



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

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TAKEDA PHARMACEUTICALS
PROTOCOL

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**

Sponsor:	Takeda Pharmaceutical Company Limited 1-1 Doshomachi 4-chome, Chuo-ku, Osaka 540-8645, Japan		
Study Number:	Vonoprazan-3001		
IND Number:	Not Applicable	EudraCT Number:	Not Applicable
Compound:	TAK-438 (Vonoprazan Fumarate)		
Date:	31 August 2016	Version/Amendment Number:	Initial version

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1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

See the annex.

1.2 Principles of Clinical Studies

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

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

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2.0 STUDY SUMMARY

Clinical Study Sponsor: Takeda Pharmaceutical Company Limited		Compound: TAK-438 (vonoprazan fumarate)							
Study 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		IND No.: Not Applicable	EudraCT No.: Not Applicable						
Study Identifier: Vonoprazan-3001		Phase: 3							
Study Design: A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study will be conducted to verify the superiority of TAK-438 (TAK-438 10 mg, once daily, 4 weeks) to placebo (placebo, once daily, 4 weeks) in patients with non-erosive gastroesophageal reflux disease (NERD). The study consists of a 1-week, single-blind run-in period and a 4-week, double-blind treatment period. The subjects will receive the study drug (TAK-438 placebo tablet) for the 1-week single-blind run-in period. After the run-in period, eligible subjects will be randomized into TAK-438 10 mg or placebo treatment groups in a 1:1 ratio. The randomized subjects will receive the assigned study drug (TAK-438 10 mg tablet or TAK-438 placebo tablet) for the 4-week double-blind treatment period.									
Primary Objective: The primary objective of this study is to verify the superiority of TAK-438 to placebo in patients with NERD.									
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.									
Subject Population: Patients aged 20 years or older, with NERD									
Planned Number of Subjects: TAK-438 10 mg group: 237 subjects Placebo group: 237 subjects Estimated total: 474 subjects		Planned Number of Sites: Estimated total: approximately 45 sites in Japan							
Dose Level(s): Run-in period: One TAK-438 placebo tablet will be orally administered once daily. Treatment period: One TAK-438 DB tablet will be orally administered once daily. <table><tr><td>Study Group</td><td>Study Drug</td></tr><tr><td>TAK-438 10 mg</td><td>1 TAK-438 10 mg tablet</td></tr><tr><td>Placebo</td><td>1 TAK-438 placebo tablet</td></tr></table>		Study Group	Study Drug	TAK-438 10 mg	1 TAK-438 10 mg tablet	Placebo	1 TAK-438 placebo tablet	Route of Administration: Oral	
Study Group	Study Drug								
TAK-438 10 mg	1 TAK-438 10 mg tablet								
Placebo	1 TAK-438 placebo tablet								
Duration of Treatment: Run-in period: 1 week Treatment period: 4 weeks		Study Length: Run-in period: 1 week Treatment period: 4 weeks							

Main Criteria for Inclusion:

Subject eligibility is determined according to the following criteria prior to entry into the study:

Primary Inclusion Criteria:

Subjects are eligible to enter the run-in period if they meet all of the following criteria:

1. The subject with NERD.
2. The subject is endoscopically confirmed to have the modified LA Classification Grade N or M at the start of the run-in period (Visit 1).
To allow efficacy evaluation in the subjects with Grade N as well as in those with Grade M, the target number of subjects in each grade is at least 30% of the total number of subjects. Enrollment of patients with either Grade N or M will end when the number of enrolled subjects with each grade exceeds 332, or 70% of the total planned number of subjects.
3. The subject experiences recurrent heartburn^{***} on at least 2 days a week over the last 3 weeks prior to the start of the run-in period (Visit 1).
*Heartburn is defined as a burning sensation arising from the stomach or behind the breastbone, and the symptoms commonly appear or is exacerbated postprandially, or through forward-bending position and abdominal compression.
**Based on the result of hearing from the subjects, their severity is categorized as follows:
Without symptoms: no symptoms, no hindrance to daily activities.
With symptoms: mild (not very painful), moderate (rather painful), severe (painful).
4. The subject is either a male or female outpatient with a minimum age of 20 years at the time of informed consent signing. However, subjects who are hospitalized only for examination purposes are also allowed to participate.

