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

SAP Approve Date: 23 July 2019

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438_304

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

PHASE 3

Version: 3.0

Date: 23 July 2019

Prepared by:

PPD

Based on:

Protocol Version: Amendment 03

Protocol Date: 30 August 2018

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

^{13}C-UBT	**^{13}Carbon Urea Breath Test**
AE	**adverse event**
ALT	**alanine aminotransferase**
AST	**aspartate aminotransferase**
BID	**twice daily**
CI	**confidence interval**
CMH	**Cochran–Mantel–Haenszel**
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**
hCG	**human chorionic gonadotropin**
HP	***Helicobacter pylori***
HP+	***Helicobacter pylori* infected**
HP-	**non-*Helicobacter pylori* infected**
LLN	**lower limit of normal**
MedDRA	**Medical Dictionary for Regulatory Activities**
PPI	**proton pump inhibitor**
PPS	**per protocol set**
PTE	**pretreatment event**
Q1	**25th percentile**
Q3	**75th percentile**
QD	**once daily**
QOL	**quality of life**
SAF	**safety analysis set**
SD	**standard deviation**
TEAE	**Treatment-emergent adverse event**
ULN	**upper limit of normal**
VAS	**visual analogue scale**
WHO Drug	**World Health Organization Drug Dictionary**

4.0 OBJECTIVES

4.1 Primary Objectives

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

4.2 Secondary Objectives

To demonstrate the noninferiority of *Helicobacter pylori* (HP) eradication with TAK-438 versus lansoprazole.

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

4.3 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 *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, ie,

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

Enrollment of *Helicobacter pylori* (*H pylori)* negative (ie, non-*Helicobacter pylori* infected) (HP-) subjects will be initiated first, until the availability of PK and safety data from a drug-drug interaction study to assess the effects of co-administration of TAK-438 with clarithromycin, amoxicillin, and bismuth as quadruple therapy in *Helicobacter pylori* infected (HP+) subjects.

Treatment Period:

A schematic of the study design is included as Figure 4.a. A schedule of assessments is listed in Table 4.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 *Helicobacter pylori* (*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 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 the TAK-438 or lansoprazole once daily (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 at Week 4 or at Week 6 will discontinue treatment at that time, and enter into the Follow-up period.

Subject (HP+ or HP-) without healing at Week 6 will discontinue treatment at Week 6 and enter into Follow-up period.

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 or without confirmed ulcer healing during the treatment period.

The recovery of serum gastrin-17 level and pepsinogen I/II ratio in Follow-up period (Visits F-1 [follow-up 2 weeks posttreatment] and F-2 [follow-up 4 weeks posttreatment]) 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 4-week Follow-up.

All HP+ subjects will provide a follow-up ^{13}C-UBT at 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 proton pump inhibitor (PPI) or other anti-acid secretory agents or antibiotics, during the safety follow-up period (please see protocol Table 7.a). This should be documented during the F-2 visit.

Figure 4.a Schematic of Study Design

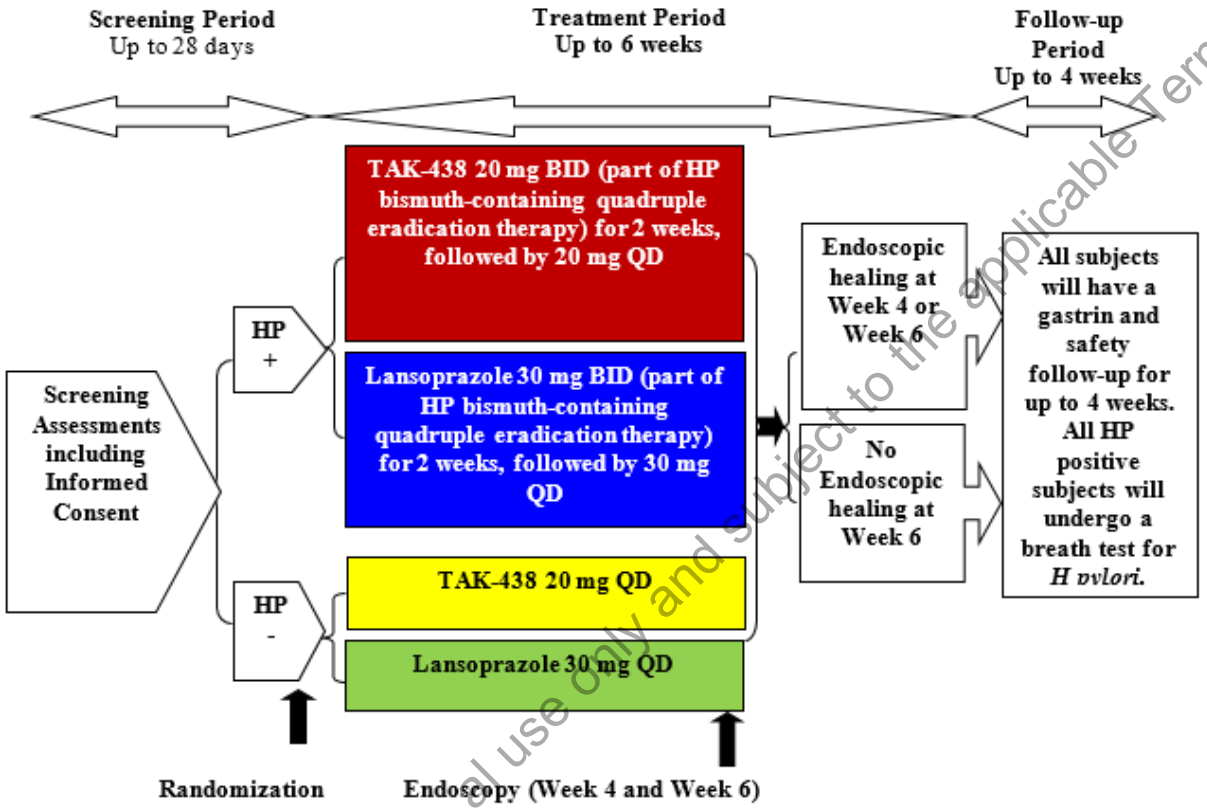

Table 4.a Schedule of Study Procedures

	Screening Period	Treatment Period (b)					Follow-up Period (d)	
Study Day/Week:		**D1 (a, u)**	**W2 (D15)**	**W4 (D29) (u)**	**W6 (D43) (u)**	**ET Visit (c)**	**2w Post-treatment**	**4w Post-treatment**
Visit Windows (Days):	**D -28 to D -1**	**-**	**±3d**	**±3d**	**±3d**	**Within 14d of last dose**	**D15 to 28**	**D29 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		
Liver function test (r)			X					
Serum gastrin-17 / Pepsinogen I/II levels (total and ratio)		X		X	X	X	X(s)	X(t)
Urine pregnancy test - human chorionic gonadotropin (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		
Electrocardiogram (ECG)	X(k)			X(j)	X	X		
Endoscopy	X(k)			X	X	X		
^{13}C-UBT to confirm H infection status	X(g)							X(n)
Investigator review of gastrointestinal symptoms		X	X	X	X	X		
Quality of life (QOL) questionnaire - Euro Quality of Life-5D-5L (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		
Pretreatment event (PTE) assessment	X	X						
AE assessment		X	X	X	X	X	X	X

D=Day, W=Week, ET=Early Termination.
(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 3.9.6.
(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 the 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 for a maximum of 4 weeks until the recovery of serum gastrin-17 level and pepsinogen I/II ratio are confirmed or for a maximum of 4 weeks. and the 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, providing that the subject has not been using agents that affect the digestive organs since that examination. 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 at least 4 weeks after eradication therapy for all 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) Liver function tests include alanine aminotransferase (ALT), aspartate aminotransferase (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.

5.0 ANALYSIS ENDPOINTS

Primary Endpoint

The primary endpoint for this study is the percentage of subjects with endoscopically confirmed healing* of duodenal ulcer 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.

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-UBT at F-2.
- 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.

Additional Endpoints

Additional efficacy endpoints include:

- QOL measurement 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), serious adverse events (SAEs), laboratory test values, ECG, vital signs, serum gastrin-17, and pepsinogen I/II values (total and ratio).

6.0 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% confidence interval (CI) with a -6% noninferiority margin. This sample size 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

All CIs, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values will be rounded to 4 decimal places prior to assessment of statistical significance.

Means, 25th percentile (Q1), medians, and 75th percentile (Q3) will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Minimum and maximum values will be presented using the same number of decimal places as the recorded data. CIs about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. The proportion will be reported to 1 decimal place.

For continuous variables, the number of subjects with non-missing values, mean, Q1, median, Q3, SD, minimum, and maximum values will be tabulated unless otherwise noted.

