Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-438 10 mg Once-daily in the Treatment of Non-Erosive Gastroesophageal Reflux Disease

NCT Number: NCT02954848

Statistical analysis plan Approve Date: 09-May-2018

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 information or company confidential information.

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

- Named persons or organizations associated with the study.
- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- 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.

If needed, certain appendices that contain a large volume of personally identifiable information or company confidential information may be removed in their entirety if it is considered that they do not add substantially to the interpretation of the data (eg, appendix of investigator's curriculum vitae).

Note; This document was translated into English as the language on original version was Japanese.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Vonoprazan-3001

A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Oral TAK-438 10 mg Once-daily in the Treatment of Non-Erosive Gastroesophageal Reflux Disease

A Double-Blind, Phase 3 Study of TAK-438 (10 mg) in the Treatment of Non-Erosive Gastroesophageal Reflux Disease

PHASE 3

Version**:** Amendment2

Date**:** 9 May 2018

Prepared by:

PPD

Based on:

Protocol Version: Initial

Protocol Date: 31 August 2016

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AIDS	acquired immune deficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BMI	body mass index
C_{max}	maximum observed plasma concentration
CRO	contract research organization
CYP	cytochrome P450
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GER	gastroesophageal reflux
GERD	gastroesophageal reflux disease
GGT	gamma glutamyl transferase
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
H. pylori	*Helicobacter pylori*
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
LA Classification	Los Angeles Classification
LDH	lactate dehydrogenase
LSBE	long-segment Barrett's esophagus
MAV	Markedly Abnormal Values
MedDRA	Medical Dictionary for Regulatory Activities
NERD	non-erosive gastroesophageal reflux disease
PGx	pharmacogenomics
PPI	proton pump inhibitor
PT	preferred term
QOL	quality of life
RNA	ribonucleic acid
SAE	serious adverse event
SOC	system organ class
SSBE	short-segment Barrett's esophagus
TAK-438	vonoprazan fumarate
TEAE	treatment emergent adverse event
ULN	upper limit of normal

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective of this study is to verify the superiority of TAK-438 to placebo in patients with NERD.

4.2 Secondary Objectives

The secondary objectives of this study are to assess the safety of TAK-438 in patients with NERD compared with that of placebo, to determine if the response after 2-week treatment with TAK-438 would allow prediction of the response after 4-week treatment with TAK-438.

4.3 Study Design

<Study Design>

This is a phase 3, double-blind, placebo-controlled, parallel-group, multicenter study to verify the superiority of TAK-438 to placebo in the efficacy in patients with NERD of the modified LA Classification Grade N or M. This study consists of 1-week single-blind run-in period and 4-week double-blind treatment period. After the informed consent is obtained, placebo will be administered for 1 week in single-blind fashion as a run-in period. Upon completion of the run-in period, subject eligibility for this study will be confirmed and only subjects who meet all of the the entry criteria will be randomized in a ratio of 1:1 to receive TAK-438 10 mg or placebo for the 4-week, double-blind, treatment period.

The target number of the subjects stratified by the Central Adjudication Committee (CAC) according to endoscopic findings with the modified LA Classification Grade N or M at the start of the run-in period (Visit 1) is at least 30% (143 subjects) of the total planned number of subjects for each grade. (Enrollment of patients with either Grade N or M is to end when the number of enrolled subjects with each Grade exceeds 332 subjects, or 70% of the total planned number of subjects.)

<Treatment/Assessment Duration>

This study consists of a 1-week, single-blind, run-in period and a 4-week, double-blind treatment period.

Run-in Period

The subjects will undergo endoscopic examination within 28 days after signing of the informed consent to select patients with the modified LA Classification Grade N or M. Then, the subjects will enter the run-in period and take 1 tablet of the study drug for the run-in period (TAK-438 placebo tablet) orally once daily after breakfast for 1 week.

The study drugs to be taken during the run-in period will be prescribed after all examinations and assessments scheduled at the start of the run-in period (Visit 1) are completed. The subjects will receive the first dose of the study drug for the run-in period before leaving the sites.

Treatment Period

After subject eligibility is confirmed, the eligible subjects will be randomized to receive TAK-438 10 mg or placebo. The start date of the study drug for the treatment period is defined as Day 1.

The subjects will enter the treatment period after randomization and take 1 tablet for the treatment period (TAK-438 10 mg tablet or TAK-438 placebo tablet) orally once daily after breakfast for 4 weeks.

The study drugs to be taken during the treatment period will be prescribed after all examinations and assessments scheduled at the start of the treatment period (Visit 2) are completed. The subjects will receive the first study drug for the treatment period before leaving the sites.

After 2 weeks and 4 weeks of treatment (Visit 3 and Visit 4), the subjects are required to visit the sites without taking the study drug. After 2 weeks of treatment (Visit 3), the subjects will receive the study drug after completing all examinations and assessments scheduled for the visit, but before leaving the sites.

<Others>

This study will be conducted at approximately 45 sites in Japan. The planned number of subjects to be randomized is 237 per group, or 474 in total.

