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

NCT Number: NCT02388737

SAP Approve Date: 08 January 2019

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information 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.

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-438_305

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

PHASE 3

Version: 2

Date: 08 January 2019

Prepared by:

PPD

1.0 APPROVAL SIGNATURES

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

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

TDC Approvals:

PPD

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
ECG	electrocardiogram
EQ-5D-5L	the 5-level version of the EuroQOL five dimensions questionnaire
FAS	full analysis set
GGT	γ-glutamyl transferase
H. pylori	Helicobacter pylori
HRQoL	Health-Related Quality of Life
LA classification	Los Angeles classification
LDH	lactate dehydrogenase
LLN	lower limit of normal
LS means	least square means
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures analysis
PPI	proton pump inhibitor
PPS	per protocol set
QOL	quality-of-life
QTcF	Fridericia's corrected QT
SAP	statistical analysis plan
Tbili	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO Drug	World Health Organization Drug Dictionary
WMWodds	Wilcoxon-Mann-Whitney odds

4.0 OBJECTIVES

4.1 PRIMARY OBJECTIVES

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

4.2 SECONDARY OBJECTIVES

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

4.3 ADDITIONAL OBJECTIVES

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

4.4 STUDY DESIGN

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

This study is comprised of 2 treatment periods: An open-label, single-arm period in which subjects receive Lansoprazole 30 mg for up to 8 weeks (Healing Phase), and a double-blind, parallel-group period in which subjects are randomized at a 1:1:1 ratio to TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily for up to 24 weeks (Maintenance Phase). To enroll in the study subjects must have ongoing erosive esophagitis or have completed Study TAK-438_303. Subjects with ongoing erosive esophagitis are required to undergo the Healing Phase. Once erosive esophagitis healing is confirmed by endoscopy, these subjects may be randomized to 1 of 3 treatments in the Maintenance Phase. Subjects with endoscopic-confirmed healing of erosive esophagitis following the completion of Study TAK-438_303 will be randomized into the Maintenance Phase without carrying out the open-label Healing Phase. Subjects who previously entered the study (prior to Protocol Amendment 06) after confirmation of healed erosive esophagitis following treatment with a proton pump inhibitor (termed "*de novo*" subjects) are no longer eligible to enter the study; any ongoing subjects may continue being treated in the Maintenance Phase. A schematic of the study design is included in Figure 4.a.

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

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

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

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

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

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

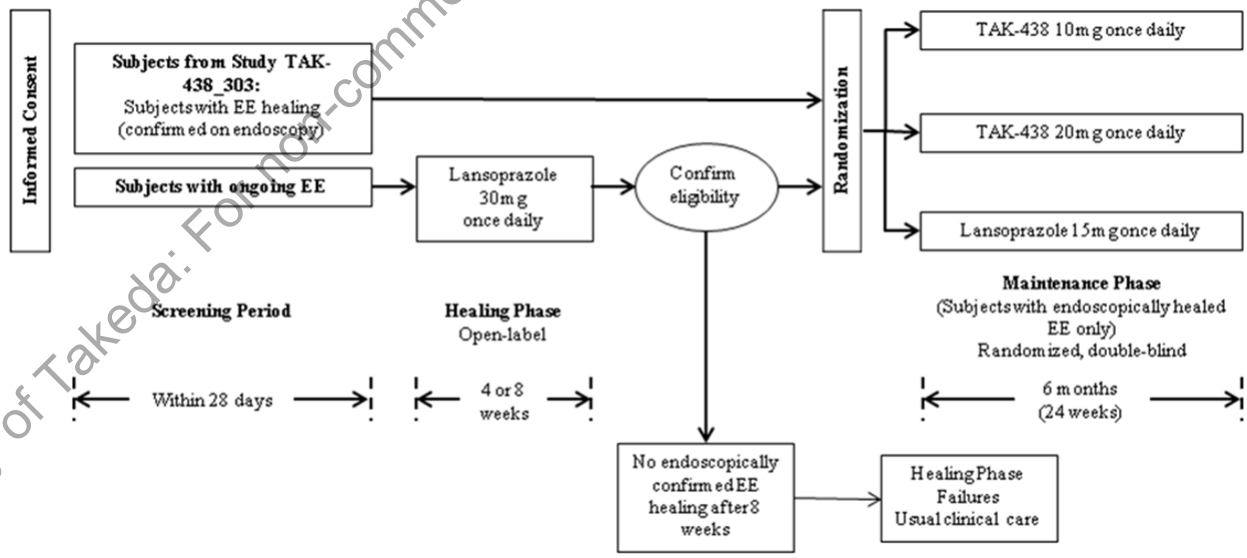


Figure 4.a Schematic of Study Design

5.0 ANALYSIS ENDPOINTS

Primary Endpoint

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

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

Secondary Endpoint

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

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

Additional Endpoints

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

6.0 DETERMINATION OF SAMPLE SIZE

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

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

Based on results from an earlier study of Lansoprazole as maintenance therapy for erosive esophagitis (AG-1749/CCT-202), the point estimate for the difference (Lansoprazole 15 mg group – famotidine group) was calculated as -57.6% with the upper limit of the confidence interval being -30.7%. Therefore, the non-inferiority margin is specified as 10%.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 GENERAL CONSIDERATIONS

7.1.1 Definitions

The following definitions and calculation formulas will be used.

- TEAE: An adverse event whose date of onset occurs on or after the start of the Maintenance Phase drug. A TEAE whose relationship to the Maintenance Phase drug is missing will be considered drug-related. A TEAE whose intensity is missing will be considered severe.
- Descriptive statistics: number of subjects, mean, standard deviation, maximum, minimum, and quartiles
- Study Day: The day before the first dose of the Maintenance Phase drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. Other study days are defined relative to Study Day 1, eg, the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2.
- Follow-up Day: The day after the last dose of the Maintenance Phase drug will be defined as Follow-up Day 1. Other follow-up days are defined relative to Follow-up Day 1.
- Duration of exposure to study drug (days): date of last dose of Maintenance Phase drug - date of first dose of Maintenance Phase drug + 1.
- Study drug compliance (%): (number of days the subject answered "Yes" in the subject diary to the question "Study medication taken?") / duration of exposure to study drug * 100 (rounded to 1 decimal place).
- Age (years): The following only applies to subjects from countries other than Korea. If the date informed consent obtained or the date of birth is missing, then age will be missing. If the month and the day of the date informed consent obtained is before the month and the day of the date of birth, then age will be calculated as follows: the year of the date informed consent obtained - the year of the date of birth - 1. For all others, age will be calculated as follows: the year of the date informed consent obtained - the year of the date of birth.
- BMI (kg/m^2): weight (kg) / (height (m))^2 (rounded to 1 decimal place).
- Pepsinogen I/II Ratio: Pepsinogen I (µg/L) / Pepsinogen II (µg/L) (rounded to 1 decimal place).
- QTcF interval (msec): QT interval (msec) / (RR interval (sec))$^{0.33}$ (rounded to the nearest whole number).
- Confidence interval for one sample proportion: Exact (Clopper-Pearson) confidence interval will be used.
- Confidence interval for two sample proportion difference: Wald confidence interval will be used.
- Significant TEAE: Any TEAE (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment, dose increase, dose reduction, or significant additional concomitant therapy.