7.1.1 Study Definitions

The following definitions and calculation formulas will be used.

- Descriptive statistics: number of subjects with non-missing values, mean, SD, maximum, minimum, Q1, median, Q3.
- Percentage of subjects with endoscopically confirmed healing of duodenal ulcer (ie, the rate of endoscopic healing): The proportion of subjects in whom the disappearance of all white coats associated with duodenal ulcers has been endoscopically confirmed.
- Screening Failure: Subject who is not eligible prior to randomization.
- Treatment Emergent Adverse Event (TEAE): An AE whose date of onset occurs on or after the start of study drug. A TEAE whose relationship to study drug is missing will be considered drug-related. A TEAE whose intensity is missing will be considered severe.
- Significant TEAE: Any TEAE (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment, dose increase, dose reduction, dose interrupted or significant additional concomitant therapy.
- 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.

- CI for one sample proportion: Exact (Clopper-Pearson) CI will be used.
- CI for two sample proportion difference: Wald CI will be used unless otherwise specified.
- CI for two sample proportion difference for efficacy endpoints of healing rate of duodenal ulcer: Newcombe methods will be used.
- Age (years): Age was obtained at screening visit and presented in years.
- Multiracial: Any subject who selects more than one race category will be classified as 'Multiracial'.
- BMI (kg/m^2): weight (kg) / $(\text{height (m)})^2$ (rounded to 1 decimal place).
- Time Since Onset of Current Ulcers (Days): Time since onset of current ulcers to informed consent signed.
- Time Since Onset of Recurrent Ulcers (Days): Time since onset of recurrent ulcers to informed consent signed.
- Pepsinogen I/II Ratio: Pepsinogen I (µg/L) / Pepsinogen II (µg/L) (rounded to 1 decimal place).
- QTcF interval (msec): QT interval (msec) / $(\text{RR interval (sec)})^{0.33}$ (rounded to the nearest whole number).

Definition of Study Days and Baseline

- Study Days: Study Day 1 is defined as the date on which a subject is administered their first dose of the medication ['Date of Dose' in First Dose (QD Treatment) CRF page for HP-subjects; 'Date of Dose' in First Dose (BID Treatment) for HP+ subjects]. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

The day after the last dose of the study medication will be defined as Follow-up Day 1. Other follow-up days are defined relative to Follow-up Day 1.

If the date of an event is on or after the date of first dose then Study Day = date of event – date of first dose + 1. If the date of an event is prior to the date of first dose then Study Day = date of event – date of first dose.

- Baseline values are defined as the last observed value before the first dose of study medication on Day 1 (including a screening value or unscheduled assessment, if necessary).

Duration of Exposure

- Duration of exposure to double-blind study medication (days): date of last dose of double-blind study medication - date of first dose of double-blind study medication + 1.

Table 7.a Electronic Case Report Form (eCRF) Data to be Applied for Duration of Exposure

	eCRF Data to be Applied for Duration of Exposure	
	Date of First Dose	**Date of Last Dose**
Double-Blind Study Medication		
For HP+ subjects	**'Date of Dose' in First Dose (BID Treatment)**	**'Date of Last Dose' in End of Study**
For HP- subjects	**'Date of Dose' in First Dose (QD Treatment)**	**'Date of Last Dose' in End of Study**
Each Companion Drug		
For HP+ subjects in the first 2 weeks	**'Date of Dose' in First Dose (BID Treatment)**	**'Date of Dose End' in Last Dose (BID treatment)**

Study Drug Compliance

- Study drug compliance (%).

= (number of days the study medication taken) / duration of exposure to study medication x 100% (rounded to 1 decimal place)

= (number of study medication dispensed – number of study medication returned) ÷ Θ / (date of last dose -date of first dose +1) x 100%

Θ: Number of tablet/capsules required to be taken per day.

❖ **Overall study drug compliance for double-blind study medication (HP+ subjects)=**

$$\frac{\sum_{i=1}^{2}[(\text{number of study medication dispensed} - \text{number of study medication returned}) \div \Theta_i]}{\text{date of last dose of study medication - date of first dose of study medication + 1}} \text{x100\%}$$

Θ_1: Number of tablet/capsules required to be taken per day in the first 2 weeks for HP+ subjects.

Θ_2: Number of tablet/capsules required to be taken per day in Weeks 3-6 for HP+ subjects.

❖ **Overall study drug compliance for double-blind study medication (HP- subjects)=**

$$\frac{(\text{number of study medication dispensed} - \text{number of study medication returned}) \div \Theta}{\text{date of last dose of study medication - date of first dose of study medication + 1}} \text{x100\%}$$

Θ: Number of tablet/capsules required to be taken per day in the 6 weeks for HP- subjects.

❖ **Study drug compliance for each companion drug=**

$$\frac{(\text{number of study medication dispensed} - \text{number of study medication returned}) \div \Theta}{\text{date of last dose of BID treatment - date of first dose of BID treatment + 1}} \text{x100\%}$$

Θ: Number of tablet/capsules required to be taken per day.

Table 7.b Number of Study Drug to Be Taken Per Day

Planned Dose	Θ: Number of Tablet/Capsules Required to Be Taken Per Day	
Double-Blind Study Medication		
For HP+ subjects in the first 2 weeks		
TAK-438 20 mg (or TAK-438 20 mg matching placebo) BID	**2**	**tablets**
Lansoprazole 30 mg (or lansoprazole 30 mg matching placebo) BID	**2**	**capsules**
For HP+ subjects in Weeks 3-6 and HP- subjects for 6 weeks		
TAK-438 20 mg (or TAK-438 20 mg matching placebo) QD	**1**	**tablets**
Lansoprazole 30 mg (or lansoprazole 30 mg matching placebo) QD	**1**	**capsules**
Each Companion Drug		
For HP+ subjects in the first 2 weeks		
Amoxicillin 1 g BID	**4**	**capsules**
Clarithromycin 500 mg BID	**2**	**tablets**
Bismuth potassium citrate/bismuth tripotassium dicitrate 600 mg BID	**4**	**tablets**

Note: Amoxicillin 500 mg/cap, Clarithromycin 500 mg/tab, bismuth potassium citrate/bismuth tripotassium dicitrate 300 mg/tab.

7.1.2 Definition of Study Visit Windows

For each visit, all evaluable observation (ie, non-missing) obtained in the corresponding time interval (ie, window) will be used. This window will establish a time interval around which data will be considered for the analysis of the scheduled visit pertaining to that window. If more than one observation lies within the same visit window, the observation with the closest Study Day to the scheduled Study Day will be used. If there are two observations equidistant to the scheduled Study Day, the later observation will be used. If there are two observations with the same Study Day, the earlier observation will be used. The visit windows and applicable study day ranges are presented in Table 7.c.

Table 7.c Visit Analysis Window for Efficacy and Safety Variables

		Visit Window (Days)				
Visit	**Scheduled Visit Day**	**(a) Variables Scheduled at Week 4, Week 6**	**(b) Variables Scheduled at Week 2, Week 4, Week 6**	**(c) Variables Scheduled at Week 2, Week 4, Week 6**	**(d) Variables Scheduled at Week 2, Week 4, Week 6, F-1, F-2**	**Serum gastrin-17, Pepsinogen I/II (total and ratio) Scheduled at Week 4, Week 6, F-1, F-2**	**^{13}C-UBT Scheduled at F-2**
Baseline	1	Day -14 – <=1	Day -14 – <=1	Day -28 – <=1	Day -28 – <=1	<=1	Day -14 – <=1
Week 2	15		2 – 21 and <= 14 Days after the Last Dose	2 – 21 and <= 14 Days after the Last Dose	2 – 21 and <= 14 Days after the Last Dose		
Week 4	29	2 – 35 and <= 14 Days after the Last Dose	22 – 35 and <= 14 Days after the Last Dose	22 – 35 and <= 14 Days after the Last Dose	22 – 35 and <= 14 Days after the Last Dose	2 – 35 and <= 14 Days after the Last Dose	
Week 6	43	36 – 57 and <= 14 Days after the Last Dose	36 – 57 and <= 14 Days after the Last Dose	36 – 57 and <= 14 Days after the Last Dose	36 – 57 and <= 14 Days after the Last Dose	36 – 57 and <= 14 Days after the Last Dose	
2 Weeks Post-Treatment (F-1)	Follow-up Day 15				Follow-up Day 15 - 28	Follow-up Day 15 - 28	
4 Weeks Post-Treatment (F-2)	Follow-up Day 29				Follow-up Day 29 - 42	Follow-up Day 29 – 42 (e)	Day 2 - (f)

Note: Baseline values are defined as the last observed value before the first dose of study medication on Day 1 (including a screening value or unscheduled assessment, if necessary). Any value collected on Day 1 but after the administration of first dose will be grouped under Week 2.
Note: All efficacy data in treatment period (eg, week 2, 4 and 6) tested 15 days after last dose were excluded from the analysis. The day after the last dose of the study medication will be defined as 1 Day after the last dose.
(a) Clinical laboratory tests including hematology, serum chemistries (variables other than ALT, AST, total bilirubin, and direct bilirubin), and urinalysis tests, Endoscopy, ECG.
(b) Variables of liver function tests including ALT, AST, total bilirubin, and direct bilirubin.
(c) Vital signs, Urine pregnancy test (hCG), Gastrointestinal symptoms, QOL questionnaire (EQ-5D-5L).
(d) Physical examination.
(e) Only if no serum gastrin-17 or pepsinogen I/II recovery at F-1 visit.
(f) ^{13}C-UBT should be repeated for HP+ subjects at F-2 to ascertain HP eradication status. If subjects have administered antibiotics (defined as "J01" of the second level ATC code), PPIs (defined as "A02BC" of the fourth level ATC code), or study drug within 14 days prior to 13C-UBT, the data will be excluded from the analysis.