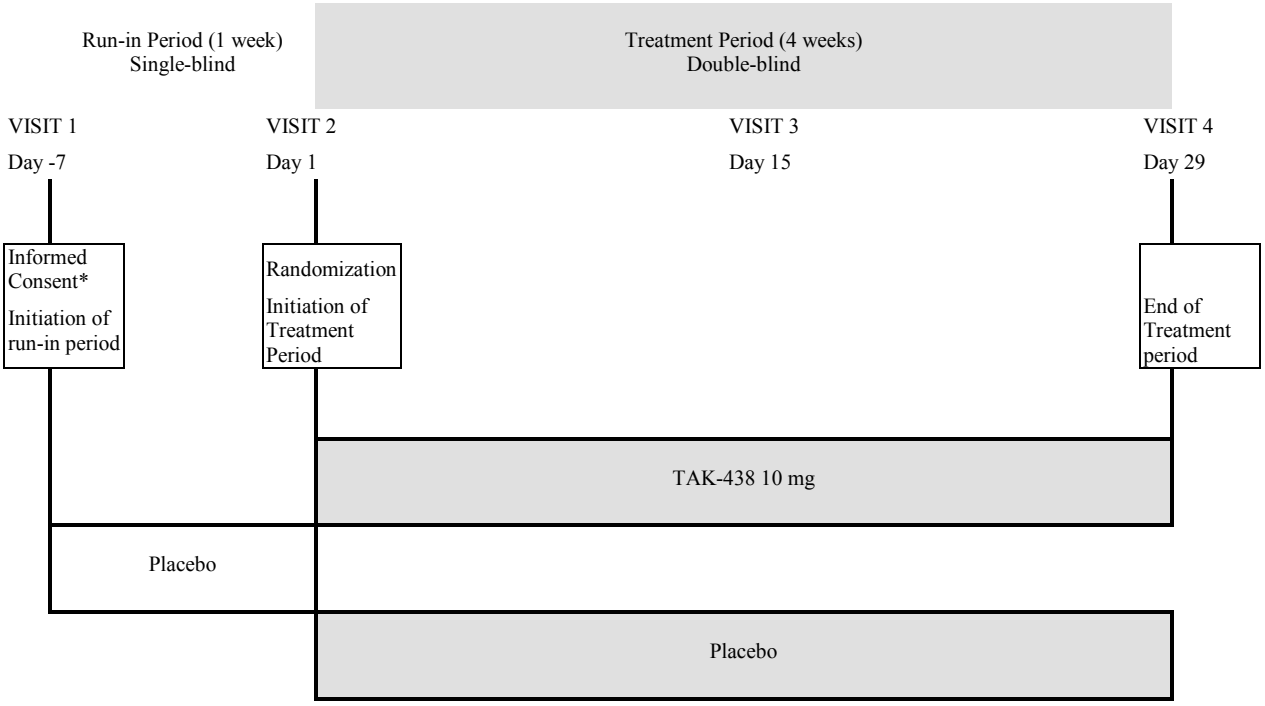
The subjects are required to visit the sites 4 times in total: at the start of the run-in period (Visit 1), at the start of the treatment period (Visit 2), after 2 weeks of treatment (Visit 3), and after 4 weeks of treatment (Visit 4).

Endoscopic findings will be assessed by the CAC, and the subject eligibility will be confirmed based on the decision by the investigator.

<Schematic of Study Design>

A schematic of the study design is included as Figure 4-1. A schedule of assessments is listed in Table 4-1.

Figure 4-1 Schematic of Study Design



*Informed consent must be obtained within 28 days prior to the start of the run-in period (Visit 1).

Table 4-1 Schedule of Study Procedures

Period	**Run-in Period**	**Treatment Period**			
Timing	Start of run-in period	Start of treatment period	Week 2	Week 4	Early termination
Day	Day –7	Day 1*	Day 15	Day 29	–
Visit Windows (Days)	–10 to –7	1	12 to 18	26 to 32	Within 7 days after last dose
Visit Number	**1**	**2**	**3**	**4**	–
Informed consent (a)	X				
Primary inclusion/exclusion criteria	X				
Secondary inclusion/exclusion criteria		X			
Demographics and medical history	X				
Medication history	X				
History of taking acid suppressants	X				
Physical examination	X	X	X	X	X
Vital signs	X	X	X	X	X
Weight and height	X				
Concomitant medications	←	—	—	—	→
Concurrent medical conditions	X				
Clinical laboratory tests (b)	X	X	X	X	X
Anti-*H. pylori* antibody	X (e)				
Serum gastrin pepsinogen I/II levels		X	X	X	X
PGx sample (c)			X (f)		X (f)
Pregnancy test (hCG) (d)	X	X	X	X	X
ECG	X (g)			X	X
Patient diary	←	—	—	—	→
QOL survey	X	X	X	X	X
Endoscopy	X (g)				
Randomization		X			
Start of study drug for the run-in period	X (h)				
Start of study drug for the treatment period		X (i)			
Review treatment compliance		X	X	X	X
AE assessment	←	—	—	—	→

*The start date of the study drug for the treatment period is defined as Day 1.
(a) Informed consent to participate in the study will be obtained from the subjects within 28 days before the start of the run-in Period (Visit 1).
(b) Hematology, chemistry, and urinalysis tests.
(c) To be taken from subjects who gave informed consent to participate in PGx research.
(d) To be performed only in female subjects of childbearing potential.
(e) Anti-*H. pylori* antibody measurements need to be made between Day -10 and Day 1.
(f) To be taken after 2 weeks of treatment as a rule, with the visit window for this sampling being from the start of the study drug in the treatment period to the end of the treatment period/the early termination of the study. In subjects who discontinue the study drug, PGx samples will be collected only in those whose samples remain to be collected at that time point.
(g) Any results available from ECG and endoscopy performed in a routine clinical setting within 7 days prior to the start of the run-in period (before signing of informed consent) may obviate the need for ECG and endoscopy scheduled at the start of the run-in period (Visit 1).
(h) The subject is to take the study drug for the run-in period before going home after completion of all assessments at the start of the run-in period (Visit 1).
(i) The subject is to take the study drug for the treatment period before going home after completion of all assessments at the start of the treatment period (Visit 2).

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

Heartburn during the treatment period. The following variables of the primary endpoint in the TAK-438 10 mg group are compared with those in the placebo group:

- Primary variable: proportion of days without symptoms.
- Secondary variable: cumulative rate of improvement in symptoms.
- Additional variable: severity of symptoms.