7.1.2 Analysis Sets

Analysis of efficacy variables will be conducted in the full analysis set (FAS) defined as all randomized subjects who receive at least 1 dose of the Maintenance Phase drug and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment. Randomized subjects who were accidentally unblinded due to IWRS system error will be excluded.

The primary efficacy endpoint and the secondary efficacy endpoint will also be analyzed in the per protocol set 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 or #4
- Subjects who met exclusion criteria #8, #11, #12, #13, or #14
- Subjects with study drug 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 the Maintenance Phase drug and will be based on the treatment received in the Maintenance Phase.

7.1.3 Handling of Rate of Endoscopic Recurrence of Erosive Esophagitis

7.1.3.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the first 12 Weeks of Treatment in the Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed between Study Day 2 and Study Day 127 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis.

7.1.3.2 Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-Week Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed after Study Day 2 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis.

7.1.4 Handling of Data When Calculating Mean Severity According to Subject Diary

Each subjective symptom of erosive esophagitis as recorded in subject diaries (ie, heartburn, gastric acid regurgitation) will be handled as below.

Severity will be scored as follows. None: 0, Mild: 1, Moderate: 2, Severe: 3.

For each subject, the mean severity will be calculated as follows at each visit. If the denominator is missing, then the calculated result should also be missing.

Mean severity = (total score of the severity recorded for the visit) / (number of days the severity of symptom is recorded) (rounded to 2 decimal places)

(Note: Severity recorded as "Not Completed" will be treated as missing.)

The following visits will be used.

Visit	Time Interval (days)	
	Study Day	Follow-up Day
Baseline*	Day -6 – Day 1	
Week 4	Day 2 – Day 29	up to and including Follow-up Day 1
Week 8	Day 30 – Day 57	up to and including Follow-up Day 1
Week 12	Day 58 – Day 85	up to and including Follow-up Day 1
Week 16	Day 86 – Day 113	up to and including Follow-up Day 1
Week 20	Day 114 – Day 141	up to and including Follow-up Day 1
Week 24	Day 142 – Day 169	up to and including Follow-up Day 1

*: Will not be included in the analysis, however, data will be created.

7.1.5 HRQoL (EQ-5D-5L)

All evaluable data (ie, non-missing) obtained in the corresponding time interval will be used in evaluating the EQ-5D-5L index value and EQ VAS score. 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.

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.

The following visits will be used.

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-28 – 1	
Week 4	Study Day: 29	2 – 57	up to and including Follow-up Day 14
Week 12	Study Day: 85	58 – 127	up to and including Follow-up Day 14
Week 24	Study Day: 169	128 – 211	up to and including Follow-up Day 14

7.1.6 Handling of Other Endpoints

For each visit, all evaluable observation (ie, non-missing) obtained in the corresponding time interval will be used. 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.

The following visits will be used.

Weight, BMI, Endoscopy (esophageal hiatal hernia)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	up to and including Study Day 1	

Endoscopy (Barrett's mucosa), 12-lead ECG

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	up to and including Study Day 1	
Week 12	Study Day: 85	2 – 127	up to and including Follow-up Day 14
Week 24	Study Day: 169	128 – 211	up to and including Follow-up Day 14

Clinical laboratory tests (ALT, AST, total bilirubin, and direct bilirubin)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline*	Study Day: 1	-28 – 1	
Week 2	Study Day: 15	2 – 22	up to and including Follow-up Day 14
Week 4	Study Day 29	23 – 36	up to and including Follow-up Day 14
Week 6	Study Day: 43	37 – 50	up to and including Follow-up Day 14
Week 8	Study Day: 57	51 - 71	up to and including Follow-up Day 14
Week 12	Study Day: 85	72 – 127	up to and including Follow-up Day 14
Week 24	Study Day: 169	128 – 211	up to and including Follow-up Day 14

*: For the clinical laboratory tests of the subjects who participated in the TAK-438_303 study, if the last study visit coincides with the first visit in the 305 study or if the subject was randomized in the 305 study within 7 days after completing the last visit in the 303 study, then the data obtained at the last visit can be used as the baseline data for the 305 study.

Clinical laboratory tests (other than ALT, AST, total bilirubin, and direct bilirubin), Gastrin, Pepsinogen I/II, Vital signs

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline*	Study Day: 1	-28 – 1	
Week 4	Study Day 29	2 – 57	up to and including Follow-up Day 14
Week 12	Study Day: 85	58 – 127	up to and including Follow-up Day 14
Week 24	Study Day: 169	128 – 211	up to and including Follow-up Day 14

*: For the clinical laboratory tests, gastrin, and pepsinogen I/II of the subjects who participated in the TAK-438_303 study, if the last study visit coincides with the first visit in the 305 study or if the subject was randomized in the 305 study within 7 days after completing the last visit in the 303 study, then the data obtained at the last visit can be used as the baseline data for the 305 study.

7.2 STUDY SUBJECTS, DEMOGRAPHICS, AND OTHER BASELINE CHARACTERISTICS

7.2.1 Disposition of Subjects

7.2.1.1 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.

7.2.1.2 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, Multiple]

Analytical Methods: **(1) Screen Failures**

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.2.1.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status	[Yes, No]
Primary Reason for Subject Not Being Eligible	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Did Not Meet Entrance Criteria, Healing Phase Failure, 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.

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

Analysis Set:	Randomized Set	
Analysis Variables:	Randomization Status	[Yes]
Stratum:	Country	[China, Malaysia, South Korea, 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.

7.2.1.5 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variables:	Maintenance Phase Drug Administration Status	[No]
	Reason for Not Being Treated	[Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Pregnancy, Lack of Efficacy, Other]
	Maintenance Phase Drug Completion Status	[Completed Maintenance Phase Drug, Prematurely Discontinued Maintenance Phase Drug]
	Reason for Discontinuation of Maintenance Phase Drug	[Pretreatment Event/Adverse Event, Major 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 maintenance phase drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of maintenance phase drug, the total number of subjects who prematurely discontinued the maintenance phase drug will be used as the denominator.

(2) Flow Chart of Subject Distribution

Flow chart will be provided.

7.2.1.6 Protocol Deviations and Analysis Sets

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.

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.

7.2.2 Demographics and Other Baseline Characteristics

7.2.2.1 Summary of Demographics and Other Baseline Characteristics

Analysis Set: Randomized Set
Full Analysis Set

Analysis Variables:		
	Country	[China, Malaysia, South Korea, Taiwan]
	Participation in TAK-438_303 Study	[Yes, No]
	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, Multiple]
	Height (cm)	[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
	Weight (kg) (Baseline)	[Min<= - <50.0, 50.0<= - <60.0, 60.0<= - <70.0, 70.0<= - <80.0, 80.0<= - <=Max]

BMI (kg/m^2) (Baseline)	[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, No]
History of H. pylori Eradication Therapy	[Yes (End of Treatment: Within the Past 1 Year), Yes (End of Treatment: More than 1 Year), No]
LA Classification (Time of Diagnosis)	[Grade A, Grade B, Grade C, Grade D] [Grade A/B, Grade C/D]
Barrett's Mucosa (Baseline)	[Present (3 cm or Greater), Present (Less than 3 cm), Absent, Unknown]
Esophageal Hiatal Hernia (Baseline)	[Present (2 cm or Greater), Present (Less than 2 cm), Absent, Unknown]
HRQoL (EQ-5D-5L)	
EQ-5D-5L Index Value (Baseline)	
EQ VAS Score (Baseline)	

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.

