lansoprazole 30 mg and 47.5% for placebo in the other study, corresponding to a difference of 32.8%. A noninferiority margin of -6% is specified, which is less than the difference between lansoprazole and famotidine in the Japanese study and less than half of the difference between lansoprazole and placebo in the US studies.

# 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 (contract research organization) and by the IRB or IEC.

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

## 14.2 Protocol Deviations

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

## 14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

## 15.0 ETHICAL ASPECTS OF THE STUDY

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

### 15.1 IRB and/or IEC Approval

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

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

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

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

### 15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all

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

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

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

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

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

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

## 15.3 Subject Confidentiality

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

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

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

## 15.4 Publication, Disclosure, and Clinical Trial Registration Policy

### 15.4.1 Publication and Disclosure

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

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

### 15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, Takeda will, at a minimum register all clinical trials conducted in subjects 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, 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

1. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease--where next? Aliment Pharmacol Ther 2005;22(2):79-94.

## Appendix A Schedule of Study Procedures

| | Screening Period | Treatment Period (b) | | | | | Follow-up Period (d) | |
|---|---|---|---|---|---|---|---|---|
| **Study Day/Week:** | | **Day 1 (a, u)** | **Week 2 (Day 15)** | **Week 4 (Day 29) (u)** | **Week 6 (Day 43) (u)** | **Early Termination Visit (c)** | **2 Weeks Post-treatment** | **4 Weeks Post-treatment** |
| **Visit Windows (Days):** | **Day -28 to Day -1** | **-** | **±3 days** | **±3 days** | **±3 days** | **Within 14 days of last dose** | **Day 15 to 28** | **Day 29 to 42** |
| **Visit Number:** | **1** | **2** | **3** | **4** | **5** | **-** | **F-1** | **F-2** |
| Informed consent | X | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | |
| Demographics and medical history | X | | | | | | | |
| Medication history | X | | | | | | | |
| Physical examination | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | | |
| Weight and height | X | | | | | | | |
| Concomitant medications | X | X | X | X | X | X | X (e) | X (e) |
| Concurrent medical conditions | X | | | | | | | |
| Clinical laboratory tests (f) | X(g) | | | X | X | X | | |
| LFT (r) | | | X | | | | | |
| Serum gastrin-17 / Pepsinogen I/II levels (total and ratio) | | X | | X | X | X | X(s) | X(t) |
| Urine pregnancy test (hCG) (h) | X | X | X | X | X | X | | |
| Hepatitis B and C tests (o) | X(g) | | | | | | | |
| FSH (i) | X | | | | | | | |
| Guidance on avoidance of pregnancy (h) | X | X | X | X | X | X | | |
| ECG | X(k) | | | X(j) | X | X | | |
| Endoscopy | X(k) | | | X | X | X | | |

Footnotes are on last table page.

## Appendix A Schedule of Study Procedures (continued)

| | Screening Period | Treatment Period (b) | | | | | Follow-up Period (d) | |
|---|---|---|---|---|---|---|---|---|
| **Study Day/Week:** | | **Day 1 (a, u)** | **Week 2 (Day 15)** | **Week 4 (Day 29) (u)** | **Week 6 (Day 43) (u)** | **Early Termination Visit (c)** | **2 weeks post-treatment** | **4 weeks post-treatment** |
| **Visit Windows (Days):** | **Day -28 to Day -1** | **-** | **± 3 days** | **± 3 days** | **± 3 days** | **within 14 days of last dose** | **Day 15 to 28** | **Day 29 to 42** |
| **Visit Number:** | **1** | **2** | **3** | **4** | **5** | **-** | **F-1** | **F-2** |
| $^{13}$C-UBT to confirm *H* infection status | X(g) | | | | | | | X(n) |
| Investigator review of gastrointestinal symptoms | | X | X | X | X | X | | |
| QOL questionnaire (EQ-5D-5L) (p) | X | | X | X | X | X | | |
| Randomization via IWRS | | X(l) | | | | | | |
| Obtain subject number via IWRS | X | | | | | | | |
| Dispense TAK-438/ lansoprazole via IWRS | | X | X | X(m) | | | | |
| Dispense companion drug via IWRS | | X(q) | | | | | | |
| Drug return/ accountability/ compliance | | | X | X | X | X | | |
| Register subject as discontinued or completed via IWRS | | | X(j) | X | X | X | | |
| PTE assessment | X- - - - - - - | X- | - - - - - - - | - - - - - - - | - - - - - - - | - - - - - - - - - - | - - - - - - - - - - | - - - - - - - - - |
| AE assessment | | X | X | X | X | X | X | X |

Footnotes are on last table page.