5.2 Secondary Endpoints

The primary endpoint is stratified as follows:

- The primary endpoint in subject subgroups stratified by the response (improved or not improved) at Week 2.
- The primary endpoint in subject subgroups stratified by endoscopic finding (Grade N or M).
- The primary endpoint in subject subgroups stratified by the combination of endoscopic finding (Grade N or M) and response (improved or not improved) at Week 2.
- The primary endpoint in subject subgroups stratified by the response (improved or not improved) to acid suppressants (proton pump inhibitors [PPIs], histamine H_2-receptor antagonists [H_2RAs], or other agents [anticholinergics or anti-gastrin drugs]) in subjects who had a medication history of any of these drugs.

5.3 Additional Endpoints

<Efficacy>

Quality of life (QOL)

Regurgitation during the treatment period

<Safety>

Treatment emergent adverse events (TEAEs), clinical laboratory test values, electrocardiogram (ECG) findings, vital signs, serum gastrin and pepsinogen I/II levels

In this study, samples for pharmacogenomics (PGx) will be collected and stored for exploratory investigation of markers enabling the prediction of drug response.

In this study using TAK-438, or in a set of clinical trials, if variability is seen in responsiveness to study drug and it is suspected to attribute its cause to subject's gene polymorphism, PGx analyses should reveal the following as required:

- Gene polymorphism and safety and/or tolerability of study drug.

Gene polymorphism and efficacy of study drug.

6.0 DETERMINATION OF SAMPLE SIZE

The planned sample size is 474 subjects in total, 237 subjects for each group.

The number of evaluable subjects required for the primary endpoint will be 460 in total, 230 for each group.

Justification of the planned sample size

In a phase 3 double-blind study of lansoprazole (AG-1749/CCT-206) evaluating the proportion of days without heartburn in those given AG-1749 15 mg and placebo, the mean proportion of days without heartburn and their standard deviations (SD) were shown to be 51.03%±28.388% in the placebo group versus 63.21%±32.200% in the AG-1749 15 mg group. Additionally, in the postmarketing study for lansoprazole (AG-1749/CCT-971), the mean proportion of days without heartburn and their SD were shown to be 46.83%±32.350% in the placebo group and 55.36%±34.545% in the AG-1749 15 mg group. In a phase 3 double-blind study of TAK-438 (TAK-438/CCT-201), the mean proportion of days without heartburn and their SD were shown to be 22.63%±28.202% in the placebo group and 28.89%±34.853% in the TAK-438 10 mg group.

Assuming that, based on these results and assessment method of heartburn in this study, the difference between the TAK-438 10 mg group and the placebo group will be 10% with a common SD of 32%, 230 subjects per treatment group will be required to ensure 90% power of the Wilcoxon rank sum test with a significance level of 5%. Thus, it is appropriate that 237 subjects will be required for each treatment group, taking into account some dropouts, 3%, after randomization.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using CCI [redacted]

A statistical test for the primary endpoint will be reported as 1-sided and will be assessed at α=0.025 significance level and all confidence intervals will be reported as 2-sided unless otherwise stated. P-values will be rounded to 4 decimal places prior to assessment of statistical significance.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. Confidence intervals for continuous variables will be calculated based on t-statistics and ones for categorical variables will be based on Wald confidence intervals without using any model, unless otherwise stated.

7.1.1 Study Definitions

- QTcF interval (msec): QT interval (msec) / (RR interval (sec))$^{0.33}$ (rounded to the nearest whole number)
- Duration of Exposure to Study Drug in Run-in Period: Date of last dose of study drug in run-in period - date of first dose of study drug in run-in period + 1
- Study Drug Compliance in Run-in Period: Number of days with "Compliance of Study Drug" in diary of "Yes" during run-in period/duration of exposure to study drug in run-in period* 100 (rounded to 1 decimal places)
- Duration of exposure to double-blind study drug (days) : Date of last dose of double-blind study drug - date of first dose of double-blind study drug + 1
- Double-blind study drug compliance (%) : Number of days with "Compliance of Study Drug" in diary of "Yes" during treatment period/duration of exposure to double-blind study drug * 100 (rounded to 1 decimal places)

- Assessment target period in run-in period for proportion of days without symptoms and severity of symptoms: from latest day of first dosing date in run-in period to Day -1
- Assessment target period in treatment period for proportion of days without symptoms and severity of symptoms: from Day1 to last dosing date in treatment period
- The severity in diary will be conversed as follows for analysis of severity of symptoms. No symptom = 0, No hindrance to daily activities = 1, Mild = 2, Moderate = 3, Severe = 4
- Proportion of days without symptoms: Number of days with severity of "No symptom" or "No hindrance to daily activities"/ Number of days without severity of "Not done" * 100 (rounded to 1 decimal places)
  - In the case that the denominator is missing or 0, it will be regarded as missing.
- Severity of symptoms: (sum total of severity in diary from Day 1 to day of last dose)/ Number of days without severity of "Not done" (rounded to 2 decimal places)
  - In the case that the denominator is missing or 0, it will be regarded as missing.
- Response to acid suppressants will be the scale as follows:
  - scale of response to PPIs, for subjects who has taken PPIs within 180 days prior to informed consent.
  - scale of response to H2RAs, for subjects who has taken H2RAs within 180 days prior to informed consent, but not PPIs.
  - scale of response to other agents (anticholinergics or anti-gastrin drugs), for subjects who has taken only other agents (anticholinergics or anti-gastrin drugs) within 180 days prior to informed consent.
- As for response to acid suppressants, if it is "Heartburn has been resolved" or "Heartburn has not been resolved but relieved", we will regard it as "Improved". if it is " Heartburn has remained unchanged"or "Heartburn has been worsened", we will regard it as "Not Improved"
- The severity in QOL except "Physical Component Summary" and "Mental Component Summary" will be conversed based on Table 7-1 and Table 7-2

- The severity of "Physical Component Summary" and "Mental Component Summary" will be conversed based on following formula.
  score = total sum of {(score for each subscale) x (coefficient for each subscale)} + intercept
  - Coefficient for each subscale and intercept is described in Table 7-3.
  - If any score in subscale is missing, score for "Physical Component Summary" and "Mental Component Summary is also missing.