7.2.2.2 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.

7.2.2.3 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.

7.2.3 Treatment Compliance

7.2.3.1 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set
Full Analysis Set

Analysis Variables: Duration of Exposure to Study Drug (days) [1<= - <=84, 85<= - <=168, 169<= - <=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 in Maintenance Phase**

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.3 EFFICACY ANALYSIS

The full analysis set will be the main analysis set used. The per protocol set will be used for analyses performed secondarily on the primary efficacy endpoint and secondary efficacy endpoints in order to examine the robustness of the results.

7.3.1 Primary Efficacy Endpoint

7.3.1.1 Primary Analysis

Analysis Set: Full Analysis Set

Analysis Variable: Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase (%)

Analytical Methods: **(1) Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase**

Frequency distributions will be provided by treatment group along with rates and the two-sided 95% confidence intervals. The differences in the rates between each TAK-438 group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals using the Wald method will be provided. The non-inferiority margin will be set to 10%. Details concerning interpretation are described in section 7.3.4.5.

7.3.1.2 Secondary Analysis

Analysis Set: Per Protocol Set

Analysis Variable: Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase (%)

Analytical Methods: **(1) Sensitivity Analysis**

To check the robustness of the results, the same analyses as those in section 7.3.1.1 will be performed using the per protocol set.

7.3.2 Secondary Efficacy Endpoint

7.3.2.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase

Analysis Set: Full Analysis Set

Analysis Variable: Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase (%)

Analytical Methods: **(1) Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase**

Frequency distributions will be provided by treatment group along with rates and the two-sided 95% confidence intervals. The differences in the rates between each TAK-438 group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will also be provided.

7.3.2.2 Sensitivity Analysis

Analysis Set: Per Protocol Set

Analysis Variable: Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase (%)

Analytical Methods: **(1) Sensitivity Analysis**

To check the robustness of the results, the same analyses as section 7.3.2.1 will be performed using the per protocol set.

7.3.3 Additional Efficacy Endpoints

7.3.3.1 Gastrointestinal Symptoms Based on Subject Diary

Heartburn Symptoms

Analysis Set: Full Analysis Set

Analysis Variables: Mean Severity of Symptoms

Subgroups: Barrett's Mucosa (Baseline) [Present, Absent]

Visit: Week 4, Week 8, Week 12, Week 16, Week 20, Week 24

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

i) Descriptive statistics will be provided for each visit.

ii) The difference in the medians between each TAK-438 group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals will be provided for each visit using the Hodges-Lehmann estimator. Wilcoxon rank-sum tests will be used to test for treatment differences at each visit.

iii) WMWodds of each TAK-438 group to the Lansoprazole group and the two-sided 95% confidence intervals will be provided for each visit based on Wilcoxon-Mann-Whitney test statistics.

Subgroup Analysis (Baseline Barrett's Mucosa)

- The same analyses as all of the above will be conducted for the defined subgroups.

Gastric Acid Regurgitation

Analysis Set: Full Analysis Set

Analytical Methods: The same analyses as those in section 7.3.3.1 "Heartburn Symptoms" will be conducted for the gastric acid regurgitation.

7.3.3.2 HRQoL (EQ-5D-5L)

EQ-5D-5L Index Value

Analysis Set: Full Analysis Set

Analysis Variables: EQ-5D-5L Index Value

Covariates: LA Classification (Time of Diagnosis) [Grade A/B, Grade C/D]
EQ-5D-5L Index Value (Baseline)

Visit: Baseline, Week 4, Week 12, Week 24

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 each TAK-438 group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence intervals 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 LA classification at the time of diagnosis 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% confidence intervals will be provided for each treatment group. The difference in the LS means between each TAK-438 group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence interval will be provided. The difference in the LS means will be tested for treatment differences.

(3) MMRM

The changes from baseline (each post baseline visit – baseline) in the analysis variable will be analyzed using a mixed model repeated measures analysis (MMRM) model with the changes from baseline in the analysis variable as the response, and treatment, LA classification at the time of diagnosis, baseline value of the analysis variable, visit, treatment-by-visit interaction, baseline-by-visit interaction, and LA grade-by-visit interaction as fixed effects. LS means and the two-sided 95% confidence intervals will be provided by visit for each treatment group. The differences in the LS means between each TAK-438 group and the Lansoprazole group (each TAK-438 group - the Lansoprazole group) and the two-sided 95% confidence intervals will be provided for each visit. The differences in the LS means will be tested for treatment differences. An unstructured variance-covariance matrix will be used to model the within-subject errors and Satterthwaite's method will be used to approximate the degrees of freedom.

EQ VAS Score

Analysis Set: Full Analysis Set
Analysis Variables: EQ VAS Score
Covariates: LA Classification (Time of Diagnosis) [Grade A/B, Grade C/D]
EQ VAS Score (Baseline)
Analytical Methods: The same analyses as those in section 7.3.3.2 "EQ-5D-5L Index Value" will be conducted for the EQ VAS score.

7.3.3.3 Barrett's Mucosa

Analysis Set: Full Analysis Set
Analysis Variables: Barrett's Mucosa (Change) [Increased, Unchanged, Reduced, Disappeared, Unknown]
Subgroups: Barrett's Mucosa (Baseline) [Present (3 cm or Greater), Present (Less than 3 cm), Absent, Unknown]
Visit: Week 12, Week 24
Analytical Methods: **(1) Frequency distribution of Barrett's Mucosa (Change) by Baseline Barrett's Mucosa**
Frequency distribution will be provided for each subgroup and visit by treatment group.

7.3.4 Statistical/Analytical Issues

7.3.4.1 Adjustments for Covariates

Analysis Set: Full Analysis Set
Analysis Variable: Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase (%)
Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase (%)
Stratified Variable: LA Classification (Time of Diagnosis) [Grade A/B, Grade C/D]
Analytical Methods: **(1) CMH Test for the Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase**
(2) CMH Test for the Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase
A CMH test with LA Classification at the time of diagnosis as a stratification factor will be used to compare the above analysis variable between each TAK-438 group and the Lansoprazole group for treatment differences. Mantel-Haenszel estimate of risk difference between each TAK-438 group and the Lansoprazole group (each TAK-438 group – the Lansoprazole group) and the two-sided 95% confidence interval using the Wald method will also be provided.

7.3.4.2 Handling of Dropouts or Missing Data

For the primary endpoint "rate of endoscopic recurrence of erosive esophagitis during the 24-week maintenance phase" and the secondary efficacy endpoint "rate of endoscopic recurrence of erosive esophagitis during the first 12

weeks of treatment in the maintenance phase", missing data will be handled according to the details described in 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.

7.3.4.3 Interim Analyses and Data Monitoring

No interim analysis is planned in this study.

7.3.4.4 Multicenter Studies

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

7.3.4.5 Multiple Comparison/Multiplicity

Adjustment for multiplicity will be performed for the primary endpoint "rate of endoscopic recurrence of erosive esophagitis during the 24-week maintenance phase" and the secondary efficacy endpoint "rate of endoscopic recurrence of erosive esophagitis during the first 12 weeks of treatment in the maintenance phase" in the following order under the closed testing procedure and the analysis will be conducted using the full analysis set.