(a) The day of first investigational drug administration for Treatment period is Day 1. The day before first investigational drug administration for Treatment period is Day -1.
(b) If and when endoscopic healing of duodenal ulcer has been confirmed in the subject, he/she will complete the treatment period and move directly into the Follow-up period.
(c) Conduct Final Visit procedures for subjects discontinued from treatment early per Section 9.3.6.
(d) The subject will move on to the Follow-up period after discontinuation of treatment, either after Visit 4 (Week 4) for subjects with endoscopic healing of duodenal ulcer[s] only, or after Visit 5 (Week 6) for all subjects regardless of ulcer healing. All subjects will complete the scheduled Follow-up period visits until the recovery of serum gastrin-17 level and pepsinogen I/II ratio are confirmed or for a maximum of 4 weeks. HP+ subjects will provide the $^{13}$C-UBT sample at F-2.
(e) The use of gastric mucosal protective agents may be allowed during the Follow-up period. F-2 will be performed for $^{13}$C-UBT.
(f) Hematology, serum chemistries, and urinalysis tests will be done at the central laboratory. Local laboratories may be used to perform laboratory tests only under special circumstances, on case by case basis with sponsor's agreement.
(g) Visit window: Day –14 to Day 1 (predose).
(h) Women of childbearing potential.
(i) Only if menopause is suspected.
(j) ECG and registration in IWRS of study completion to be performed at Week 4 only for those subjects in whom endoscopic healing is confirmed; thereafter those subjects will move directly into the Follow-up period.
(k) Visit window: Day –14 to Day 1 (predose). If endoscopy with associated images has been performed within 14 days prior to Day 1, the study-specific endoscopy may be waived in favor of the existing results. If an ECG has been performed within 14 days prior to randomization, the study-specific ECG may be waived.
(l) Subjects must not have been given any other agent affecting the digestive organs on the day of randomization and must take the first dose of study medication on the day of randomization during the Day 1 visit.
(m) To be performed as appropriate for those subjects in which endoscopic healing has not been confirmed during visits involving endoscopy.
(n) $^{13}$C-UBT should be repeated for HP+ subjects at F-2 to ascertain HP eradication status.
(o) Hepatitis B and C analysis in accordance with Section 9.1.8 Table 9.b will be conducted at the central laboratory. Hepatitis B and C tests performed as per local routine practice within 14 days prior to randomization (Day 1), before signing of informed consent form will be accepted.
(p) EQ-5D-5L questionnaire shall be the first priority in all procedures (except signing the ICF) at each visit.
(q) Only for HP+ subjects.
(r) LFTs include ALT, AST, total bilirubin and direct bilirubin.
(s) Completed by subjects with or without ulcer healing regardless of HP status.
(t) Completed by subjects with or without ulcer healing regardless of HP status, only if no serum gastrin-17 or pepsinogen I/II recovery at F-1 visit.
(u) The subject will be instructed to present to the clinic prior to taking the study medication at the visits during the treatment phase in which serum gastrin and pepsinogen I/II levels will be measured or endoscopy will be performed. The study medication will be taken by the subject after completion of assessments on the days of those study visits.

## Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The investigator agrees to assume the following responsibilities:

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

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

## Appendix C Elements of the Subject Informed Consent

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

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

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

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. 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 subjects, 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. Male subjects must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
26. 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 Detailed Description of Amendments to Text

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

**Change 1:** Removal of reference to Study TAK-438_115 as part of rationale for study design.

The primary change occurs in Section 4.2 Rationale for the Proposed Study:

Deleted text: ~~An ongoing drug-drug interaction study in Korea, TAK-438_115, is investigating the possible pharmacokinetic (PK) and safety effects of the co-administration of TAK-438 with clarithromycin, amoxicillin, and bismuth as a quadruple therapy in HP+ subjects.~~

**Rationale for Change:**

TAK-438_115 is now complete and found no evidence of interaction between TAK-438 and quadruple therapy with clarithromycin, amoxicillin, and bismuth in subjects who are HP+.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY

Section 6.1 Study Design and footnote to Figure 6.a

Section 7.1 Inclusion Criteria, criterion #3

**Change 2**Subjects with no ulcer healing at Week 6 could be treated with another course of PPI or other anti-acid secretory agents or antibiotics, at the discretion of the investigator.