Table 7-1 Scoring for "General Health", "Physical Functioning", "Role - Physical", and " Bodily Pain"

Subscale	Severity	Score
General Health	Very Poor	26.89
	Poor	34.38
	Fair	40.40
	Good	50.27
	Very Good	58.54
	Excellent	63.38
Physical Functioning	Could not do physical activities	16.69
	Quite a lot	27.59
	Somewhat	41.45
	Very little	47.77
	Not at all	53.54
Role - Physical	Could not do daily work	21.80
	Quite a lot	27.91
	Some	40.65
	A little bit	47.42
	Not at all	54.09
Bodily Pain	Very Severe	21.68
	Severe	31.59
	Moderate	38.21
	Mild	46.10
	Very mild	52.46
	None	60.35

Table 7-2 Scoring for "Vitality", "Social Functioning", "Mental Health", and "Role - Emotional"

Subscale	Severity	Score
Vitality	None	28.68
	A little	38.51
	Some	44.48
	Quite a lot	53.74
	Very much	60.01
Social Functioning	Could not do social activities	26.00
	Quite a lot	29.15
	Somewhat	37.65
	Very little	45.60
	Not at all	55.14
Mental Health	Extremely	27.59
	Quite a lot	36.30
	Moderately	44.94
	Slightly	50.72
	Not at all	56.93
Role - Emotional	Could not do daily activities	19.98
	Quite a lot	31.42
	Somewhat	42.24
	Very little	48.04
	Not at all	54.19

Table 7-3 Coefficient for each subscale and intercept

Subscale and intercept	Physical Component Summary	Mental Component Summary
General Health	0.23024	-0.0202
Physical Functioning	0.40672	-0.19972
Role - Physical	0.38317	-0.16579
Bodily Pain	0.33295	-0.15992
Vitality	0.07537	0.16737
Social Functioning	-0.01275	0.27264
Mental Health	-0.30469	0.57583
Role - Emotional	-0.14083	0.42927
intercept	0.67371	4.34744

7.1.2 Definition of Study Days

When calculating Study Day relative to a reference date (ie, date of first dose of double-blind study drug [Day 1]) , if the date of the observation is on the same date or after the reference date, it will be calculated as: date of observation - reference date + 1; otherwise, it will be calculated as: date of observation - reference date. Hence, reference day is always Day 1 and there is no Day 0.

When calculating Follow-up Day relative to a reference date (ie, date of last dose of double-blind study drug [Follow-up Day 0]) , it will be calculated as: date of observation - reference date. Hence, reference day is always Follow-up Day 0.

7.1.3 Definition of Study Visit Windows

All evaluable data (ie, non-missing) will be handled according to the following rules.

For each visit, observation 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.

Clinical laboratory tests, Vital signs and, Serum gastrin pepsinogen I/II levels

Visit	Scheduled Study Day	Time Interval (days)

	(days)	Study Day	Follow-up Day
Baseline	Study Day: 1	-10 - 1	
Week 2	Study Day: 15	2 - 22	< 15
Week 4	Study Day: 29	23 - 32	< 15

ECG

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-17 - 1	
Week 4	Study Day: 29	2 - 32	< 15

QOL survey

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Start of run-in period	Study Day: -1	-10 - -1	
Start of treatment period	Study Day: 1	1	
Week 2	Study Day: 15	2 - 22	< 15
Week 4	Study Day: 29	23 - 32	< 15

Weight and height and Anti-*H. pylori* antibody

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-10 - 1	

Endoscopy

Visit	Scheduled Study Day (days)	Time Interval (days)	
		Study Day	Follow-up Day
Baseline	Study Day: 1	-17 - 1	

7.1.4 Methods for Handling Missing Data

All available efficacy and safety data will be included in data listing and tabulations. No imputation of values for missing data will be performed unless otherwise specified.

- For clinical laboratory tests, values less than the lower limit of quantification will be treated as zero when calculating the descriptive statistics.

If the year is present but the month is missing, then the month will be treated as January for the calculation.

7.2 Analysis Sets

The FAS, the main analysis set used for primary efficacy analysis, will be defined as all subjects who were randomized and received at least one dose of the study drug. The safety analysis set will be defined as all subjects who received at least one dose of double-blind study drug.

The per-protocol set will consist of all FAS subjects whose primary endpoint is evaluable and who had no major protocol deviation listed below:

- Subjects who did not meet inclusion criteria #3, #4, #5, #8, #9 or, #10
- Subjects who met exclusion criteria #6, #7, #8, #9, #10, #11, #12,#13, #14 or, #17
- Subjects who have violated the rules specified in section 7.3
- Subjects with double-blind study drug compliance of less than 75%
- Subjects whose emergency key was unblinded for reasons other than SUSAR
- Subjects whose duration in run-in period was 6 days or less
- Subjects whose endoscopy performance date was not satisfied with any following condition:
  - Endoscopy performed from Day -10 to -7
  - Endoscopy performed in a routine clinical setting within 7 days prior to the start of the run-in period (before signing of informed consent)

7.3 Disposition of Subjects

7.3.1 Study Information

Analysis Set: All Subjects Who Signed the Informed Consent Form

Analysis

Variable(s) : 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
Method(s) : (1) Study Information
Study information shown in the analysis variables section will be provided.