- The primary endpoint "rate of endoscopic recurrence of erosive esophagitis during the 24-week maintenance phase" will be tested for non-inferiority between the TAK-438 20 mg group and the Lansoprazole group. In other words, if the upper bound of the 95% confidence interval of the treatment difference (the TAK-438 20 mg group – the Lansoprazole group) is ≤10%, the non-inferiority for TAK-438 20 mg relative to Lansoprazole will be declared.
- If the previous test is successful, the primary endpoint will be tested for non-inferiority between the TAK-438 10 mg group and the Lansoprazole group. In other words, if the upper bound of the 95% confidence interval of the treatment difference (the TAK-438 10 mg group – the Lansoprazole group) is ≤10%, the non-inferiority for TAK-438 10 mg relative to Lansoprazole will be declared.
- If the previous test is successful, the primary endpoint will be tested for superiority between the TAK-438 20 mg group and the Lansoprazole group. The upper bound of the 95% confidence interval of the treatment difference (the TAK-438 20 mg group -the Lansoprazole group) will be compared to 0%.
- If the previous test is successful, the primary endpoint will be tested for superiority between the TAK-438 10 mg group and the Lansoprazole group.
- If the previous test is successful, the secondary endpoint "rate of endoscopic recurrence of erosive esophagitis during the first 12 weeks of treatment in the maintenance phase" will be tested for superiority between the TAK-438 20 mg group and the Lansoprazole group.
- If the previous test is successful, the secondary endpoint will be tested for superiority between the TAK-438 10 mg group and the Lansoprazole group.

Other analyses in this study will be done only for exploratory purposes and multiplicity adjustments will not be made.

7.3.4.6 Use of an "Efficacy Subset" of Subjects

In addition to analyses on the primary and secondary efficacy endpoints using the full analysis set, sensitivity analyses will also be performed using the per protocol set to examine the robustness of the results.

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

For the primary efficacy endpoint, non-inferiority for each TAK-438 group relative to the Lansoprazole group will be confirmed in the full analysis set using a non-inferiority margin of 10%.

7.3.4.8 Subgroup Analysis

Analysis Set:	Full Analysis Set	
Analysis Variable:	Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase (%) Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase (%)	
Subgroups:	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender	[Male, Female]
	BMI (kg/m^2) (Baseline)	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	LA Classification (Time of Diagnosis)	[Grade A/B, Grade C/D]
	Barrett's Mucosa (Baseline)	[Present, Absent]
	Esophageal Hiatal Hernia (Baseline)	[Present (2 cm or Greater), Present (Less than 2 cm), Absent, Unknown]

Analytical Methods:

(1) Subgroup Analysis for the Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase

(2) Subgroup Analysis for the Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase

The same analyses as those in section 7.3.1.1 will be performed for each of the above subgroups, except for non-inferiority testing.

7.4 SAFETY ANALYSIS

7.4.1 Treatment-Emergent Adverse Events

7.4.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

Categories: Relationship to Study Drug [Related, Not Related]
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) Relationship of Treatment-Emergent Adverse Events to Study Drug (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 Study Drug Discontinuation (number of events, number and percentage of subjects)
5) Relationship to Study Drug of Treatment-Emergent Adverse Events Leading to 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) Relationship of Serious Treatment-Emergent Adverse Events to Study Drug (number of events, number and percentage of subjects)
8) Serious Treatment-Emergent Adverse Events Leading to 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), and 7)
  A subject with occurrences of TEAE in both categories (ie, Related and Not Related) 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), and 7)
  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.

7.4.1.2 Displays of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variables: TEAE

Categories: Intensity [Mild, Moderate, Severe]

Time of Onset (day) [1<= - <=84, 85<= - <=168, 169<= - <=Max]

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) Drug-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 Drug-Related Treatment-Emergent Adverse Events by System Organ Class, and Preferred Term

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

(8) Drug-Related Treatment-Emergent Adverse Events Leading to 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 Drug-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) Drug-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) Drug-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

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 calculating the percentages for "Subjects With Any TEAEs", the number of subjects with at least one of these most frequent non-serious TEAEs will be used as the numerator.

7.4.2 Pretreatment Events and Adverse Events in the Healing Phase

7.4.2.1 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.

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

7.4.2.2 Displays of Adverse Events in the Healing Phase

Analysis Set: All Subjects Who Entered the Healing Phase

Analysis Variables: AE in the Healing Phase

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

AEs 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) Adverse Events in the Healing Phase by System Organ Class and Preferred Term

(2) Serious Adverse Events in the Healing Phase 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 AE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of AE within a PT will be counted only once in that PT.

7.4.3 Laboratory and Other Safety Data

7.4.3.1 Laboratory Test Results

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)

Visit: ALT, AST, Total Bilirubin, and Direct Bilirubin:
Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24
Variables other than ALT, AST, Total Bilirubin, and Direct Bilirubin:
Baseline, Week 4, Week 12, Week 24

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 maintenance 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 maintenance phase will be provided. Further details are given in Appendix.

Urinalysis

Analysis Set: Safety Analysis Set

Analysis Variables : Protein [Neg, Trace, 30 mg/dL, 100 mg/dL, 300 mg/dL, >=2000 mg/dL]

Sugar [Neg, 100 mg/dL, 250 mg/dL, 500 mg/dL, 1000 mg/dL, >=2000 mg/dL]

Visit: Baseline, Week 4, Week 12, Week 24

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

(1) 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.

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

Visit: Baseline, Week 4, Week 12, Week 24

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.

7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

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 4, Week 12, Week 24

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 maintenance 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.

12-lead ECG

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 12, Week 24

Analytical Methods: For each variable other than interpretation, 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 maintenance 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.

7.4.5 Subgroup Analysis for China

Analysis Population: Subjects in China

Subjects in Countries other than China

Analytical Methods: (1) The same analyses as those in section 7.2 to 7.4.4 will be conducted for the subjects in China.

(2) The same analyses as those in section 7.2 to 7.4.4 will be conducted for the subjects in countries other than China.

7.4.6 Subgroup Analysis for Taiwan

Analysis Population: Subjects in Taiwan

Analytical Methods: (1) The same analyses as those in section 7.2 to 7.4.4 will be conducted for the subjects in Taiwan.

7.4.7 Subgroup Analysis for Safety Analysis Set Excluding Accidentally Unblinded Subjects

Analysis Population: Safety Analysis Set Excluding the Accidentally Unblinded Subjects

Safety Analysis Set Excluding the Accidentally Unblinded Subjects in China

Safety Analysis Set Excluding the Accidentally Unblinded Subjects in Countries other than China

Safety Analysis Set Excluding the Accidentally Unblinded Subjects in Taiwan

Analytical Methods: The same analyses as those in sections 7.4.1.1 and 7.4.1.2 ((1), (4) to (17)) will be conducted in the safety analysis set that excludes subjects who were accidentally unblinded due to IWRS system error.

The same analyses will be conducted for the subjects in China and countries other than China.

The same analyses will be conducted for the subjects in Taiwan.

7.4.8 Significance Level and Confidence Coefficient

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

7.4.9 Changes in the Statistical Analysis Plan

The changes from the original SAP (Version: 1, Date: 20 November 2015) to the amended SAP were described below with a rationale for changes provided.

Page 1, TITLE PAGE

Existing Text

PPD

Revised Text

PPD

Rationale for Amendment

The responsible person has been changed.