7.1.3 Data Handling Rules

7.1.3.1 Handling of Rate of Endoscopic Healing

A subject in whom the disappearance of all white coats associated with duodenal ulcers has been endoscopically confirmed at Week 4 or Week 6 will be considered as a healed subject. Subjects

who do not have any endoscopy data during this period will be treated as missing. Subjects who do not meet this requirement will be considered as 'not healed'. Healing rate will be calculated from the healed and not healed subjects.

7.1.3.2 Handling of Percentage of Subjects with Posttreatment Resolution of Each Gastrointestinal Symptom Associated with Duodenal Ulcer at Week 2 through 6

Each gastrointestinal symptom 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) in "Gastrointestinal Symptoms" eCRF page. 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 "Gastrointestinal Symptoms" eCRF page. Subjects with symptoms at baseline who do not have any information on date of resolution or end of treatment status will be excluded from the efficacy analysis for the corresponding symptom. Subjects without any symptom at baseline will also be excluded from the efficacy analysis for the corresponding symptom.

Percentage of subjects with posttreatment resolution of each gastrointestinal symptom associated with duodenal ulcer at Week 2 through 6 = (number of subjects with date of resolution reported in "If Yes, and resolved, date of resolution" field at the specified gastrointestinal symptom) / (number of subjects with "Yes" selected for the specified gastrointestinal symptom associated with duodenal ulcer at the start of treatment period) * 100 (rounded to 1 decimal place).

7.1.3.3 Handling of EQ-5D-5L

The EQ-5D-5L index values will be calculated from the EQ-5D-5L descriptive system scores based on the EQ-5D-5L Crosswalk value sets. If any of the questions are not answered, the EQ-5D-5L index value of the day will be treated as missing.

7.1.4 Conventions for Missing AE Dates

Imputing Missing or Partial Dates for AEs is described in Appendix 9.1 Flowcharts for Imputing Missing or Partial Dates for AEs and Concomitant Medications (Guideline for Data Handling Rule Version 1.0, dated of September 20, 2011).

AEs with onset occurring from the time that the subject is first administered study drug (visit 2, randomization) to the subject's last study visit (ie, early termination or follow-up visit) should be included in data listings but not summary tables.

7.1.5 Conventions for Missing Concomitant Medication Dates

Imputing Missing or Partial Dates for Concomitant Medications is described in Appendix 9.1 Flowcharts for Imputing Missing or Partial Dates for AEs and Concomitant Medications.

7.2 Analysis Sets

Subjects whose sites failed CFDA inspection will be excluded from all analysis sets.

Analysis of efficacy variables will be conducted in the full analysis set defined as all subjects who were randomized and received at least 1 dose of the study drug (ie, TAK-438 or lansoprazole or matching placebo). Subjects in this set will be analyzed according to the original randomization.

The primary efficacy endpoint will also be analyzed in the per-protocol analysis set (PPS) defined as all FAS subjects who did not have any of the major protocol deviations listed below. Analyses will be based on the randomized treatment.

- Subjects who did not meet inclusion criteria #3.
- Subjects who met exclusion criteria #8, #11, #12, #13, #14, #15, #16, #17, or #18.
- Subjects with study medication compliance of less than 70%.
- Subjects who have been unblinded prior to database lock.
- Subjects who have violated the rules specified in section 7.3 of the protocol.

Analysis of safety variables will be conducted in the safety analysis set defined as all subjects who take at least 1 dose of study medication (ie, TAK-438 or lansoprazole or matching placebo) and will be based on the treatment received.

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set:	All Subjects Who Signed the Informed Consent Form
Analysis Variables:	Date First Subject Signed Informed Consent Form
	Date of Last Subject's Last Visit/Contact
	MedDRA Version
	WHO Drug Version
	SAS Version Used for Creating the Datasets
Analytical Methods:	**(1) Study Information**
	Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set:	All Subjects Who Were Not Randomized	
Analysis Variables:	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender	[Male, Female]
	Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiracial]
Analytical Methods:	**(1) Screen Failures**	
	Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.	

7.3.3 Subject Eligibility

Analysis Set:	All Subjects Who Signed the Informed Consent Form	
Analysis Variables:	Is the subject eligible for randomization into the Treatment Phase?	[Yes, No]
	Primary Reason for Subject Not Being Eligible	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Did Not Meet Entrance Criteria, Other]

Analytical Methods: **(1) Eligibility for Randomization**

Frequency distributions will be provided. When calculating the percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Randomized by Country, Site, and Treatment Group

Analysis Set:	Randomized Set	
Analysis Variables:	Randomization Status	[Yes]
Stratum:	Country	[China, Korea, Philippines, Taiwan]
	Site	[Site numbers will be used as categories]

Analytical Methods: **(1) Number of Subjects Randomized by Country, Site, and Treatment Group**

Frequency distribution will be provided for each stratum by treatment group and overall.

7.3.5 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variables:	Double-Blind Study Drug Administration Status	[No]
	Reason for Not Being Treated with Double-Blind Study Drug	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Lack of Efficacy, Other]
	Double-Blind Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Double-Blind Study Drug	[Pretreatment Event/Adverse Event, Significant Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Lack of Efficacy, Other]

Analytical Methods: **(1) Disposition of Subjects**

Frequency distributions will be provided for each treatment group and overall. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of study drug, the total number of subjects who prematurely discontinued the study drug will be used as the denominator.

(2) Flow Chart of Subject Distribution

Flow chart will be provided.

7.3.6 Protocol Deviations and Analysis Sets

7.3.6.1 Protocol Deviations

Analysis Set:	Randomized Set	
Analysis Variables:	Protocol Deviation	[Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria]

Analytical Methods: **(1) Protocol Deviations**

Frequency distribution will be provided by treatment group and overall for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

7.3.6.2 Analysis Sets

Analysis Set:	Randomized Set	
Analysis Variables:	Analysis Sets	
	Full Analysis Set	[Included]
	Per Protocol Set	[Included]
	Safety Analysis Set	[Included]
Analytical Methods:	**(1) Analysis Sets**	
	Frequency distributions will be provided by treatment group and overall.	

7.4 Demographic and Other Baseline Characteristics

Analysis Set:	Randomized Set	
Analysis Variables:	Country	[China, Korea, Philippines, Taiwan]
	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender	[Male, Female]
	Race	[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiracial]
	Height (cm)	[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
	Weight (kg)	[Min<= - <50, 50<= - <60, 60<= - <70, 70<= - <80, 80<= - <=Max]
	BMI (kg/m^2)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	Smoking Classification	[The Subject Has Never Smoked, The Subject Is a Current Smoker, The Subject Is an Ex-smoker]
	Consumption of Alcohol	[Drink Everyday, Drink a Couple of Days Per Week, Drink a Couple of Days Per Month, Never Drink]
	Consumption of Caffeine	[Yes (More Than 5 Times Per Week), No (Never Drink or Less Than 5 Times Per Week)]
	History of H. pylori Eradication Therapy	[Yes (Therapy Received Ever), No (Never Receive Any Therapy)]
	H. pylori Infection Status (Result of ^{13}-C Urea Breath Test)	[Positive, Negative]

	Characteristics of Duodenal Ulcers	
	Location (a)	[Superior Part (Including Bulb), Descending Part]
	Number of Ulcers Found	
	Ulcer Morphology (a)	[Circular, Ellipsoidal, Other]
	Ulcer Size (a)	[Minuscule (<5 mm), Minor (>=5 mm/<10 mm), Intermediate (>=10 mm/<=20 mm), Large (>20 mm/<30 mm), Giant (>=30 mm)]
	History of Duodenal Ulcers	
	Time Since Onset of Current Ulcers (Days)	
	Use of NSAIDs or Low-dose Aspirin (Except Topical Preparations) at the Time of Ulcer Onset	[Yes, No]
	Type of Ulcers	[Primary, Recurrent]
	Time Since Onset of Recurrent Ulcers (Days)	
	EQ-5D-5L	
	EQ-5D-5L Index Value (Screening)	
	EQ Visual Analogue Scale (VAS) Score (Screening)	
Analytical Methods:	**(1) Summary of Demographics and Other Baseline Characteristics** Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.	