7.3.2 Screen Failures

Analysis Set: All Subjects Who Were Not Randomized
Analysis
Variable(s) : Age (years) [Min<= - <65, 65<= - <75, 75<= - <=Max]
Gender [Male, Female]
Analytical
Method(s) : (1) Screen Failures
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

7.3.3 Subject Eligibility

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis
Variable(s) : Eligibility status [Eligible for Randomization, Not Eligible for Randomization]
Primary Reason for Subject Not Being Eligible [Adverse Event, Death, Lost to Follow-up, Pregnancy, Protocol Deviation, Screen Failure, Study Terminated by Sponsor, Withdrawal by Subject, Other]
Analytical
Method(s) : (1) Eligibility for Randomization
Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

7.3.4 Number of Subjects Randomized by Site and Treatment Group

Analysis Set:	Randomized Set	
Analysis Variable(s) :	Randomization status	[Randomized]
Stratum:	Site	[Site numbers will be used as categories]
Analytical Method(s) :	(1) Number of Subjects Randomized by Site and Treatment Group Frequency distribution will be provided for each stratum by treatment group and overall.	

7.3.5 Disposition of Subjects

Analysis Set:	Randomized Set	
Analysis Variable(s) :	Double-blind study drug administration status	[Randomized but Not Treated]
	Reason for Not Being Treated	[Adverse Event, Death, Lack of Efficacy, Lost to Follow-up, Pregnancy, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Lack of Treatment Compliance, Other]
	Double-Blind Study Drug Completion Status	[Completed Study Drug, Prematurely Discontinued Study Drug]
	Reason for Discontinuation of Study Drug	[Adverse Event, Death, Lack of Efficacy, Lost to Follow-up, Pregnancy, Protocol Deviation, Study Terminated by Sponsor, Withdrawal by Subject, Lack of Treatment Compliance, Other]
Analytical Method(s) :	(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, the total number of subjects who prematurely discontinued will be used as the denominator.

7.3.6 Protocol Deviations

Analysis Set: Randomized Set

Analysis Variable(s): Protocol Deviation [Entry Criteria, Concomitant Medication, Procedure Not Performed Per Protocol, Study Medication, Withdrawal Criteria, Major GCP Violations]

Analytical Method(s): (1) Protocol Deviations

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

7.3.7 Analysis Sets

Analysis Set: Randomized Set

Analysis Variable(s):

Handling of Subjects and Subject Data	[Categories are based on the specifications in Handling Rules for Analysis Data]
Analysis Sets	
Full Analysis Set	[Included]
Per Protocol Set	[Included]
Safety Analysis Set	[Included]

Analytical

Method(s) : (1) Subjects Excluded from Analysis Sets
(2) Analysis Sets
Frequency distributions will be provided by treatment group for (1), and by treatment group and overall for (2). For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

7.4 Demographic and Other Baseline Characteristics

Analysis Set: Randomized Set

Analysis

Variable(s) :		
	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Gender	[Male, Female]
	Height (cm)	[Min<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max]
	Weight (kg) at Baseline	[Min<= - <50, 50<= - <60, 60<= - <70, 70<= - <80, 80<= - <=Max]
	BMI (kg/m^2) at 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 Every day, Drink a Couple of Days Per Week, Drink a Couple of Days Per Month, Never Drink]
	Consumption of Caffeine	[Yes, No]
	Endoscopic Finding by PI	[Grade N, Grade M]
	Endoscopic Finding by CAC	[Grade N, Grade M, Grade A, Grade B, Grade C, Grade D]
	Barrett Mucosa	[Yes (Less than 3 cm), No, Unknown]

Esophageal Hiatal Hernia	[Yes (2 cm or More), Yes (Less than 2 cm), No, Unknown]
Factors Which Cause Heartburn and Improvement in Living Habits Physical Factors	
Kyphosis	[Yes, No]
Evident Obesity	[Yes, No]
Movement	
Forward Flexion	[Yes, No]
Lying in Bed	[Yes, No]
Other (Movement)	[Yes, No]
Diet	
Fatty Foods (Fried Foods, Stodge, etc.)	[Yes, No]
Carbohydrates (Grains, Potatoes, etc.)	[Yes, No]
Sweet Foods (Chocolate, etc.)	[Yes, No]
Acidic Foods (Citrus Fruits, Carbonated Beverages, etc.)	[Yes, No]
Spices (Pepper, Curry, etc.)	[Yes, No]
Other (Diet)	[Yes, No]
Habits	
Smoking	[Yes, No]
Caffeine Ingestion	[Yes, No]
Drinking Alcohol	[Yes, No]
The above factors are not applicable, or other factors can not be specified	[Yes, No]
Improving Lifestyle	[Yes, No]
Severity of Symptoms at Baseline	
Heartburn	[0.00, 0.00< - <=1.00, 1.00< - <=2.00, 2.00< - <=3.00, 3.00< - <=4.00]
Regurgitation	[0.00, 0.00< - <=1.00, 1.00< - <=2.00, 2.00< - <=3.00, 3.00< - <=4.00]

Has subject taken PPIs within 180 days prior to informed consent?	[Yes, No]
Has subject taken H2RAs within 180 days prior to informed consent?	[Yes, No]
Has subject taken other agents (anticholinergics or anti-gastrin drugs) within 180 days prior to informed consent?	[Yes, No]
Response to Acid Suppressants	[Heartburn has been resolved, Heartburn has not been resolved but relieved, Heartburn has remained unchanged, Heartburn has been worsened] [Improved, Not Improved]
History of *H.pylori* Eradication	[Within the last year, More than one year before, No]
Serological Determination for *H.pylori*	[Positive, Negative]
Gastrin (pg/mL) at Baseline	[Min<= - <200, 200<= - <=Max]
Pepsinogen I/II at Baseline	[Min<= - <=2.0, 2.0< - <=3.0, 3.0< - <=Max]

Analytical Method(s) : (1) Summary of Demographics and Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.5 Medical History and Concurrent Medical Conditions

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medical History
Concurrent Medical Conditions

Analytical Method(s) : (1) Medical History by System Organ Class and Preferred Term
(2) Concurrent Medical Conditions by System Organ Class and Preferred Term