The primary change occurs in Section 6.1 Study Design:

Added text: **For subjects with no ulcer healing at Week 6 of treatment, the investigator may follow local clinical practice and these subjects may be treated with another course of PPI or other anti-acid secretory agents, or antibiotics, during the safety follow-up period (please see Table 7.a). This should be documented during the follow-up**

**Rationale for Change:**

To allow investigator's to treat subjects with no ulcer healing during the study according to local practice

**Change 3** Exclusion criterion 10 concerning subjects participating in another clinical study within 30 days of Visit 1, is deleted.

The primary change occurs in Section 7.2 Exclusion Criteria:

Deleted text: ~~10. The subject has participated in another clinical study within the past 30 days from Visit 1.~~

**Rationale for Change:**

Exclusion criterion 10 has been removed to align the current protocol with the protocol for the pivotal study. This criterion will be covered under exclusion criterion #1 that excludes subjects receiving any investigational compound within 90 days prior to the treatment period.

**Change 4:** Exclusion criterion 12 is deleted to allow subjects with ulcer size >2 cm in any diameter and those with >3 separate duodenal ulcers to enter the study.

The primary change occurs in Section 7.2 Exclusion Criteria:

Deleted text: ~~12. Subjects with any duodenal ulcer of >2 cm in any diameter or with >3 separate duodenal ulcers in total as evident by endoscopy within 14 days prior to randomization.~~

**Rationale for Change:**

Exclusion criterion 12 was originally intended to prevent subjects with potential malignant ulcers being recruited into the study. However, the retained exclusion criteria specifically exclude inclusion of subjects with a diagnosis of gastric malignancy or a duodenal ulcer whose morphology suggested malignancy as evident by endoscopy within 14 days prior to randomization.

**Change 5:** A footnote is added to Table 9.b to clarify that subjects with negative hepatitis C virus antibody test results may be randomized before hepatitis C-viral load-RNA test results are available.

The primary changes occur in Section 9.1.8 Procedures for Clinical Laboratory Samples Table 9.b:

Initial wording:

| **Table 9.b** | **Clinical Laboratory Tests** |
|---|---|
| **Hepatitis B & C Analysis** | |
| HBsAg | |
| HCV antibody | |
| HCV-viral load-RNA | |

Amended or new wording:

| **Table 9.b** | **Clinical Laboratory Tests** |
|---|---|
| **Hepatitis B & C Analysis** | |
| HBsAg | |

HCV antibody
HCV-viral load-RNA **(b)**

**(b) Subjects with negative HCV antibody test results may be randomized before HCV-viral load-RNA test results are available. If the HCV-viral load-RNA test result is positive, the subject will be withdrawn from the study.**

**Rationale for Change:**

To clarify that while all subjects will undergo testing for both HCV antibody and HCV-viral load-RNA, subjects with negative HCV antibody test results may be randomized before the results of the HCV-viral load-RNA test are available.

**Change 6:** Procedure for retesting of abnormal liver function tests, and a clarification concerning elevated serum gastrin and pepsinogen I and II levels, which are physiological responses to increased gastric pH and the suppression of gastric acid secretion.

The primary changes occur in Section 9.1.8 Procedures for Clinical Laboratory Samples:

Initial wording: Given the possibility that the use of TAK-438 or lansoprazole may be associated with increases in serum gastrin-17 and pepsinogen I/II levels, the subjects will be examined for gastrin-17 and pepsinogen I/II levels (total and ratio) to investigate the magnitude of these increases during the Treatment and Follow-up periods (as appropriate).