Page 2, Section 1.0 APPROVAL SIGNATURES

Existing Text

PPD

Revised Text

PPD

Rationale for Amendment

The Responsible persons have been changed for Biostatistics and Clinical Science. The Responsible person has not been needed for Pharmacovigilance.

Page 7, Section 4.1 PRIMARY OBJECTIVES

Existing Text

To demonstrate the non-inferiority of TAK-438 to Lansoprazole in the reduction of relapse of erosive esophagitis in subjects in the Maintenance Phase (24 weeks) in whom endoscopic healing of erosive esophagitis has been

confirmed after treatment with TAK-438 or a PPI, as well as to determine the clinically recommended dose of TAK-438 for maintenance therapy in erosive esophagitis.

Revised Text

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

Rationale for Amendment

The description has been revised in the protocol.

Page 7, Section 4.2 SECONDARY OBJECTIVES

Existing Text

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

Revised Text

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

Rationale for Amendment

The description has been revised in the protocol.

Page 7~8, Section 4.4 STUDY DESIGN

Existing Text

This is a phase III, multicenter, double-blind, parallel-group comparative study of TAK-438 (10 mg or 20 mg) in subjects in whom endoscopic healing of erosive esophagitis has been confirmed with TAK-438 or following proton pump inhibitor (PPI) treatment, to demonstrate the non-inferiority of TAK-438 to Lansoprazole in their maintenance treatment (6 months or 24 weeks) as well as to determine the clinically recommended dose for TAK-438 for maintenance therapy in erosive esophagitis.

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

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

This study will be conducted at a total of around 60 sites across Asia with an estimated total of 200 subjects randomized to each treatment group totaling 600 for the study.

The study will consist of a Screening Phase of up to 28 days followed by a Treatment Phase of up to 24 weeks. There will be 5 subject visits scheduled: the start of the Screening Phase (Visit 1), the start of the Treatment Phase (Visit 2), after 4 weeks of treatment (Visit 3), after 12 weeks of treatment (Visit 4), after 24 weeks of treatment (Visit 5), and a Follow-up phase.

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

Revised Text

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

This study is comprised of 2 treatment periods: An open-label, single-arm period in which subjects receive Lansoprazole 30 mg for up to 8 weeks (Healing Phase), and a double-blind, parallel-group period in which subjects are randomized at a 1:1:1 ratio to TAK-438 10 mg, 20 mg or Lansoprazole 15 mg once daily for up to 24 weeks (Maintenance Phase). To enroll in the study subjects must have ongoing erosive esophagitis or have completed Study TAK-438_303. Subjects with ongoing erosive esophagitis are required to undergo the Healing Phase. Once erosive esophagitis healing is confirmed by endoscopy, these subjects may be randomized to 1 of 3 treatments in the Maintenance Phase. Subjects with endoscopic-confirmed healing of erosive esophagitis following the completion of Study TAK-438_303 will be randomized into the Maintenance Phase without carrying out the open-label Healing Phase. Subjects who previously entered the study (prior to Protocol Amendment 06) after confirmation of healed erosive esophagitis following treatment with a proton pump inhibitor (termed "*de novo*" subjects) are no longer eligible to enter the study; any ongoing subjects may continue being treated in the Maintenance Phase. A schematic of the study design is included in Figure 4.a.

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

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

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

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

endoscopic-confirmed healed erosive esophagitis after 8 weeks treatment (Healing Phase Failures) will not be randomized into the Maintenance Phase and should be treated using routine clinical care.

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

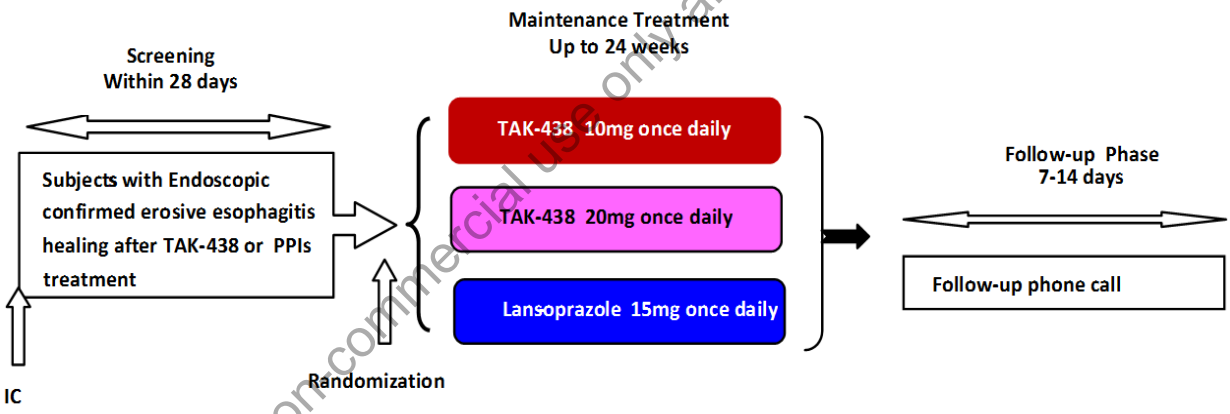
All subjects receiving TAK-438 must undergo a total of 8 weeks of LFT monitoring visits with visits occurring every 2 weeks. For subjects entering the Maintenance Phase of the current study within 7 days of completing Study TAK-438_303, the requirement for 8 weeks of monitoring can be totalled across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

Rationale for Amendment

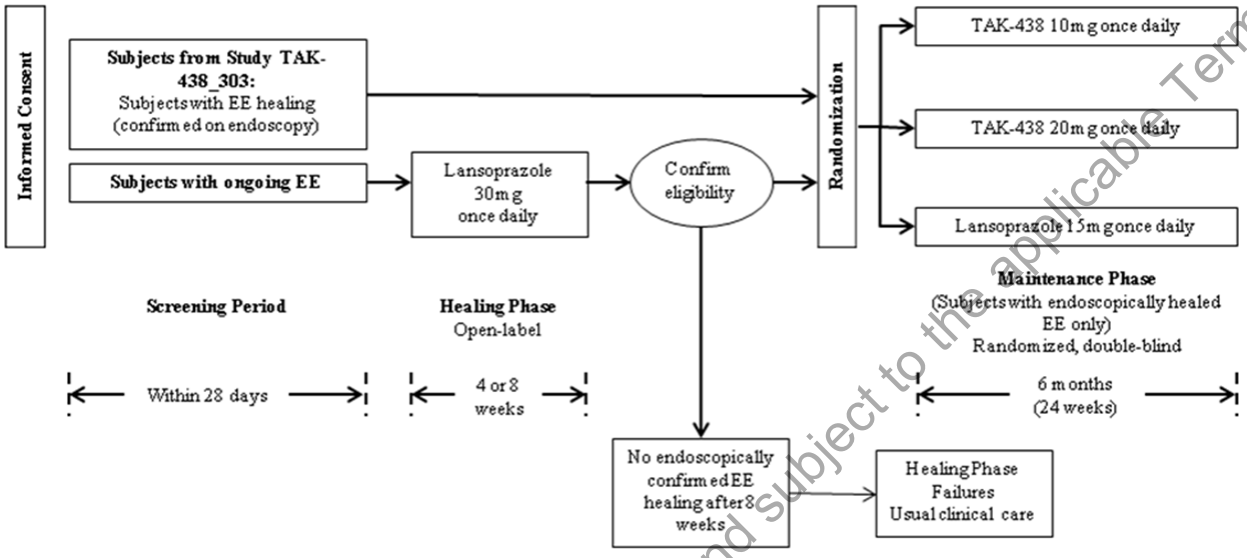
The descriptions have been revised in the protocol.