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

7.5 Medical History and Concurrent Medical Conditions

Analysis Set:	Safety Analysis Set
Analysis Variables:	Medical History Concurrent Medical Conditions
Analytical Methods:	**(1) Medical History by System Organ Class and Preferred Term** **(2) Concurrent Medical Conditions by System Organ Class and Preferred Term** Frequency distributions will be provided for each treatment group. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set

Analysis Variables: Medication History
Concomitant Medications

Analytical Methods: **(1) Medication History by Preferred Medication Name**

(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

Frequency distributions will be provided for each treatment group. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports.
A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

7.7 Study Drug Exposure and Compliance

7.7.1 TAK-438/Lansoprazole and Matching Placebo Exposure and Compliance

Analysis Set: Safety Analysis Set

Analysis Variables:		
	Duration of Exposure to Study Drug (days)	[1<= - <=14, 15<= - <=28, 29<= - <=42, 43<= - <=Max]
	Study Drug Compliance (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]

Analytical Methods: **(1) Study Drug Exposure and Compliance**

Frequency distributions of TAK-438/Lansoprazole and matching placebo for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.7.2 Companion Drugs Exposure and Compliance

Analysis Set: Safety Analysis Set with HP+ Subjects at baseline

Analysis Variables:		
	Duration of Exposure to Amoxicillin(days)	[1<= - <=14, 15<= - <=Max]
	Duration of Exposure to Clarithromycin (days)	[1<= - <=14, 15<= - <=Max]
	Duration of Exposure to Bismuth(days)	[1<= - <=14, 15<= - <=Max]
	Amoxicillin Compliance (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]
	Clarithromycin Compliance (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]
	Bismuth Compliance (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]

Analytical Methods: **(1) Companion Drugs Exposure and Compliance**

Frequency distributions of each companion drug (amoxicillin, clarithromycin, and bismuth potassium citrate/bismuth tripotassium dicitrate) for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

7.8.1.1 Primary Analysis

Analysis Set: Full Analysis Set

Analysis Variable: Percentage of subjects with endoscopically confirmed healing* of duodenal ulcer 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.

Analytical Methods: 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. If the lower bound of the 95% CI is ≥-6%, non-inferiority for TAK-438 relative to lansoprazole with regard to duodenal ulcer healing will be declared.

7.8.1.2 Secondary Analysis

Analysis Set: Per Protocol Set

Analysis Variable: Percentage of subjects with endoscopically confirmed healing* of duodenal ulcer 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.

Analytical Methods: A sensitivity analysis will be performed to check the robustness of the results, the same analyses as those in section 7.8.1.1 will be performed using the PPS.

7.8.2 Secondary Efficacy Endpoint(s)

7.8.2.1 Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at Week 4

Analysis Set: Full Analysis Set

Analysis Variable: Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at Week 4 (%)

Analytical Methods: The healing rate of duodenal ulcer at Week 4 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 and the 2-sided 95% CIs using newcombe methods will be provided. 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. Details concerning interpretation are described in section 7.8.4.5.

7.8.2.2 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

Analysis Set:	Full Analysis Set with HP+ Subjects at baseline
Analysis Variable:	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 (%)
Analytical Methods:	Frequency distributions will be provided by treatment group along with rates and the two-sided 95% CIs. Also, the differences in the rates between the TAK-438 group and the lansoprazole group (the TAK-438 group – the lansoprazole group) and the two-sided 95% CIs will be provided.

7.8.2.3 Percentage of Subjects with Posttreatment Resolution of Gastrointestinal Symptoms Associated with Duodenal Ulcer at Weeks 2 Through 6

Analysis Set:	Full Analysis Set
Analysis Variable:	Percentage of Subjects with Posttreatment Resolution of Gastrointestinal Symptoms Associated with Duodenal Ulcer at Weeks 2 Through 6 (%)
Analytical Methods:	For each symptom (epigastric pain [postprandial, fasting, nocturnal], abdominal bloating, nausea/vomiting, heartburn, lack of appetite), Frequency distributions will be provided by treatment group along with rates and the two-sided 95% CIs. Also, the differences in the rates between the TAK-438 group and the lansoprazole group (the TAK-438 group – the lansoprazole group) and the two-sided 95% CIs will be provided.

7.8.3 Additional Efficacy Endpoint(s)

Additional efficacy endpoints include:

7.8.3.1 QOL Measurement EQ-5D-5L

EQ-5D-5L Index Value

Analysis Set:	Full Analysis Set	
Analysis Variables:	EQ-5D-5L Index Value	
Covariates:	*H pylori* status (Baseline)	[HP+, HP-]
	EQ-5D-5L Index Value (Baseline)	
Visit:	Baseline, Week 2, Week 4, Week 6	

Analytical Methods: **(1) Summary of EQ-5D-5L Index Value**

Descriptive statistics will be provided for each visit for the observed values and for each post-baseline visit for the changes from baseline (each post-baseline visit - baseline) by treatment group. The mean differences in the changes from baseline between the TAK-438 group and the lansoprazole group (the TAK-438 group – the lansoprazole group) and the two-sided 95% CIs will be provided for each post-baseline visit. Two sample t-tests will be used to test for treatment differences at each post-baseline visit.

(2) ANCOVA

The changes from baseline (each post baseline visit - baseline) in the analysis variable will be analyzed using an ANCOVA model with treatment and baseline *H pylori Status* as factors and baseline EQ-5D-5L index value as a covariate. The ANCOVA analysis will be performed at each post baseline visit.

LS means and the two-sided 95% CIs will be provided for each treatment group. The difference in the LS means between the TAK-438 group and the lansoprazole group (the TAK-438 group – the lansoprazole group) and the two-sided 95% CI will be provided. The difference in the LS means will be tested for treatment differences.

EQ VAS Score

Analysis Set: Full Analysis Set

Analysis Variables: EQ VAS Score

Covariates: *H pylori* Status (Baseline) [HP+, HP-]

EQ VAS Score (Baseline)

Analytical Methods: The same analyses as those in section 7.8.3.1 "EQ-5D-5L Index Value" will be conducted for the EQ VAS score.

7.8.3.2 Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at either Week 4 or Week 6 Based on Their Baseline H pylori Status

Analysis Set: Full Analysis Set

Analysis Variable: Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at either Week 4 or Week 6 Based on Their Baseline *H pylori* Status [HP+, HP-]

Analytical Methods: **(1) 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 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.

7.8.3.3 Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at Week 4 Based on Their Baseline H pylori Status

Analysis Set: Full Analysis Set

Analysis Variable: Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at Week 4 Based on Their Baseline *H pylori* Status [HP+, HP-]

Analytical Methods: The same analyses as those in section 7.8.3.2 "Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at either Week 4 or Week 6 Based on Their Baseline *H pylori* Status" will be applied.

7.8.3.4 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

Analysis Set: Full Analysis Set with HP+ Subjects at baseline

Analysis Variable: 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 (%)

Analytical Methods: **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 and the 2-sided 95% CI will be provided by treatment group and *H pylori* status at Follow-up Visit F2. 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 *H pylori* status at Follow-up Visit F-2 as a stratified factor will be provided.

7.8.3.5 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

Analysis Set: Full Analysis Set with HP+ Subjects at baseline

Analysis Variable: 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 (%)

Analytical Methods: The same analyses as those in section 7.8.3.4 "Percentage of Subjects with Endoscopically Confirmed Healing of Duodenal Ulcer at either Week 4 or Week 6 Based on Their *H pylori* Status at Follow-up Visit F-2" will be applied.

7.8.4 Statistical/Analytical Issues

7.8.4.1 Adjustments for Covariates

Analysis Set: Full Analysis Set

Analysis Variable: Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 or 6 (%)

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 at Weeks 2 through 6 (%)

Stratified Variable: *H pylori* status (Baseline) [HP+, HP-]

Analytical Methods: **(1) CMH Test for Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 or 6 (%)**
(2) CMH Test for Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 (%)
(3) CMH Test for Percentage of subjects with posttreatment resolution of gastrointestinal symptoms associated with duodenal ulcer at Weeks 2 through 6 (%)
A Cochran–Mantel–Haenszel (CMH) test with baseline *H pylori* status as a stratification factor will be used to compare the above analysis variable between the TAK-438 group and the lansoprazole group for treatment differences. Mantel-Haenszel estimate of risk difference between the TAK-438 group and the lansoprazole group (the TAK-438 group – the lansoprazole group) and the two-sided 95% CI using the Wald method will also be provided.