Amended or new wording: **(Note for ALT/AST and total bilirubin: >ULN to ≤2 × ULN. Kindly re-test LFT in 2 weeks to monitor abnormal LFT. This abnormal LFT value should not be reported as AE unless is clinically significant. An unscheduled visit may be performed if necessary.)**

~~Given the possibility that the use of~~ TAK-438 or lansoprazole may be associated with increases in serum gastrin-17 and pepsinogen I/II levels~~, the~~**. Thus, all** subjects will be examined for gastrin-17 and pepsinogen I/II levels (total and ratio) to investigate the magnitude of these increases during the Treatment and Follow-up periods ~~(as appropriate)~~. **Increases in serum gastrin and pepsinogen I/II levels are physiological responses to gastric acid suppression and elevated content pH due to the pharmacological action of the study drugs.**

**Rationale for Change:**

Because ALT, AST, or total bilirubin >2 × ULN will result in discontinuation and withdrawal of a subject, close monitoring of the LFT is required. Increases in serum gastrin and pepsinogen I/II level are due to the pharmacological action of TAK-438 or lansoprazole.

Section 2.0 STUDY SUMMARY

Section 7.2 Exclusion Criteria

**Change 7:** The liver function test at Visit 3 is clarified as a fasting clinical laboratory test.

The primary change occurs in Section 9.3.3 Treatment Period – Visit 3:

| | |
|---|---|
| Initial wording: | • Liver function tests. |
| Amended or new wording: | • ~~Liver function tests~~ **Fasting clinical laboratory test for liver function**. |

**Rationale for Change:**

To clarify that clinical laboratory tests for liver function are performed after fasting, as specified in Section 9.1.8.

**Change 8:** The sample sizes for the overall study population and the Chinese subpopulation have been recalculated on the basis of an estimated dropout rate of 10% (previously 20%), resulting in sample size re-estimation.

The primary change occurs in Section 13.3 Determination of Sample Size:

| | |
|---|---|
| Initial wording: | Assuming that the true Week 6 duodenal ulcer healing rate is 95.5% for both TAK-438 and lansoprazole, and assuming that the dropout rate is up to 20%, a sample size of 385 subjects per group will provide 92% power to establish noninferiority using a 2-sided 95% CI with a -6% noninferiority margin and to provide a sample size of 269 subjects for regulatory requirements in China. Furthermore, assuming the proportion of subjects with *H pylori* infection at Baseline is about 80%, a sample size of 308 subjects per group will provide 85% power for noninferiority based on same effect size as overall population. The assumption of rate for ulcer healing is based on historical studies with lansoprazole. |
| Amended or new wording: | Assuming that the true Week 6 duodenal ulcer healing rate is 95.5% for both TAK-438 and lansoprazole, and assuming that the dropout rate is up to ~~20%~~ **10%**, a sample size of ~~385~~ **265** subjects per group **in the overall population, including no fewer than 238 Chinese subjects per group,** will provide ~~92%~~ **at least 80%** power to establish noninferiority **in the Chinese population** using a 2-sided 95% CI with a -6% noninferiority margin ~~and provide a sample size of 269 subjects for regulatory requirements in China~~. **This sample size will also provide 83.9% power to establish noninferiority in the overall population.** ~~Furthermore, assuming the proportion of subjects with *H pylori* infection at baseline is about 80%, a sample size of 308 subjects per group with *H pylori* infection at baseline will provide 85% power for noninferiority based on the same effect size as overall population. The assumption of rate for ulcer healing is based on historical studies with lansoprazole.~~ |

**Rationale for Change:**

Data from completed studies indicate that the dropout rate used for the power calculations should be reduced to 10%. In the Japanese Study CCT-102, in subjects with duodenal ulcer, the dropout rate was 5.9% and in Study TAK-438_303, in subjects with erosive esophagitis, it was 4.8%. Additionally, in Japanese Studies CCT-301 and CCT-302, in subjects with gastric or duodenal ulcers, the dropout rates were 8.4% and 7.6%, respectively.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 6.1 Study Design.

**Change 9:** *H pylori* eradication data from this study (TAK-438_304) will be pooled with data from TAK-438_302.

The primary change occurs in Section 13.1.3 Efficacy Analysis (3):

Initial wording:

- If the previous test is successful, the secondary endpoint of eradication rate of *H pylori* will be tested for superiority between the TAK-438 group and the lansoprazole group based on the FAS. If the lower bound of the 95% CI of the difference is ≥0%, superiority for TAK-438 relative to lansoprazole with regard to *H pylori* eradication will be declared.

Amended or new wording:

- If the previous test is successful, the secondary endpoint of eradication rate of *H pylori* will be tested for superiority between the TAK-438 group and the lansoprazole group based on the FAS. If the lower bound of the 95% CI of the difference is ≥0%, superiority for TAK-438 relative to lansoprazole with regard to *H pylori* eradication will be declared.