Page 8, Section 4.4 STUDY DESIGN

Existing Figure



Revised Figure



Rationale for Amendment

The figure (Figure 4.a) has been revised in the protocol.

Page 9, Section 5.0 ANALYSIS ENDPOINTS

Existing Text

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

Revised Text

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

Rationale for Amendment

The description has been revised in the protocol.

Page 10, Section 6.0 DETERMINATION OF SAMPLE SIZE

Existing Text

Assuming that the true Week 24 recurrence rate is 30.4% for lansoprazole, 22.0% for TAK-438 10 mg, and 13.6% for TAK-438 20 mg, and assuming that the dropout rate is up to 20%, a sample size of 185 subjects per group will provide an overall power of 90% to establish non-inferiority using a 2-sided 95% CI with a 10% non-inferiority margin. 200 subjects per group will be included to allow adequate numbers for the regulatory requirements of various countries.

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

Based on results from an earlier study of Lansoprazole as maintenance therapy for erosive esophagitis (AG-1749/CCT-202), the point estimate for the difference (Lansoprazole 15 mg group – Famotidine group) was calculated as -57.6% with the upper limit of the confidence interval being -30.7%. Therefore, the non-inferiority margin is specified as 10%.

Revised Text

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

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

Based on results from an earlier study of Lansoprazole as maintenance therapy for erosive esophagitis (AG-1749/CCT-202), the point estimate for the difference (Lansoprazole 15 mg group – famotidine group) was calculated as -57.6% with the upper limit of the confidence interval being -30.7%. Therefore, the non-inferiority margin is specified as 10%.

Rationale for Amendment

The description with the targeted sample size has been revised in the protocol.

Page 11, Section 7.1.1 Definitions

Existing Text

TEAE: An adverse event whose date of onset occurs on or after the start of study drug.

Revised Text

TEAE: An adverse event whose date of onset occurs on or after the start of the Maintenance Phase drug. A TEAE whose relationship to the Maintenance Phase drug is missing will be considered drug-related. A TEAE whose intensity is missing will be considered severe.

Rationale for Amendment

The Maintenance Phase has been added in the protocol, and the handling rules for missing data for TEAE have been added.

Page 11, Section 7.1.1 Definitions

Existing Text

- Study Day: The day before the first dose of the study medication will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. Other study days are defined relative to Study Day 1, eg, the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2.
- Follow-up Day: 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.

- Duration of exposure to study drug (days): date of last dose of study drug - date of first dose of study drug + 1

Revised Text

- Study Day: The day before the first dose of the Maintenance Phase drug will be defined as Study Day -1 and the day of the first dose will be defined as Study Day 1. Other study days are defined relative to Study Day 1, eg, the day prior to Study Day 1 is Day -1 and the day after Study Day 1 is Day 2.
- Follow-up Day: The day after the last dose of the Maintenance Phase drug will be defined as Follow-up Day 1. Other follow-up days are defined relative to Follow-up Day 1.
- Duration of exposure to study drug (days): date of last dose of Maintenance Phase drug - date of first dose of Maintenance Phase drug + 1

Rationale for Amendment

The Maintenance Phase has been added in the protocol.

Page 11, Section 7.1.1 Definitions

Added Text

Pepsinogen I/II Ratio: Pepsinogen I (µg/L) / Pepsinogen II (µg/L) (rounded to 1 decimal place)

Significant TEAE: Any TEAE (not including serious TEAEs) that led to an intervention, including withdrawal of drug treatment, dose increase, dose reduction or significant additional concomitant therapy.

Rationale for Amendment

The calculation formula for the above variable has been added with the number of decimal places. The significant TEAE should be analyzed and the definition of this type of TEAE has been added.

Page 11~12, Section 7.1.2 Analysis Sets

Existing Text

Analysis of efficacy variables will be conducted in the full analysis set (FAS) defined as all randomized subjects who receive at least 1 dose of study medication and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment.

The primary efficacy endpoint and the secondary efficacy endpoint will also be analyzed in the per protocol set 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 or #4
- Subjects who met exclusion criteria #8, #11, #12, #13, or #14
- 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 and will be based on the treatment received.

Revised Text

Analysis of efficacy variables will be conducted in the full analysis set (FAS) defined as all randomized subjects who receive at least 1 dose of the Maintenance Phase drug and have at least 1 post-baseline endoscopy, and will be based on the randomized treatment. Randomized subjects who were accidentally unblinded due to IWRS system error will be excluded.

The primary efficacy endpoint and the secondary efficacy endpoint will also be analyzed in the per protocol set 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 or #4
- Subjects who met exclusion criteria #8, #11, #12, #13, or #14
- Subjects with study drug 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 the Maintenance Phase drug and will be based on the treatment received in the Maintenance Phase.

Rationale for Amendment

The Maintenance Phase has been added in the protocol. Accidental unblinding was identified in the study on Dec 16, 2015. It was confirmed that the treatment details of 93 subjects randomized in the study were accidentally unblinded to the site investigators, clinical project managers, and the CRA team through the IWRS subject visit notification emails. The accidental unblinding was caused by an IWRS system error. The randomized subjects who were accidentally unblinded due to IWRS system error should be excluded from the FAS and the PPS.

Page 12, Section 7.1.3 Handling of Rate of Endoscopic Recurrence of Erosive Esophagitis

Existing Text

7.1.3.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the 12-Week Treatment

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed between Study Day 2 and Study Day 127 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the study medication administration will be excluded from the analysis.

7.1.3.2 Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-Week Treatment

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed after Study Day 2 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the study medication administration will be excluded from the analysis.

Revised Text

7.1.3.1 Rate of Endoscopic Recurrence of Erosive Esophagitis During the first 12 Weeks of Treatment in the Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed between Study Day 2 and Study Day 127 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis.

7.1.3.2 Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-Week Maintenance Phase

A subject who is diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed after Study Day 2 (up to and including Follow-up Day 14) will be considered as a relapsed 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 relapsed'. Recurrence rate will be calculated from the relapsed and not relapsed subjects, however, any subjects diagnosed as LA classification grade A, B, C, or D from endoscopy tests performed before the Maintenance Phase drug administration will be excluded from the analysis.

Rationale for Amendment

The Maintenance Phase has been added, and the description has been revised in the protocol.

Page 12, Section 7.1.4 Handling of Data When Calculating Mean Severity According to Subject Diary

Existing Text

Mean severity = (total score of the severity recorded for the visit) / (number of days the severity of symptom is recorded) * 100 (rounded to 2 decimal places)

Revised Text

Mean severity = (total score of the severity recorded for the visit) / (number of days the severity of symptom is recorded) (rounded to 2 decimal places)

Rationale for Amendment

The expression "* 100" has been deleted because of clerical error.

Page 14, Section 7.1.6 Handling of Other Endpoints

Existing Text

Study Day: -28 – 1 (2 places)

Revised Text

Study Day: up to and including Study Day 1 (2 places)

Rationale for Amendment

The time intervals should be changed because the Healing Phase has been added in the protocol.