7.8.4.2 Handling of Dropouts or Missing Data

For the primary endpoint "Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 or 6" and the secondary efficacy endpoints "Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4" and "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", missing data will be handled according to section 7.1.3.

Values below the lower limit of quantification will be treated as zero when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit values when calculating the descriptive statistics.

7.8.4.3 Interim Analyses and Data Monitoring

No interim analysis is planned in this study.

7.8.4.4 Multicenter Studies

Treatment-by-center interaction will not be explored in this study.

7.8.4.5 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.

7.8.4.6 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary efficacy endpoint using the FAS, sensitivity analyses will also be performed using the PPS to examine the robustness of the results.

7.8.4.7 Active-Control Studies Intended to Show Equivalence or Non-Inferiority

For the primary efficacy endpoint, non-inferiority for TAK-438 relative to lansoprazole will be confirmed in the FAS using a non-inferiority margin of 6% as described in section 7.8.1.1 "Primary Analysis".

For the secondary efficacy endpoint of eradication rate of H pylori, non-inferiority for TAK-438 relative to lansoprazole will be confirmed in the FAS using a non-inferiority margin of 10% as described in section 7.8.2.2 "Secondary Analysis".

7.8.4.8 Subgroup Analysis

Analysis Set:	Full Analysis Set	
Analysis Variable:	Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 or 6 (%) 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 at Weeks 2 through 6 (%)	
Subgroups:	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender	[Male, Female]
	H pylori status (Baseline)	[HP+, HP-]
Analytical Methods:	For subgroup of age and gender, summaries (1), (2), and (3) will be provided by treatment group. For subgroup of *H pylori* status (Baseline), summaries (3) will be provided by treatment group. **(1) Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 or 6 (%)** **(2) Percentage of subjects with endoscopically confirmed healing of duodenal ulcer at Week 4 (%)** **(3) Percentage of subjects with posttreatment resolution of gastrointestinal symptoms associated with duodenal ulcer at Weeks 2 through 6 (%)** The same analyses as those in section 7.8.1 and 7.8.2 will be performed for each of the above subgroups.	

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.9.1 Pharmacokinetic Analysis

Not applicable.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not applicable.

7.11 Safety Analysis

7.11.1 Treatment-Emergent Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variables:	TEAE	
Categories:	Relationship to TAK-438/Lansoprazole	[Yes, No]
	Relationship to Clarithromycin	[Yes, No]
	Relationship to Amoxicillin	[Yes, No]
	Relationship to Bismuth	[Yes, No]
	Intensity	[Mild, Moderate, Severe]

Analytical Methods: The following summaries will be provided for each treatment group.

(1) Overview of Treatment-Emergent Adverse Events

1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

2.1) Relationship of Treatment-Emergent Adverse Events to TAK-438/Lansoprazole (number of events, number and percentage of subjects)

2.2) Relationship of Treatment-Emergent Adverse Events to Clarithromycin (number of events, number and percentage of subjects)

2.3) Relationship of Treatment-Emergent Adverse Events to Amoxicillin (number of events, number and percentage of subjects)

2.4) Relationship of Treatment-Emergent Adverse Events to Bismuth (number of events, number and percentage of subjects)

3) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

4) Treatment-Emergent Adverse Events Leading to Double-Blind Study Drug Discontinuation (number of events, number and percentage of subjects)

5) Relationship to TAK-438/Lansoprazole of Treatment-Emergent Adverse Events Leading to Double-Blind Study Drug Discontinuation (number of events, number and percentage of subjects)

6) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

7.1) Relationship of Serious Treatment-Emergent Adverse Events to TAK-438/Lansoprazole (number of events, number and percentage of subjects)

7.2) Relationship of Serious Treatment-Emergent Adverse Events to Clarithromycin (number of events, number and percentage of subjects)

7.3) Relationship of Serious Treatment-Emergent Adverse Events to Amoxicillin (number of events, number and percentage of subjects)

7.4) Relationship of Serious Treatment-Emergent Adverse Events to Bismuth (number of events, number and percentage of subjects)

8) Serious Treatment-Emergent Adverse Events Leading to Double-Blind Study Drug Discontinuation (number of events, number and percentage of subjects)

9) Treatment-Emergent Adverse Events Resulting in Death (number of events, number and

percentage of subjects)

10) Treatment-Emergent Adverse Events Corresponding to Liver Function Test Abnormalities (number of events, number and percentage of subjects)

11) Significant Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2), 5), 7.1), 7.2), 7.3) and 7.4)
  A subject with occurrences of TEAE in both categories (ie, Yes and No) will be counted once in the Related category.
- Summary for 3)
  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.
- Summaries other than 2), 3), 5), 7.1), 7.2), 7.3) and 7.4)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

For each summary, the total number of events will be calculated.

7.11.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set:	Safety Analysis Set	
Analysis Variables:	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of Onset (day)	[1<= - <=14, 15<= - <=28, 29<= - <=42, 43<= - <=Max]
Stratified Variable:	*H pylori* status (Baseline)	[HP+, HP-]

Analytical Methods: The following summaries will be provided using frequency distribution for each treatment group.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by SOC only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(2) Treatment-Emergent Adverse Events by System Organ Class

(3) Treatment-Emergent Adverse Events by Preferred Term

(4.1) TAK-438/Lansoprazole-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(4.2) Clarithromycin-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(4.3) Amoxicillin-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(4.4) Bismuth-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(5) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(6) Intensity of TAK-438/Lansoprazole-Related Treatment-Emergent Adverse Events by

System Organ Class, and Preferred Term

(7) Treatment-Emergent Adverse Events Leading to Double-Blind Study Drug Discontinuation by System Organ Class and Preferred Term

(8) TAK-438/Lansoprazole-Related Treatment-Emergent Adverse Events Leading to Double-Blind Study Drug Discontinuation by System Organ Class and Preferred Term

(9) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(10) Serious TAK-438/Lansoprazole-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(11) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

(12) Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(13) Treatment-Emergent Adverse Events Corresponding to Liver Function Test Abnormalities by System Organ Class and Preferred Term

(14) TAK-438/Lansoprazole-Related Treatment-Emergent Adverse Events Corresponding to Liver Function Test Abnormalities by System Organ Class and Preferred Term

(15) Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(16) TAK-438/Lansoprazole-Related Significant Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(17) Most Frequent Non-Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

(18) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term stratified by *H pylori* status at Baseline

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (5), (6) and (11)
  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.
- Summary tables for (5) and (6)
  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.
- Summary table for (11)
  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT. When calculating percentages for each time interval, the number of subjects at risk (ie, subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.
- Summary table for (12)

Most frequent TEAEs refer to PTs whose percentages are at least 2% in any one of the treatment groups.

- Summary table for (17)
  Most frequent non-serious TEAEs refer to PTs that are not serious whose percentages are at least 5% in any one of the treatment groups. If there are no PTs whose percentages exceed 5%, the threshold is lowered to 2%. When counting the number of "Subjects with Any TEAEs", subjects with at least one of these most frequent non-serious TEAEs will be counted.

7.11.2 Pretreatment Events

7.11.2.1 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables: PTE

Analytical Methods: The following summaries will be provided using frequency distribution.

Pretreatment Events will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term

(2) Serious pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

A subject with multiple occurrences of Pretreatment Event within a SOC will be counted only once in that SOC. A subject with multiple occurrences of Pretreatment Event within a PT will be counted only once in that PT.

7.11.3 Clinical Laboratory Evaluations

7.11.3.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variables: **Hematology**

Red Blood Cells ($\times 10^{12}$/L)	White Blood Cells ($\times 10^{9}$/L)	Hemoglobin (g/L)
Hematocrit (%)	Platelets ($\times 10^{9}$/L)	

White Blood Cell Fractions (Neutrophils (%), Eosinophils (%), Basophils (%), Monocytes (%), Lymphocytes (%))

Serum Chemistry

ALT (U/L)	ALP (U/L)	AST (U/L)
GGT (U/L)	Total Bilirubin (µmol/L)	Direct Bilirubin (µmol/L)
LDH (U/L)	CK (CPK) (U/L)	Albumin (g/L)
Total Protein (g/L)	Creatinine (µmol/L)	BUN (mmol/L)
Uric Acid (mmol/L)	Total Cholesterol (mmol/L)	Triglycerides (mmol/L)
Glucose (mmol/L)	Potassium (mmol/L)	Sodium (mmol/L)

Magnesium (mmol/L)	Calcium (mmol/L)	Inorganic Phosphorus (mmol/L)
Chloride (mmol/L)	Serum Iron (μmol/L)	Vitamin B_{12} (pmol/L)

Note: 1) Fasting laboratory test in planned per protocol. 2) The central laboratory will perform laboratory tests for hematology, serum chemistries, hepatitis and urinalysis.