**The noninferiority margin for *H pylori* eradication is based on literature on omeprazole/amoxicillin/clarithromycin/bismuth quadruple therapy (bismuth-containing).**

**Limited data are available from clinical trials with PPI/amoxicillin/clarithromycin/bismuth quadruple therapy (bismuth-containing). In previous phase 3 trials, the eradication rate of *H pylori* with PPI-based triple therapy in HP+ subjects with gastric or duodenal ulcers was shown to be 86.4% to 89.2% for lansoprazole/amoxicillin/clarithromycin, 78.8% to 83.0% for omeprazole/amoxicillin/ clarithromycin, and 85.7% to 91.4% for rabeprazole/amoxicillin/clarithromycin; the range of these eradication rates (78.8% to 91.4%) corresponds to a difference of ≥10%. Hence the noninferiority margin is specified as -10%.**

New text also added to Section 13.1.3 Efficacy Analysis:

Added text:

**(7) Pooled analysis for eradication rate of *H pylori***

**Eradication rate difference between the TAK-438 treatment group and the lansoprazole group (the TAK-438 treatment group minus the lansoprazole group) and the 2-sided 95% CI will be provided. Eradication rate of *H pylori* and its 2-sided 95% stratified Newcombe CI with study as a stratified factor will be provided by treatment group, using pooled FAS dataset from studies TAK-438_302 and TAK-438_304.**

**Furthermore, assuming that the true eradication rate of *H pylori* is 90% for both TAK-438 and lansoprazole bismuth-containing quadruple therapies, a sample size of more than 150 HP+ subjects per group across both studies TAK-438_302 and TAK-438_304 will provide over 80% power to establish noninferiority using a 2-sided 95% CI with a -10% noninferiority margin in the Chinese population.**

**Rationale for Changes:**

Study TAK-438_302 is no longer powered separately for analysis of *H pylori* eradication as it is now proposed to evaluate HP eradication using pooled data from the current study and from Study TAK-438_302, instead of undertaking separate evaluations from each study.

**Change 10:** Study-specific endoscopy may be waived at the investigator's discretion if endoscopy with associated images has been performed within 14 days before Day 1..

The primary change occurs in Section 9.1.14 Endoscopy:

Added text:

**Study-specific endoscopy may be waived at the investigator's discretion if endoscopy with associated images has been performed within 14 days before Day 1.**

**Rationale for Change:**

To waive the need for repeat endoscopy fewer than 14 days after a prescreening endoscopy has been undertaken.

Appendix A Schedule of Study Procedures, footnote l, also contains this change.

**Change 11:** Time of dosing of TAK-438 amended to after breakfast or dinner (previously after breakfast only).

The primary change occurs in Section 8.1.3 Dose and Regimen:

| | |
|---|---|
| Initial wording: | *H pylori* negative subjects will be dispensed one blister card containing TAK-438 or lansoprazole (with appropriate placebo) after randomization at Visit 2 and at subsequent visits as required. HP- subjects will be required to take one tablet (containing either TAK-438 or placebo) and one capsule (containing either lansoprazole or placebo) daily (QD) after breakfast at about the same time as he/she usually does, with approximately 240 ml water. |
| Amended or new wording: | *H pylori* negative subjects will be dispensed 1 blister card containing TAK-438 or lansoprazole (with appropriate placebo) after randomization at Visit 2 and at subsequent visits as required. HP- subjects will be required to take 1 tablet (containing either TAK-438 or placebo) and 1 capsule (containing either lansoprazole or placebo) daily (QD) after breakfast **or dinner** at about the same time as he/she usually does, with approximately 240 mL water. **The preference is for the dose to be given after breakfast; however, if the first randomization visit was scheduled in the late afternoon, it is acceptable for the dose to be taken after dinner.** |

**Rationale for Change:**

To correct an inconsistency between the dosing instructions and the study drug label. The drug label indicates that study drugs will be taken after breakfast or dinner, while the protocol previously stated that study drugs will be taken after breakfast only. The preference is for subjects to take study drugs after breakfast. However, if the first randomization is scheduled late in the afternoon, it is acceptable for the dose to be taken after dinner.