Page 15, Section 7.1.6 Handling of Other Endpoints

Existing Text

Clinical laboratory tests, Gastrin, Pepsinogen I/II, Vital signs

Revised Text

Clinical laboratory tests (ALT, AST, total bilirubin, and direct bilirubin)

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline*	Study Day: 1	-28 – 1	
Week 2	Study Day: 15	2 – 22	up to and including Follow-up Day 14
Week 4	Study Day 29	23 – 36	up to and including Follow-up Day 14
Week 6	Study Day: 43	37 – 50	up to and including Follow-up Day 14
Week 8	Study Day: 57	51 - 71	up to and including Follow-up Day 14
Week 12	Study Day: 85	72 – 127	up to and including Follow-up Day 14
Week 24	Study Day: 169	128 – 211	up to and including Follow-up Day 14

*: For the clinical laboratory tests of the subjects who participated in the TAK-438_303 study, if the last study visit coincides with the first visit in the 305 study or if the subject was randomized in the 305 study within 7 days after completing the last visit in the 303 study, then the data obtained at the last visit can be used as the baseline data for the 305 study.

Clinical laboratory tests (other than ALT, AST, total bilirubin, and direct bilirubin), Gastrin, Pepsinogen I/II, Vital signs

Rationale for Amendment

Visit 3 (Week 2), Visit 5 (Week 6) and Visit 6 (Week 8) has been added in the protocol for evaluating liver function tests (ALT, AST, total bilirubin, and direct bilirubin).

Page 15, Section 7.1.6 Handling of Other Endpoints

Existing Text

For the clinical laboratory tests, gastrin and pepsinogen I/II, for the subjects who participated in the TAK-438_303 study

Revised Text

For the clinical laboratory tests, gastrin, and pepsinogen I/II of the subjects who participated in the TAK-438_303 study

Rationale for Amendment

The expression has been revised.

Page 16, Section 7.2.1.2 Screen Failures

Existing Text

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]

Revised Text

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple]

Rationale for Amendment

There have been subjects whose race were "Multiple".

Page 16, Section 7.2.1.3 Subject Eligibility

Existing Text

Primary Reason for Subject Not Being Eligible [Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Did Not Meet Entrance Criteria, Other]

Revised Text

Primary Reason for Subject Not Being Eligible [Pretreatment Event/Adverse Event, Major Protocol Deviation, Lost to Follow-Up, Voluntary Withdrawal, Study Termination, Did Not Meet Entrance Criteria, Healing Phase Failure, Other]

Rationale for Amendment

The category "Healing Phase Failure" has been added.

Page 17, Section 7.2.1.5 Disposition of Subjects

Existing Text

Study Drug (5 places)

Revised Text

Maintenance Phase Drug (5 places)

Rationale for Amendment

The Maintenance Phase has been added in the protocol.

Page 17, Section 7.2.1.5 Disposition of Subjects

Existing Text

(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.

Revised Text

(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 maintenance phase drug will be used as the denominator. When calculating percentages for the reasons for discontinuation of maintenance phase drug, the total number of subjects who prematurely discontinued the maintenance phase drug will be used as the denominator.

(2) Flow Chart of Subject Distribution
Flow chart will be provided.

Rationale for Amendment

The Maintenance Phase has been added in the protocol. The analysis for providing a flow chart has been added in this SAP.

Page 18, Section 7.2.2.1 Summary of Demographics and Other Baseline Characteristics

Existing Text

Analysis Set: Randomized Set

Revised Text

Analysis Set: Randomized Set, Full Analysis Set

Rationale for Amendment

The analysis for the full analysis set has been added.

Page 18, Section 7.2.2.1 Summary of Demographics and Other Baseline Characteristics

Existing Text

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White]

Revised Text

Race [American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple]

Rationale for Amendment

There have been subjects whose race were "Multiple".

Page 20, Section 7.2.3.1 Study Drug Exposure and Compliance

Existing Text

Analysis Set: Safety Analysis Set

Revised Text

Analysis Set: Safety Analysis Set, Full Analysis Set

Rationale for Amendment

The analysis for the full analysis set has been added.

Page 20, Section 7.2.3.1 Study Drug Exposure and Compliance

Existing Text

(1) Study Drug Exposure and Compliance

Revised Text

(1) Study Drug Exposure and Compliance in Maintenance Phase

Rationale for Amendment

The Maintenance Phase has been added in the protocol.

Page 21, Section 7.3.1 Primary Efficacy Endpoint

Existing Text

Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Treatment (3 places)

Revised Text

Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase (3 places)

Rationale for Amendment

The Maintenance Phase has been added in the protocol.

Page 21~22, Section 7.3.2 Secondary Efficacy Endpoint

Existing Text

Rate of Endoscopic Recurrence of Erosive Esophagitis During the 12-week Treatment (4 places)

Revised Text

Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase (4 places)

Rationale for Amendment

The Maintenance Phase has been added in the protocol and the description has been revised in the protocol.

Page 24, Section 7.3.3.3 Barrett's Mucosa

Existing Text

Present (3 cm or greater)

Revised Text

Present (3 cm or Greater)

Rationale for Amendment

The expression "greater" has been replaced with "Greater" because of clerical error.

Page 24~26, Section 7.3.4 Statistical/Analytical Issues

Existing Text

Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Treatment (7 places)
Rate of Endoscopic Recurrence of Erosive Esophagitis During the 12-week Treatment (7 places)

Revised Text

Rate of Endoscopic Recurrence of Erosive Esophagitis During the 24-week Maintenance Phase (7 places)
Rate of Endoscopic Recurrence of Erosive Esophagitis During the First 12 Weeks of Treatment in the Maintenance Phase (7 places)

Rationale for Amendment

The Maintenance Phase has been added in the protocol and the description has been revised in the protocol.

Page 25, Section 7.3.4.2 Handling of Dropouts or Missing Data

Added Text

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.

Rationale for Amendment

The handling rules of values below the lower or upper limit values for calculating the descriptive statistics have been added.

Page 27, Section 7.4.1.1 Overview of Treatment-Emergent Adverse Events

Added Text

5) Relationship to Study Drug of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation (number of events, number and percentage of subjects)

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

Rationale for Amendment

The analyses for these types of TEAEs have been added.

Page 28, Section 7.4.1.2 Displays of Treatment-Emergent Adverse Events

Existing Text

System Organ Class

Revised Text

SOC

Rationale for Amendment

The expression "System Organ Class" has been replaced with "SOC" for expression consistency.

Page 28~29, Section 7.4.1.2 Displays of Treatment-Emergent Adverse Events

Added Text

(8) Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term

(10) Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

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

(16) Drug-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

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 calculating the percentages for "Subjects With Any TEAEs", the number of subjects with at least one of these most frequent non-serious TEAEs will be used as the numerator.

Rationale for Amendment

The analyses for these types of TEAEs has been added.

Page 30, Section 7.4.2 Pretreatment Events and Adverse Events in the Healing Phase

Existing Text

7.4.2 Pretreatment Events

Revised Text

7.4.2 Pretreatment Events and Adverse Events in the Healing Phase

(omitted)

7.4.2.2 Displays of Adverse Events in the Healing Phase

Analysis Set:	All Subjects Who Entered the Healing Phase
Analysis Variables:	AE in the Healing Phase

Analytical Methods: The following summaries will be provided using frequency distribution.
AEs 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) Adverse Events in the Healing Phase by System Organ Class and Preferred Term
(2) Serious Adverse Events in the Healing Phase 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 AE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of AE within a PT will be counted only once in that PT.