Frequency distributions will be provided for each treatment group. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.
A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC.
A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

7.6 Medication History and Concomitant Medications

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Medication History
Concomitant Medications

Analytical Method(s) :
(1) Medication History by Preferred Medication Name
(2) Concomitant Medications That Started Prior to and Were Ongoing at Baseline as well as Those That Started After Baseline by Preferred Medication Name

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

7.7 Study Drug Exposure and Compliance

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Duration of Exposure to Study Drug in Run-in Period (days) [1<= - <=7, 8<= - <=Max]
Study Drug Compliance in Run-in [Min<= - <50.0, 50.0<= - <70.0,

Period (%)	70.0<= - <90.0, 90.0<= - <=Max]
Duration of Exposure to Double-Blind Study Drug (days)	[1<= - <=14, 15<= - <=28, 29<= - <=Max]
Double-Blind Study Drug Compliance (%)	[Min<= - <50.0, 50.0<= - <70.0, 70.0<= - <90.0, 90.0<= - <=Max]

Analytical Method(s) : (1) Study Drug Exposure and Compliance
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided by treatment group and overall.

7.8 Efficacy Analysis

7.8.1 Primary Efficacy Endpoint(s)

7.8.1.1 Primary Analysis

Analysis Set: Full Analysis Set

Analysis Variable(s) : Proportion of Days without Symptoms of Heartburn
Cumulative Rate of Improvement in Symptoms of Heartburn
Severity of Symptoms of Heartburn

Analytical Method(s) : For proportion of days without symptoms and severity of symptoms, descriptive statistics will be used by treatment group. The point estimate of the median difference between the treatment groups will be calculated using the Hodges-Lehmann estimation. For comparisons of the treatment groups, the Wilcoxon rank sum test will be used.
For cumulative rate of improvement in symptoms, the cumulative improvement rate of symptoms during the treatment period will be calculated for each treatment group using the Kaplan-Meier method. The symptom improvement, event date and censoring date are defined below. The cumulative improvement rate in TAK-438 10 mg group will be compared to that of the placebo group using a log-rank test.
Symptom improvement: symptoms experienced on less than 2 days of

the last 7 days.

Event date: the first day of confirmed symptom improvement that continued until the last day of study treatment.

Censoring date: 6 days prior to the last day with documentation of whether the subject experienced symptoms (applicable only to subjects without symptom improvement).

7.8.1.2 Secondary Analysis

Analysis Set: Per Protocol Set

Analysis Variable(s): Proportion of Days without Symptoms of Heartburn
Cumulative Rate of Improvement in Symptoms of Heartburn
Severity of Symptoms of Heartburn

Analytical Method(s): An analysis similar to the above "Primary analysis" will be performed using the PPS to assess the robustness of the results.

7.8.1.3 Adjustments for Covariates

Analysis Set: Full Analysis Set

Analysis Variable(s): Proportion of Days without Symptoms of Heartburn
Cumulative Rate of Improvement in Symptoms of Heartburn
Severity of Symptoms of Heartburn

Covariate(s): Endoscopic Finding [Grade N, Grade M]

Analytical Method(s): For proportion of days without symptoms and severity of symptoms and severity of symptoms of heartburn, stratified wilcoxon test will applied using endoscopic finding as covariate.
For cumulative rate of improvement in symptoms of heartburn, stratified logrank test will applied using endoscopic finding as covariate.

7.8.1.4 Examination of Subgroups

Analysis Set: Full Analysis Set

Analysis

Variable(s):	Proportion of Days without Symptoms of Heartburn	
	Cumulative Rate of Improvement in Symptoms of Heartburn	
	Severity of Symptoms of Heartburn	
Subgroup(s):	Age (years)	[Min<= - <65, 65<= - <75, 75<= - <=Max]
	Weight (kg) at Baseline	[Min<= - <50, 50<= - <60, 60<= - <70, 70<= - <80, 80<= - <=Max]
	BMI (kg/m^2) at Baseline	[Min<= - <18.5, 18.5<= - <25.0, 25.0<= - <=Max]
	Severity of Symptoms of Heartburn at Baseline	[0.00, 0.00< - <=1.00, 1.00< - <=2.00, 2.00< - <=3.00, 3.00< - <=4.00]
	Esophageal Hiatal Hernia	[Yes (2 cm or More), Yes (Less than 2 cm), No, Unknown]
Analytical Method(s):	For proportion of days without symptoms and severity of symptoms and severity of symptoms of heartburn, descriptive statistics will be provided for above each subgroup by treatment group. For cumulative rate of improvement in symptoms of heartburn, the cumulative improvement rate of symptoms during the treatment period will be calculated for above each subgroup by treatment group using the Kaplan-Meier method .	

7.8.2 Secondary Efficacy Endpoint(s)

Analysis Set:	Full Analysis Set	
Analysis Variable(s) :	Proportion of Days without Symptoms of Heartburn	
	Cumulative Rate of Improvement in Symptoms of Heartburn	
	Severity of Symptoms of Heartburn	
Stratification factor (s):	Response at Week 2 (Criteria 1)	[improved, not improved]
	Response at Week 2 (Criteria 2)	[improved, not improved]

Endoscopic Finding	[Grade N, Grade M]
Endoscopic Finding and Response at Week 2 (Criteria 1)	[Grade N and Improved, Grade N and Not Improved, Grade M and Improved, Grade M and Not Improved]
Endoscopic Finding and Response at Week 2 (Criteria 2)	[Grade N and Improved, Grade N and Not Improved, Grade M and Improved, Grade M and Not Improved]
Response to Acid Suppressants	[Improved, Not Improved]

Analytical Method(s) : For secondary endpoints will be performed similarly Section 7.8.1 stratified by factors except "Response to acid suppressants" on the FAS. In addition to that, same analysis will be performed stratified by factors "Response to acid suppressants" in subjects who had a medication history of any of these drugs.
When subjects are stratified by the response (improved or not improved) at Week 2, analyses will be performed on subjects stratified for both treatment groups and for the TAK-438 10 mg group only.