The following sections also contain this change:

- Section 6.2 Justification for Study Design, Dose, and Endpoints.
- Section 7.4 Diet, Fluid, Activity Control.

**Change 12:** Clarification of follow-up guidance on excluded medications and treatments in Table 7.a, amended for proton pump inhibitors, histamine H2 receptor antagonists, insulin, antidiabetic agents, and antibiotics.

The primary change occurs in Section 7.3 Excluded Medications and Treatments Table 7.a:

| | |
|---|---|
| Description of change: | The following modifications were made to the table:<br>The phrase 'excluding of PPIs and antibiotics' has been removed from the row describing medications that may interfere with the $^{13}$C-UBT<br>Definitions of beginning and end of exclusion periods for the different classes of medication have been revised and made more specific relative to timings relative to the $^{13}$C-UBT and applicability to HP+ subjects<br>Medications contraindicated with clarithromycin have been extended to include simvastatin, lovastatin, atorvastatin etc and other statins such as fluvastatin, pravastatin, and rosuvastatin may be allowed but used with caution.<br>$H_2$ receptor antagonists have been deleted and probencid (contraindicated with bismuth) has been added to the row describing exclusion of agents affecting digestive organs<br>In the row about the medications contradicted with bismuth, insulin or oral antibiotic medications and tetracycline antibiotics have been deleted. |

**Rationale for Change:**

To conform to $^{13}$C-UBT product insert, which states the following:

The test should be performed following at least:

- 4 weeks after a treatment against a bacterial infection.
- 2 weeks after the last administration of a medicine to reduce release of stomach acid.

Bismuth used in this study is not contraindicated with insulin and antidiabetic medication.

**Change 13** Provision has been made for the use of premedication for endoscopy to be provided at investigator's discretion.**:**

The primary change occurs in Section 9.1.14 Endoscopy:

| | |
|---|---|
| Initial wording: | • Endoscopy should be performed while subjects are fasted and according to the usual practice of the institution (i.e. in regard to premedications or concomitant therapies as long as they are not prohibited in Section 7.3 of this protocol). |
| Amended or new wording: | • Endoscopy should be performed while subjects are fasted and according to the usual practice of the institution ~~(i.e. in regard to premedications or concomitant therapies as long as they are not prohibited in Section 7.3 of this protocol)~~. **Use of pre-medications for endoscopy (e.g. analgesics, local anesthetics, anticholinergic agents, sedatives, anticholinergics/antispasmodics, antifoaming agents) may be allowed at the discretion of the Investigator as per local standard practice.** |

**Rationale for Change:**

To clarify that premedication can be administered for endoscopy according to local practice.

**Change 14:** Formulation of bismuth for use in Korean sites is specified in relevant sections of the protocol.

The primary change occurs in Section 6.1 Study Design:

| | |
|---|---|
| Initial wording: | • *H pylori* infected (HP+) subjects will take TAK-438 20 mg or lansoprazole 30 mg (blinded with matching placebo) twice daily (BID) in addition to bismuth-containing quadruple antibiotic therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate 600 mg [equivalent to 220 mg bismuth] BID) for 2 weeks. After 2 weeks of eradication therapy, subjects will be required to take only TAK-438 or lansoprazole once a day (QD) for up to 4 weeks (ie, up to a total of 6 weeks of treatment). The subject will remain in the same treatment arm throughout the study duration. |
| Amended or new wording: | • *H pylori* infected (HP+) subjects will take TAK-438 20 mg or lansoprazole 30 mg (blinded with matching placebo) twice daily (BID) in addition to bismuth-containing quadruple ~~antibiotic~~ therapy (amoxicillin 1 g BID, clarithromycin 500 mg BID, and bismuth potassium citrate/**bismuth tripotassium dicitrate** 600 mg [equivalent to 220 mg bismuth] BID) for 2 weeks. After 2 weeks of eradication therapy, subjects will be required to take only TAK-438 or lansoprazole once a day (QD) for up to 4 weeks (ie, up to a total of 6 weeks of treatment). The subject will remain in the same treatment arm throughout the study duration. |

**Rationale for Change:**

To include the formulation of bismuth available in Korea

The following sections also contain this change:

Section 2.0 STUDY SUMMARY.

Section 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling.

Section 8.1.3 Dose and Regimen.