Visit: Variables of Liver function tests including ALT, AST, Total Bilirubin, and Direct Bilirubin:

Baseline, Week 2, Week 4, Week 6

Variables other than ALT, AST, Total Bilirubin, and Direct Bilirubin:

Baseline, Week 4, Week 6

Analytical Methods: For each variable, summaries (1) and (2) will be provided by treatment group.

For applicable variables, summaries (3) and (4) will be provided by treatment group.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided for each visit.

(2) Summary of Shifts of Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided. For each laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Parameters
Overall frequency distributions of MAV during treatment phase will be provided. If a laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(4) Number and Percentage of Subjects with Elevated Liver Enzyme Laboratory Parameters
Overall frequency distributions of elevated hepatic parameters during treatment phase will be provided. Further details are given in Appendix.

ALT=Alanine Aminotransferase, ALP=Alkaline Phosphatase, AST=Aspartate Aminotransferase, GGT=γ-Glutamyl Transferase, LDH=Lactate Dehydrogenase, CK=Creatine Kinase, BUN=Blood Urea Nitrogen.

7.11.3.2 Urinalysis

Analysis Set: Safety Analysis Set

Analysis Variables: **Urinalysis**

Appearance	Color	pH
Ketones	Protein	Urine Glucose
Nitrite	Urobilinogen	Blood
Specific Gravity		

Note: For Urinalysis laboratory tests, only specific gravity variable is continuous variable with numeric results, the others are categoric variables with character results.

Visit: Baseline, Week 4, Week 6

Analytical Methods: For specific gravity variable, summaries (1) and (2) will be provided by treatment group.

For each variable other than specific gravity, summaries (2) will be provided by treatment group.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided for each visit.

(2) Summary of Shifts of Urine Laboratory Test Results
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided. For specific gravity laboratory test, the laboratory values will be classified as "Low", "Normal" or "High" and for each variable other than specific gravity will be classified as "Normal" or "Abnormal" relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.11.3.3 Serum Gastrin, Pepsinogen I/II

Analysis Set: Safety Analysis Set

Analysis Variables : Serum Gastrin (pmol/L)

Pepsinogen I (μg/L)

Pepsinogen II (μg/L)

Pepsinogen I/II Ratio

Note: 1) Fasting laboratory test in planned per protocol. 2) The central laboratory will perform laboratory tests for hematology, serum chemistries, hepatitis and urinalysis.

Visit: Baseline, Week 4, Week 6, Visit F-1, Visit F-2

Analytical Methods: The following summaries will be provided for each treatment group.

(1) Summary of Serum Gastrin and Pepsinogen I/II Results
For each visit, descriptive statistics for observed values and changes from baseline (each post-baseline visit - baseline) will be provided.

7.11.4 Vital Signs

Analysis Set: Safety Analysis Set

Analysis Variables: Body Temperature (C)

Systolic Blood Pressure (mmHg)

Diastolic Blood Pressure (mmHg)

Pulse (bpm)

Visit: Baseline, Week 2, Week 4, Week 6

Analytical Methods: For each variable, summaries (1) and (2) will be provided by treatment group.

(1) Summary of Vital Signs Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters
Overall frequency distributions of MAV during treatment phase will be provided. If a vital sign parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

7.11.5 12-Lead ECGs

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Heart Rate (bpm)	
	RR Interval (msec)	
	PR Interval (msec)	
	QT Interval (msec)	
	QTcF Interval (msec)	
	QRS Interval (msec)	
	Interpretation	["Within Normal Limits", "Abnormal, Not Clinically Significant", "Abnormal, Clinically Significant"]
Visit:	Baseline, Week 4, Week 6	

Analytical Methods: For each variable other than interpretations, summary (1) will be provided by treatment group.

For applicable variables, summary (2) will be provided by treatment group.

For interpretation, summary (3) will be provided by treatment group.

(1) Summary of ECG Parameters and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline (each post-baseline visit – baseline) will be provided for each visit.

(2) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
Overall frequency distributions of MAV during treatment phase will be provided. If an ECG laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix.

(3) Summary of Shifts of ECG Parameters
Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

7.11.6 Other Observations Related to Safety

7.11.6.1 Physical Examination

Analysis Set:	Safety Analysis Set	
Analysis Variables:	Results	["Yes", "No"]
Visit:	Screening, Baseline, Week 2, Week 4, Week 6, Visit F-1, Visit F-2	

Analytical Methods: Summary (1) will be provided by treatment group.

(1) Number and Percentage of Subjects with Any Significant Changes from Baseline
Overall frequency distributions of physical examination results during treatment phase will be provided.

7.11.7 Subgroup Analysis for China

Analysis Set: Subjects in China

Subjects in Countries other than China

Analytical Methods: **(1) The same analyses as those in section 7.3 to 7.11.6 will be conducted for the subjects in China.**

(2) The same analyses as those in section 7.3 to 7.11.6 will be conducted for the subjects in countries other than China.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

The changes from the original SAP (Version: 2.0, Date: 29 May 2019) to the amended SAP were described below with a rationale for changes provided.

- Based on the discussion, the algorithm of Visit Analysis Window on C-UBT has changed.
- Based on the discussion, the stratified analysis on the display of TEAE by SOC and PT has been added.