7.8.3 Additional Efficacy Endpoint(s)

7.8.3.1 QOL

Analysis Set: Full Analysis Set

Analysis Variable(s) : General Health
Physical Functioning
Role - Physical
Bodily Pain
Vitality
Social Functioning
Mental Health
Role - Emotional

	Physical Component Summary	
	Mental Component Summary	
Visit:	Start of run-in period, Start of treatment period, Week 2, 4	
Analytical Method(s) :	For endpoint, summary statistics at each visit will be provided by treatment group. Additionally, point estimate and its 2-sided 95% CI of the difference between each TAK-438 10 mg group and the placebo group at each visit.	

7.8.3.2 Regurgitation during the treatment period

Analysis Set:	Full Analysis Set	
Analysis Variable(s) :	Proportion of Days without Symptoms of Regurgitation Cumulative Rate of Improvement in Symptoms of Regurgitation Severity of Symptoms of Regurgitation	
Subgroup(s):	Response at Week 2 (Criteria 1)	[improved, not improved]
	Response at Week 2 (Criteria 2)	[improved, not improved]
	Endoscopic Finding	[Grade N, Grade M]
	Endoscopic Finding and Response at Week 2 (Criteria 1)	[Grade N and Improved, Grade N and Not Improved, Grade M and Improved, Grade M and Not Improved]
	Endoscopic Finding and Response at Week 2 (Criteria 2)	[Grade N and Improved, Grade N and Not Improved, Grade M and Improved, Grade M and Not Improved]
	Response to Acid Suppressants	[improved, not improved]
Analytical Method(s) :	The same analysis as described in Sections 7.8.1.1 and 7.8.2 will be performed.	

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable

7.9.1 Pharmacokinetic Analysis

Not applicable

7.9.2 Pharmacodynamic Analysis

Not applicable

7.10 Other Outcomes

Not applicable

7.11 Safety Analysis

7.11.1 Adverse Events

7.11.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set: Safety Analysis Set

Analysis Variable(s) : TEAE

Categories: Relationship to Study Drug [Related, Not Related]
Intensity [Mild, Moderate, Severe]

Analytical Method(s) : 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) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of

subjects)

7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 2) and 6)
  A subject with occurrences of TEAE in both categories (i.e., 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) , and 6)
  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

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

7.11.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	TEAE	
Categories:	Intensity	[Mild, Moderate, Severe]
	Time of Onset (day)	[1<= - <=14, 15<= - <=28, 29<= - =Max]
Analytical Method(s) :	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 System Organ Class 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) Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term
(9) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(10) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time
(11) Most Frequent Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(12) 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.

<u>Number of subjects</u>

- Summary tables other than (5), (6) and, (10)
  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 (10)
  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 (i.e., 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 (11)
  Most frequent TEAEs refer to PTs whose percentages are at least 2% in any one of the treatment groups.
- Summary table for (12)
  Most frequent Non-Serious TEAEs refer to PTs whose percentages are at least 5.0% in any one of the treatment groups. If no Non-Serious TEAEs exceed a frequency of 5.0%, the frequency cutoff of 2.0% will be used instead. Percentages will be based on the number of subjects in the safety analysis set.

7.11.1.3 Displays of Pretreatment Events

Analysis Set: All Subjects Who Signed the Informed Consent Form
Analysis Variable(s) : PTE
Analytical Method(s) : 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.

7.11.1.4 Displays of Run-in Adverse Events

Analysis Set: All Subjects Who Received Run-in Study Drug

Analysis Variable(s) : Run-in AE

Analytical Method(s) : The following summaries will be provided using frequency distribution. Run-in 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) Run-in Adverse Events by System Organ Class and Preferred Term
(2) Drug-Related Run-in Adverse Events by System Organ Class and Preferred Term
(3) Serious Run-in Adverse 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 run-in AE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of run-in AE within a PT will be counted only once in that PT.

7.11.2 Clinical Laboratory Evaluations

7.11.2.1 Hematology and Serum Chemistry

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Hematology

RBC	WBC	Hemoglobin
Hematocrit	Platelets	

White blood cell differentials (Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes)

Serum Chemistry

ALT	ALP	AST
GGT	Bilirubin (Total Bilirubin)	Direct Bilirubin
LDH	Creatine Kinase	Albumin
Protein (Total Protein)	Creatinine	Blood Urea Nitrogen
Uric acid	Total Cholesterol	Triglycerides
Glucose	Potassium	Sodium
Magnesium	Calcium	Inorganic Phosphorus
Chloride		

Visit: Baseline, Week 2, 4

Analytical Method(s) : For each variable, summaries (1) to (3) will be provided by treatment group.

For applicable variables, summaries (4) and (5) will be provided by treatment group.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit

Descriptive statistics for observed values for each visit and changes from baseline will be provided.

(2) Case Plots

Plots over time for each subject will be presented.

(3) 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.

(4) Number and Percentage of Subjects with Markedly Abnormal Values(MAV) of Laboratory Parameters
Overall frequency distributions of MAV during treatment period 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 2.

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

7.11.2.2 Urinalysis

Analysis Set: Safety Analysis Set

Analysis Variable(s) :
- Protein [-, +-, 1+, 2+, 3+, 4+]
- Glucose [-, 1+, 2+, 3+, 4+, 5+]

Visit: Baseline, Week 2, 4

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

(1) Number of Subjects in Categories 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.

(2) Summary of Shifts of Urine Laboratory Test Results

Shift tables showing the number of subjects in each category at baseline and each post-baseline visit will be provided.
For each urine laboratory test, the laboratory values will be classified as "Normal" or " Abnormal " relative to the normal reference range provided by the central laboratory. The shift tables will be based on these classifications.