Rationale for Amendment

The Healing Phase has been added in the protocol and the analyses for adverse events in the Healing Phase have been added in this SAP.

Page 31~33, Section 7.4.3 Laboratory and Other Safety Data, Section 7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

Existing Text

treatment phase (4 places)

Revised Text

maintenance phase (4 places)

Rationale for Amendment

The Maintenance Phase has been added in the protocol.

Page 31, Section 7.4.3.1 Laboratory Test Results

Existing Text

Visit: Baseline, Week 4, Week 12, Week 24

Revised Text

Visit: ALT, AST, Total Bilirubin, and Direct Bilirubin:
Baseline, Week 2, Week 4, Week 6, Week 8, Week 12, Week 24
Variables other than ALT, AST, Total Bilirubin, and Direct Bilirubin:
Baseline, Week 4, Week 12, Week 24

Rationale for Amendment

Visit 3 (Week 2), Visit 5 (Week 6) and Visit 6 (Week 8) has been added in the protocol for evaluating liver function tests (ALT, AST, total bilirubin, and direct bilirubin).

Page 32, Section 7.4.3.1 Laboratory Test Results (Serum Gastrin, Pepsinogen I/II)

Existing Text

Pepsinogen I (mcg/L), Pepsinogen II (mcg/L)

Revised Text

Pepsinogen I (µg/L), Pepsinogen II (µg/L)

Rationale for Amendment

The expression "mcg" has been replaced with "µg" for using more suitable expression.

Page 33, Section 7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety (Vital Signs)

Existing Text

Body Temperature (°C)

Revised Text

Body Temperature (C)

Rationale for Amendment

The expression "°C" has been replaced with "C" for using more suitable expression.

Page 33, Section 7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety (12-lead ECG)

Existing Text

12-lead ECG interpretations (3 places)

Revised Text

interpretations (3 places)

Rationale for Amendment

The expression "12-lead ECG" has been deleted for expression consistency with TFLs.

Page 34, Section 7.4.5 Subgroup Analysis for China

Existing Text

Analysis Population: Subjects in China

Analytical Methods: The same analyses as those in section 7.2 to 7.4 will be conducted for the subjects in China.

Revised Text

Analysis Population: Subjects in China
Subjects in Countries other than China

Analytical Methods: (1) The same analyses as those in section 7.2 to 7.4.4 will be conducted for the subjects in China.

(2) The same analyses as those in section 7.2 to 7.4.4 will be conducted for the subjects in countries other than China.

Rationale for Amendment

The analyses for the underlined part have been added.

Page 34, Section 7.4.6 Subgroup Analysis for Taiwan, Section 7.4.7 Subgroup Analysis for Safety Analysis Set Excluding Accidentally Unblinded Subjects

Added Text

7.4.6 Subgroup Analysis for Taiwan

Analysis Population: Subjects in Taiwan

Analytical Methods: (1) The same analyses as those in section 7.2 to 7.4.4 will be conducted for the subjects in Taiwan.

7.4.7 Subgroup Analysis for Safety Analysis Set Excluding Accidentally Unblinded Subjects

Analysis Population: Safety Analysis Set Excluding the Accidentally Unblinded Subjects
Safety Analysis Set Excluding the Accidentally Unblinded Subjects in China
Safety Analysis Set Excluding the Accidentally Unblinded Subjects in Countries other than China
Safety Analysis Set Excluding the Accidentally Unblinded Subjects in Taiwan

Analytical Methods: The same analyses as those in sections 7.4.1.1 and 7.4.1.2 ((1), (4) to (17)) will be conducted in the safety analysis set that excludes subjects who were accidentally unblinded due to IWRS system error.
The same analyses will be conducted for the subjects in China and countries other than China.
The same analyses will be conducted for the subjects in Taiwan.

Rationale for Amendment

The analyses for the underlined part have been added.

Page 34, Section 7.4.6 Significance Level and Confidence Coefficient

Existing Text

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

No statistical testing will be performed if there are less than 5 subjects.

Revised Text

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

Rationale for Amendment

The analysis plan has been changed that statistical testing will be performed even if there are less than 5 subjects.

Page 54, Section 8.0 REFERENCES

Added Text

Luo N, et. al. (2017) "Estimating an EQ-5D-5L Value Set for China", Value in Health, Volume 20(4): 662-669.

Rationale for Amendment

The above reference has been added.

Page 56, Section 9.1.1 Hematology, Serum Chemistry, Urinalysis, Vital Signs, and 12-lead ECG (except Upper MAV Criteria of QTcF Interval)

Existing Text

Body Temperature (°C)

Revised Text

Body Temperature (C)

Rationale for Amendment

The expression "°C" has been replaced with "C" for using more suitable expression.

8.0 REFERENCES

- DeLong ER, et. al. (1988) "Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach", Biometrics, Volume 44(3): 837-45.
- Divine G, et al. (2013) "A review of analysis and sample size calculation considerations for Wilcoxon tests", Anesth Analg, Volume 117(3): 699-710.
- Lehmann EL, et. al. (1975) "Nonparametrics: statistical methods based on ranks", Springer.
- Mason SJ, et. al. (2002) "Areas beneath the relative operating characteristics (ROC) and relative operating levels (ROL) curves: Statistical significance and interpretation", Quarterly Journal of the Royal Meteorological Society (128): 2145-2166.
- O'Brien RG, et. al. (2006) "Exploiting the link between the Wilcoxon-Mann-Whitney test and a simple odds statistic", Proceedings of the Thirty-First Annual SAS Users Group International Conference.
- Luo N, et. al. (2017) "Estimating an EQ-5D-5L Value Set for China", Value in Health, Volume 20(4): 662-669.

9.0 APPENDIX

9.1 CRITERIA FOR MARKEDLY ABNORMAL VALUES

9.1.1 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.

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

Serum Chemistry

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
ALT (U/L)	-	>3×ULN
ALP (U/L)	-	>3×ULN
AST (U/L)	-	>3×ULN
GGT (U/L)	-	>3×ULN
Total Bilirubin (µmol/L)	-	>34.2
Direct Bilirubin (µmol/L)	-	>2×ULN
CK (CPK) (U/L)	-	>5×ULN
Albumin (g/L)	<25	-
Total Protein (g/L)	<0.8×LLN	>1.2×ULN
Creatinine (µmol/L)	-	>177
BUN (mmol/L)	-	>10.7

Parameter	MAV Criteria	
	Lower Criteria	Upper Criteria
Uric Acid (mmol/L)	-	>0.773
Total Cholesterol (mmol/L)	-	>7.72
Triglycerides (mmol/L)	-	>2.5×ULN
Glucose (mmol/L)	<2.8	>19.4
Potassium (mmol/L)	<3.0	>6.0
Sodium (mmol/L)	<130	>150
Magnesium (mmol/L)	<0.5	>1.2
Calcium (mmol/L)	<1.75	>2.88
Inorganic Phosphorus (mmol/L)	<0.52	>2.00
Chloride (mmol/L)	<75	>126
Vitamin B_{12} (pmol/L)	<92	-

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

12-lead ECG

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

9.1.2 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.

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

9.2 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.

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

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
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 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	10-Jan-2019 00:39 UTC
	Biostatistics Approval	10-Jan-2019 02:19 UTC
	Clinical Science Approval	11-Jan-2019 07:14 UTC