8.0 REFERENCES

1. Fass R, Shapiro M, Swell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease—where next? Aliment Pharmacol Ther. 2005; 22:79-94.
2. Peter J, et al. A randomized, comparative study of three doses of AZD0865 and esomeprazole for healing of reflux esophagitis. Clin Gastroenterol Hepatol. 2007; 5: 12.
3. Liang J, et al. Helicobacter pylori Eradication with Ecabet Sodium, Omeprazole, Amoxicillin, and Clarithromycin Versus Bismuth,Omeprazole, Amoxicillin, and Clarithromycin Quadruple Therapy: A Randomized, Open-Label, Phase IV Trial. Helicobacter. 2012 17: 458–465.
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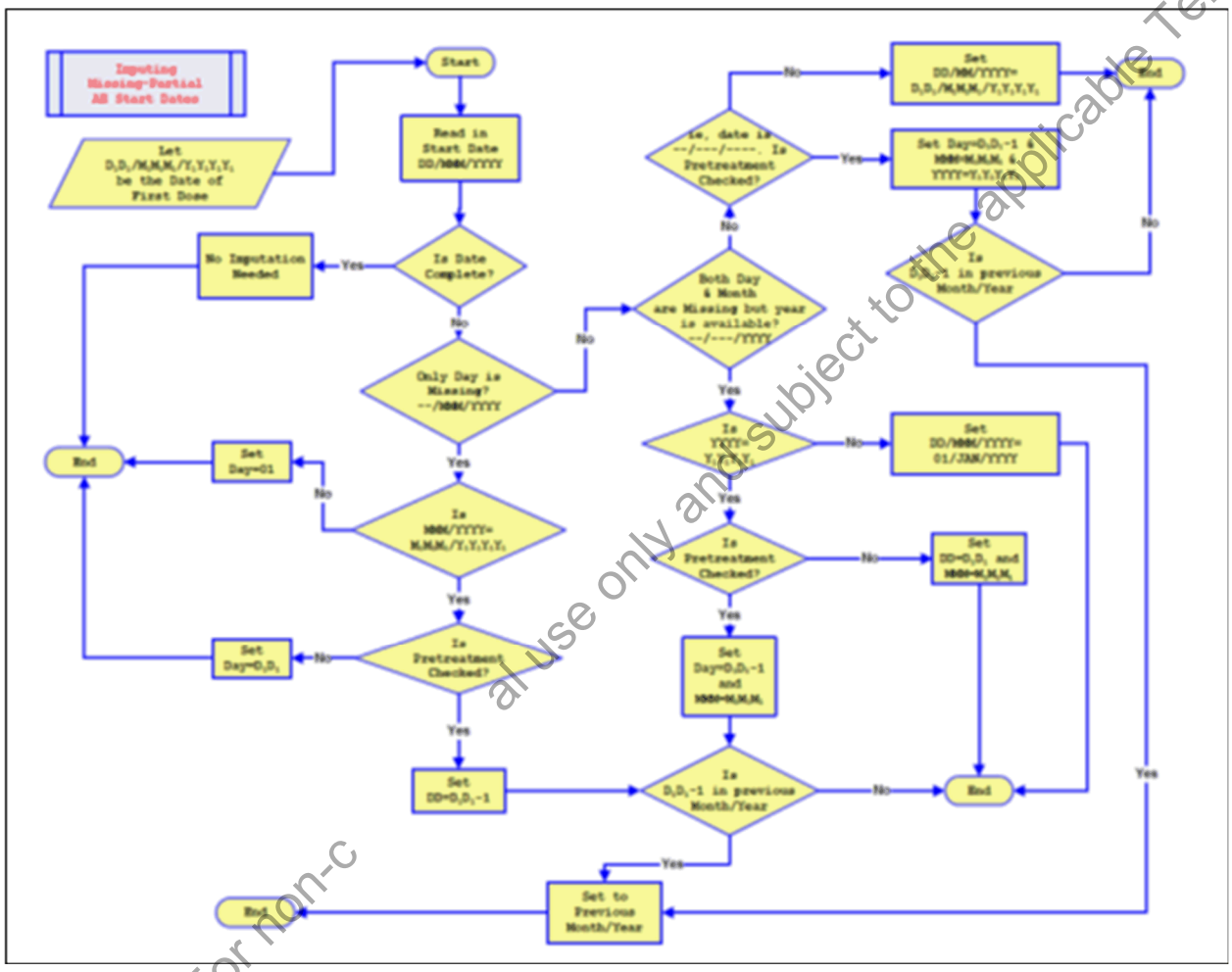
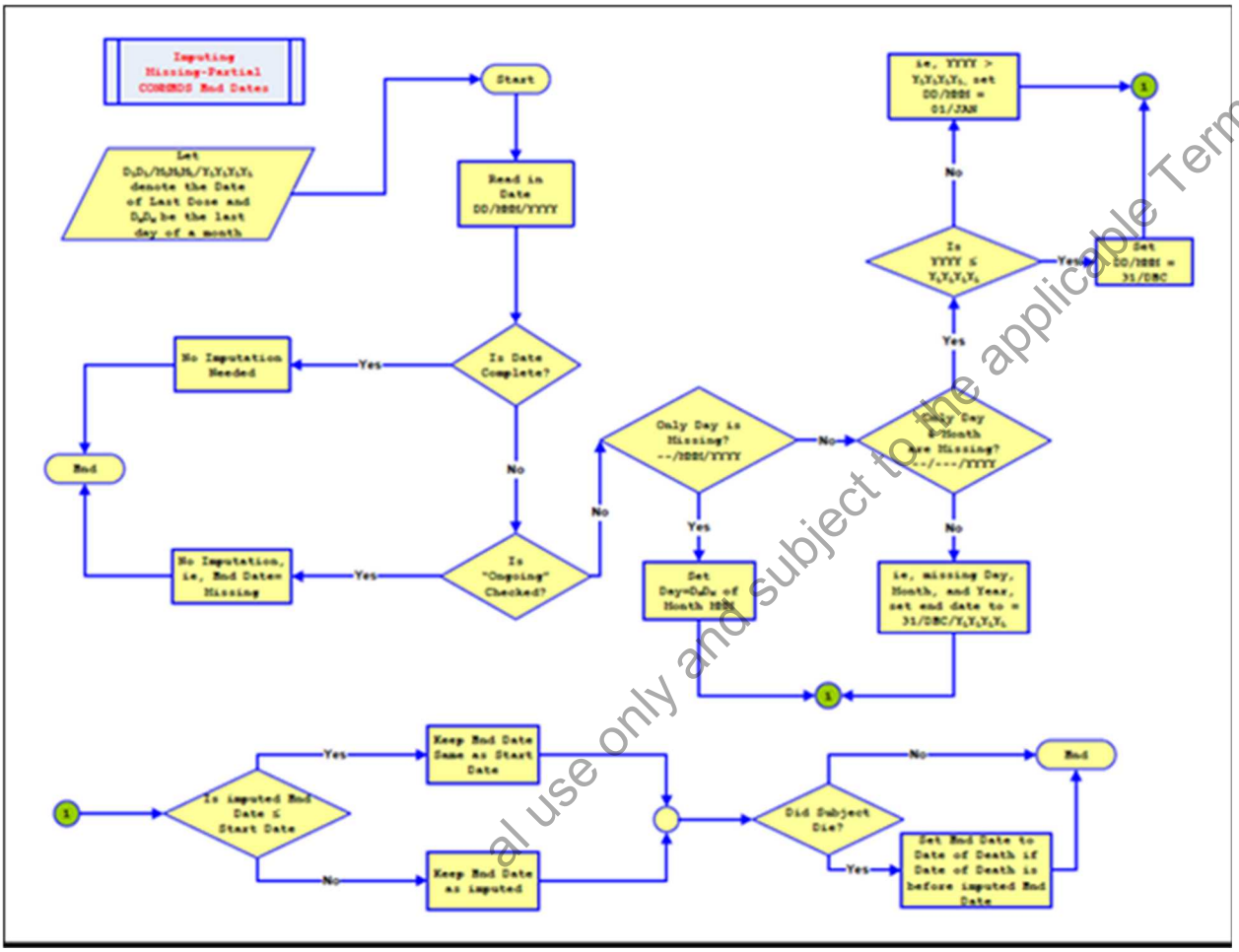
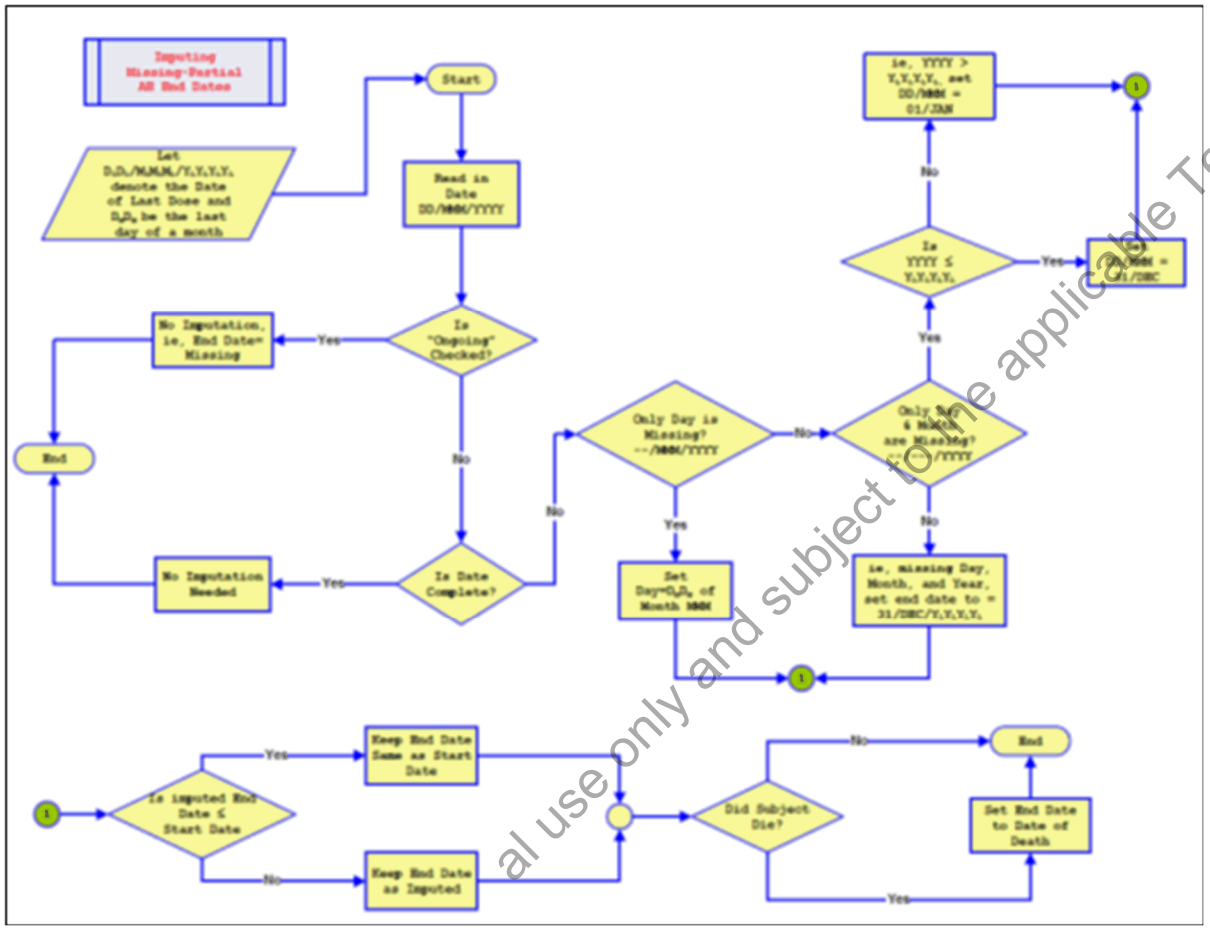
9.0 APPENDIX

9.1 Flowcharts for Imputing Missing or Partial Dates for Adverse Events and Concomitant Medications







9.2 Criteria for Markedly Abnormal Values

9.2.1 Hematology, Serum Chemistry, Urinalysis, Vital Signs, and 12-lead ECG (except Upper MAV Criteria of QTcF Interval)

For each parameter, all evaluable data (ie, non-missing data) obtained up to Follow-up Day 14 will be classified as a MAV or not. The criteria in the table below will be used.