7.11.3 Vital Signs

7.11.3.1 Vital Signs

Analysis Set: Safety Analysis Set

Analysis Variable(s) : Systolic Blood Pressure
Diastolic Blood Pressure
Pulse Rate
Body Temperature

Visit: Baseline, Week 2, 4

Analytical Method(s) : For each variable, summaries (1) and (2) will be provided by treatment group.
For applicable variables, summary (3) will be provided by treatment group.

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

(2) Case Plots
Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of Vital Signs Parameters
Overall frequency distributions of MAV during treatment period 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 2.

7.11.4 12-Lead ECGs

Analysis Set:	Safety Analysis Set	
Analysis Variable(s) :	Heart Rate	
	RR Interval	
	PR Interval	
	QRS Interval	
	QT Interval	
	QTcF Interval	
	12-Lead ECG Interpretation	[Within Normal Limits, Abnormal but not Clinically Significant, Abnormal and Clinically Significant]
Visit:	Baseline, Week 4	

Analytical Method(s) : For each variable other than 12-lead ECG interpretations, summaries (1) and (2) will be provided by treatment group.
For applicable variables, summary (3) will be provided by treatment group.
For 12-lead ECG interpretation, summary (4) 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 will be provided for each visit.

(2) Case Plots
Plots over time for each subject will be presented.

(3) Number and Percentage of Subjects with Markedly Abnormal Values of ECG Parameters
Overall frequency distributions of MAV during treatment period 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 2.

(4) Summary of Shift of 12-lead ECG Interpretation
Shift table showing the number of subjects in each category at baseline and each post-baseline visit will be provided.

7.11.5 Other Observations Related to Safety

7.11.5.1 Serum gastrin and pepsinogen I/II levels

Analysis Set: Safety Analysis Set

Analysis Variable(s): Serum Gastrin
Pepsinogen I
Pepsinogen II
Pepsinogen I/II Ratio

Visit: Baseline, Week 2, 4

Analytical Method(s): For each variable, summaries (1) will be provided by treatment group.

(1) Summary of Serum gastrin and pepsinogen I/II levels and Change from Baseline by Visit
Descriptive statistics for observed values and changes from baseline will be provided for each visit.

7.12 Interim Analysis

Not applicable

7.13 Changes in the Statistical Analysis Plan

In section 7.8.2, the description have been modified to be accordance with protocol.

8.0 REFERENCES

Fukuhara S, Suzukamo Y. Manual of the SF-8 Japanese version: Institute for Health Outcomes & Process Evaluation research, Kyoto, 2004

Appendix 1. Criteria for Elevated Liver Enzyme

Criteria for Elevated Liver Enzyme

All evaluable data (ie, non-missing) 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. The following abbreviations are used: LLN for lower limit of the normal range, ULN for upper limit of the normal range, ALT for alanine aminotransferase, AST for aspartate aminotransferase, Tbili for total bilirubin, and ALP for alkaline phosphatase.

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

Label	Criteria for Elevated Liver Enzyme	
	(a) Elevated	(b) Not Elevated
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

Classifying Subjects for the Overall Treatment Period

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.

Appendix 2. Criteria for Markedly Abnormal Values

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

For each parameter, all evaluable 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. The lower limit of the normal range and the upper limit of the normal range are abbreviated as LLN and ULN.

Hematology

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
RBC ($\times 10^6/\mu L$)	-	-	<0.8×LLN	>1.2×ULN
Platelets ($\times 10^3/\mu L$)	-	-	<75	>600
WBC ($\times 10^3/\mu L$)	-	-	<0.5×LLN	>1.5×ULN
Neutrophils (%)	-	-	<0.5×LLN	>1.5×ULN
Eosinophils (%)	-	-	-	>2×ULN
Basophils (%)	-	-	-	>3×ULN
Lymphocytes (%)	-	-	<0.5×LLN	>1.5×ULN
Monocytes (%)	-	-	-	>2×ULN
Hematocrit (%)			<0.8×LLN	>1.2×ULN
Hemoglobin (g/dL)			<0.8×LLN	>1.2×ULN

Serum Chemistry

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Total protein (g/dL)	-	-	<0.8×LLN	>1.2×ULN
Albumin (g/dL)	-	-	<2.5	-
Blood urea nitrogen (mg/dL)	-	-	-	>30
Urate (mg/dL)	-	-	-	>13.0
Creatinine (mg/dL)	-	-	-	>2.0
Total cholesterol (mg/dL)	-	-	-	>300
Triglycerides (mg/dL)	-	-	-	>2.5×ULN
Total bilirubin (mg/dL)	-	-	-	>2.0

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Sodium (mEq/L)	-	-	<130	>150
Potassium (mEq/L)	-	-	<3.0	>6.0
Chloride (mEq/L)	-	-	<75	>126
Calcium (mg/dL)	-	-	<7.0	>11.5
Inorganic phosphorus (mg/dL)	-	-	<1.6	>6.2
Alkaline phosphatase (U/L)	-	-	-	>3×ULN
Creatine kinase (U/L)	-	-	-	>5×ULN
AST (U/L)	-	-	-	>3×ULN
ALT (U/L)	-	-	-	>3×ULN
GGT (U/L)	-	-	-	>3×ULN
Glucose (mg/dL)	-	-	<50	>350
Magnesium (mg/dL)	-	-	<1.2	>3.0
Direct bilirubin (mg/dL)				>2×ULN

Vital Signs

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
Systolic Blood Pressure (mmHg)	-	-	<85	>180
Diastolic Blood Pressure (mmHg)	-	-	<50	>110
Pulse Rate (bpm)	-	-	<50	>120
Body temperature (°C)	-	-	<35.6	>37.7

12-lead ECGs

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

Classifying Subjects for the Overall Treatment Period

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.

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

All evaluable 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