**Change 15:** Provision for serum gastrin follow-up for all subjects.

The primary change occurs in Section 6.1 Study Design:

Initial wording:

For all subjects, ulcer healing rates will be assessed by endoscopy at Weeks 4 and 6 of treatment. With or without endoscopic evidence of duodenal ulcer healing, the treatment duration of the study is no more than 6 weeks.

Subjects (HP+ or HP-) with endoscopic evidence of duodenal ulcer(s) healing at Week 4 or at Week 6 will discontinue treatment at that time, and enter into the Follow-up period.

HP+ subjects with no healing at Week 6 will discontinue treatment and enter Follow-up.

HP- subjects with no ulcer healing by Week 6 of the treatment period will be considered "completed cases" and be discontinued from the study.

*Follow-up period:*

The subjects to be followed up will include both HP+ and HP- subjects with confirmed ulcer healing during the treatment period. HP+ subjects with no ulcer healing during treatment period will require one follow-up visit (F-2) to provide a post-study $^{13}$C urea breath test ($^{13}$C-UBT) to ascertain HP eradication status. HP- subjects with no ulcer healing are not required to be followed-up.

The recovery of serum gastrin-17 level in follow-up period will be monitored for a maximum of 4 weeks in subjects with endoscopic healing of duodenal ulcer confirmed during the treatment period. The follow-up period ends when the recovery of serum gastrin-17 level is confirmed. No additional follow-up is planned for subjects without recovery during the 4-week follow-up period.

Amended or new wording:

For all subjects, ulcer healing rates will be assessed by endoscopy at Weeks 4 and 6 of treatment. With or without endoscopic evidence of duodenal ulcer healing, the treatment duration of the study is no more than 6 weeks.

Subjects (HP+ or HP-) with endoscopic healing of duodenal ulcer(s) at Week 4 or Week 6 will discontinue treatment at that time, and enter into the Follow-up period.

~~HP+ subjects with no healing at Week 6 will discontinue treatment and enter Follow-up.~~

~~HP- subjects with no ulcer healing by Week 6 of the treatment period will be considered "completed cases" and be discontinued from the study.~~

**Subjects (HP+ or HP-) without ulcer healing by Week 6 of treatment period will discontinue treatment at Week 6, and enter into the Follow up period.**

*Follow-up Period:*

The subjects to be followed up will include both HP+ and HP- subjects, with **or without** confirmed ulcer healing during the treatment period. ~~HP+ subjects with no ulcer healing during treatment period will require one follow-up visit (F-2) to provide a post-study $^{13}$C urea breath test ($^{13}$C-UBT) to ascertain HP eradication status. HP- subjects with no ulcer healing are not required to be followed up.~~

The recovery of serum gastrin-17 level and **pepsinogen I/II ratio** in **the** Follow-up period will be monitored for a maximum of 4 weeks ~~in subjects with endoscopic healing of duodenal ulcer confirmed during the treatment period~~. The Follow-up period ends when the recovery of serum gastrin-17 level **and pepsinogen I/II ratio** are confirmed **or at the end of the 4-week follow-up**. ~~No additional follow-up is planned for subjects without recovery during the 4-week follow-up period.~~

**All HP+ subjects will provide a follow-up $^{13}$C-UBT at the F-2 visit to ascertain HP eradication status.**

**For subjects with no ulcer healing at Week 6 of treatment, the investigator may follow local clinical practice and these subjects may be treated with another course of PPI or other anti-acid secretory agents, or antibiotics, during the safety follow-up period (please see Table 7.a). This should be documented during the follow-up visit 2.**

**Rationale for Change:**

To ensure adequate monitoring of subjects with increased serum gastrin and pepsinogen I/II levels during the study.

The following sections also contain this change:

- Section 2.0 STUDY SUMMARY.
- Figure 6.a Schematic of Study Design.
- Section 6.2 Justification for Study Design, Dose, and Endpoints.
- Section 9.3.7 Follow-up Period – Visits F-1 and F-2.
- Appendix A Schedule of Study Procedures, footnotes d, s, and t

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Date (dd-MMM-yyyy HH:mm 'UTC') |
|---|---|---|
| PPD | Clinical Science Approval | 30-Aug-2018 08:35 UTC |
| | Biostatistics Approval | 30-Aug-2018 08:42 UTC |
| | Clinical Science Approval | 30-Aug-2018 08:44 UTC |