For each parameter and subject, classifications will be made according to the conditions i) to iii) provided below. The lower and the upper criteria will be considered separately.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that doesn't meet the MAV criteria will be considered as a subject without MAV.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV for that parameter.

Table 9.a Markedly Abnormal Values Criteria for Hematology

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Red Blood Cells ($\times 10^{12}$/L)	<0.8×LLN	>1.2×ULN
White Blood Cells ($\times 10^{9}$/L)	<0.5×LLN	>1.5×ULN
Hemoglobin (g/L)	<0.8×LLN	>1.2×ULN
Hematocrit (%)	<0.8×LLN	>1.2×ULN
Platelets ($\times 10^{9}$/L)	<75	>600
Neutrophils (%)	<0.5×LLN	>1.5×ULN
Eosinophils (%)	-	>2×ULN
Basophils (%)	-	>3×ULN
Monocytes (%)	-	>2×ULN
Lymphocytes (%)	<0.5×LLN	>1.5×ULN

LLN=Lower limit of normal, ULN=Upper limit of normal.

Table 9.b Markedly Abnormal Values Criteria for Serum Chemistry

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Alanine Aminotransferase (ALT) (U/L)	-	>3×ULN
Albumin (g/L)	<25	-
Alkaline Phosphatase (ALP) (U/L)	-	>3×ULN
Aspartate Aminotransferase (AST) (U/L)	-	>3×ULN
Total Bilirubin (µmol/L)	-	>34.2
Direct Bilirubin (µmol/L)	-	>2×ULN
Total Cholesterol (mmol/L)	-	>7.72
Triglycerides (mmol/L)	-	>2.5×ULN
Calcium (mmol/L)	<1.75	>2.88
Chloride (mmol/L)	<75	>126
Creatinine (µmol/L)	-	>177
Creatine Kinase (U/L)		>5×ULN
Blood Urea Nitrogen (BUN) (mmol/L)	-	>10.7
γ-Glutamyl Transferase (γ-GTP)	-	>3×ULN
Glucose (mmol/L)	<2.8	>19.4
Inorganic Phosphorus (mmol/L)	<0.52	>2.00
Magnesium (mmol/L)	<0.5	>1.2
Potassium (mmol/L)	<3.0	>6.0
Total Protein (g/L)	<0.8×LLN	>1.2×ULN
Sodium (mmol/L)	<130	>150
Uric Acid (mmol/L)	-	>0.773
Vitamin B_{12} (pmol/L)	<92	-

Table 9.c Markedly Abnormal Values Criteria for Vital Signs

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Body Temperature (C)	<35.6	>37.7
Systolic Blood Pressure (mmHg)	<85	>180
Diastolic Blood Pressure (mmHg)	<50	>110
Pulse (bpm)	<50	>120

Table 9.d Markedly Abnormal Values Criteria for 12-lead ECG

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Heart Rate (bpm)	<50	>120
QT Interval (msec)	<=50	>=460
QTcF Interval (msec)	<=50	See Section 9.2.2

9.2.2 12-lead ECG (Upper MAV Criteria of QTcF Interval)

All evaluable data (ie, non-missing data) obtained up to Follow-up Day 14 will be classified as a MAV or not. The criteria in the table below will be used. Note that the observed value and the change from baseline used for classification should be measurements taken on the same day.

For each subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject with at least one evaluable data after baseline that meets the MAV criteria will be classified as a subject with MAV.

ii) A subject who does not meet condition i) and has at least one evaluable data after baseline that meets any of the following will be considered as a subject without MAV.

- Observed value is less than 450 msec and not missing.
- Change from baseline is less than 30 msec and not missing, and observed value is less than 500 msec and not missing.

iii) A subject who does not meet conditions i) or ii) will be excluded from the analysis of MAV.

Table 9.e Markedly Abnormal Values Criteria for 12-lead ECG (Upper MAV Criteria of QTcF Interval)

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
QTcF Interval (msec)	-	If either of the following conditions is met: ・ observed value >=500 ・ change from baseline >= 30 and observed value >=450

9.3 Criteria for Elevated Liver Enzyme

All evaluable data (ie, non-missing data) obtained up to Follow-up Day 14 will be used to determine whether each criteria for elevated liver enzyme in the table below is met or not. If there is more than one parameter that need to be considered for a criteria, parameter measurements taken on the same day will be used. For each criteria and subject, classifications will be made according to the conditions i) to iii) provided below.

i) A subject who met criteria (a) at least once after baseline will be considered to have met the criteria for elevated liver enzyme.

ii) If condition i) is not met but if criteria (b) is met at least once after baseline, then the subject will be considered to have not met the criteria for elevated liver enzyme.

iii) If neither i) nor ii) is met, then the subject will be excluded from the analysis for the criteria for elevated liver enzyme.

Table 9.f Markedly Abnormal Values Criteria for Elevated Liver Enzyme

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
ALT > 3xULN	ALT is greater than 3 times the ULN	ALT is non-missing and less than or equal to 3 times the ULN
ALT > 5xULN	ALT is greater than 5 times the ULN	ALT is non-missing and less than or equal to 5 times the ULN
ALT > 8xULN	ALT is greater than 8 times the ULN	ALT is non-missing and less than or equal to 8 times the ULN
ALT > 3xULN with Tbili > 2xULN	ALT is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
AST > 3xULN	AST is greater than 3 times the ULN	AST is non-missing and less than or equal to 3 times the ULN
AST > 5xULN	AST is greater than 5 times the ULN	AST is non-missing and less than or equal to 5 times the ULN
AST > 8xULN	AST is greater than 8 times the ULN	AST is non-missing and less than or equal to 8 times the ULN
AST > 3xULN with Tbili > 2xULN	AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	Either AST is non-missing and less than or equal to 3 times the ULN, or the total bilirubin is non-missing and less than or equal to twice the ULN
ALT or AST > 3xULN	Either ALT or AST is greater than 3 times the ULN	Both ALT and AST are non-missing and less than or equal to 3 times the ULN
ALT or AST > 5xULN	Either ALT or AST is greater than 5 times the ULN	Both ALT and AST are non-missing and less than or equal to 5 times the ULN
ALT or AST > 8xULN	Either ALT or AST is greater than 8 times the ULN	Both ALT and AST are non-missing and less than or equal to 8 times the ULN
ALT or AST > 3xULN with Tbili > 2xULN	Either ALT or AST is greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - Both ALT and AST are non-missing and less than or equal to 3 times the ULN. - Total bilirubin is non-missing and less than or equal to twice the ULN.
ALT and AST > 3xULN	Both ALT and AST are greater than 3 times the ULN	Either ALT is non-missing and less than or equal to 3 times the ULN, or AST is

Table 9.f Markedly Abnormal Values Criteria for Elevated Liver Enzyme

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
		non-missing and less than or equal to 3 times the ULN
ALT and AST > 5xULN	Both ALT and AST are greater than 5 times the ULN	Either ALT is non-missing and less than or equal to 5 times the ULN, or AST is non-missing and less than or equal to 5 times the ULN
ALT and AST > 8xULN	Both ALT and AST are greater than 8 times the ULN	Either ALT is non-missing and less than or equal to 8 times the ULN, or AST is non-missing and less than or equal to 8 times the ULN
ALT and AST > 3xULN with Tbili > 2xULN	Both ALT and AST are greater than 3 times the ULN and the total bilirubin is greater than twice the ULN	If any of the following conditions is met: - ALT is non-missing and less than or equal to 3 times the ULN - AST is non-missing and less than or equal to 3 times the ULN - Total bilirubin is non-missing and less than or equal to twice the ULN
ALP > 3xULN	ALP is greater than 3 times the ULN	ALP is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN with ALT > 3xULN	Both ALP and ALT are greater than 3 time the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or ALT is non-missing and less than or equal to 3 times the ULN
ALP > 3xULN with AST > 3xULN	Both ALP and AST are greater than 3 times the ULN	Either ALP is non-missing and less than or equal to 3 times the ULN, or AST is non-missing and less than or equal to 3 times the ULN

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	25-Jul-2019 02:54 UTC