Secondary Inclusion Criteria:

Subjects are eligible to enter the treatment period if they meet all of the following criteria:

5. The subject's compliance to the study drug has been good (75% or better) in the run-in period.
6. The subject has experienced heartburn on at least 2 days in the last 1 week prior to randomization.
7. The subject has appropriately provided in the patient's diary all the required information during the run-in period.

Main Criteria for Exclusion:

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 84 days prior to the first dose of study drug.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent, except one with experience of receiving TAK-438 as adjunct therapy for *H. pylori* eradication, who can be enrolled in this study.
3. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has donated at least 400 mL of blood within the 90 days prior to the start of the run-in period (Visit 1).
5. Endoscopic examination for entering this study fails to diagnose NERD within 84 days before the start of the run-in period (Visit 1).
6. The subject has any complications affecting the esophagus, including Barrett's esophagus (3 cm or more, long segment Barrett's esophagus [LSBE]), eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, and esophageal stenosis; a history of radiation therapy or cryotherapy for the esophagus; or caustic or physiochemical trauma (eg, esophageal sclerotherapy). However, subjects with Barrett's mucosa (less than 3 cm, short segment Barrett's esophagus [SSBE]) or Schatzki's ring (a mucosal tissue ring lining the inferior esophageal sphincter) are permitted to participate.

7. The subject has a history of surgery or treatment affecting gastroesophageal reflux, including fundoplication and mechanical dilatation for esophageal stenosis (except Schatzki's ring), or a history of gastric or duodenal surgery (except endoscopic removal of benign polyps).
8. The subject has acute upper gastrointestinal bleeding or gastric or duodenal ulcer, characterized by a defective mucosa with white coating, within 30 days prior to the start of the run-in period (Visit 1). However, subjects with gastric or duodenal erosion are permitted to participate.
9. The subject has acute gastritis or acute exacerbation of chronic gastritis.
10. The subject has, or has a history of, Zollinger-Ellison syndrome or gastric acid hypersecretion disorders.
11. The subject has, or has a history of chest pain due to cardiac disease, or has chest pain suspectedly caused by cardiac disease within 1 year prior to the start of the run-in period (Visit 1).
12. The subject has any other concurrent upper gastrointestinal symptoms more severe than heartburn.
13. The subject has depression.
14. The subject has, has a history of, or is suspected of functional upper gastrointestinal disorders, such as functional dyspepsia and functional heartburn diagnosed by the Rome IV criteria.
15. The subject has a history of hypersensitivity or allergies to TAK-438 (including the formulation excipients).
16. The subject has a history or complication of drug abuse (defined as any illicit drug use) or of alcohol abuse within 1 years prior to the start of the run-in period (Visit 1).
17. The subject requires any excluded medications or treatments listed in Section 7.3.
18. The female subject who is pregnant, is lactating, or is intending to become pregnant or to donate ova any time between the informed consent signing and 4 weeks after the last dose of study drug.
19. The subject has any serious neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, endocrinological, or hematologic diseases.
20. The subject needs surgery requiring hospitalization during the course of the study, or surgery requiring hospitalization is scheduled for the subject during the course of the study.
21. The subject has a history of malignancy or is treated for malignancy within 5 years prior to the start of the run-in period (Visit 1). However, subjects who have recovered completely from cutaneous basal cell carcinoma or from cervical carcinoma in situ are permitted to participate.
22. The subject has acquired immunodeficiency syndrome (AIDS) or hepatitis, is a human immunodeficiency virus (HIV) carrier, or tested positive for the hepatitis B virus surface antigen (HBsAg) or the hepatitis C virus (HCV) antibody. However, subjects who tested negative for HCV antigen or HCV-RNA are permitted to participate.
23. The subject has any of the following abnormal clinical laboratory test values at the start of the run-in period (Visit 1):
 - Creatinine > 2 mg/dL.
 - ALT or AST > ULN.
 - Bilirubin (Total bilirubin) > ULN.

Main Criteria for Evaluation and Analyses:

Efficacy:

(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.

(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 H₂-receptor antagonists [H₂RAs], or other agents [anticholinergics or anti-gastrin drugs]) in subjects who had a medication history of any of these drugs.

(3) Additional Endpoints

Quality of life (QOL)

Regurgitation during the treatment period

Safety:

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

Statistical Considerations:

[Analyses for primary endpoint]

(1) Primary analyses

The primary analyses for primary endpoint will be performed based on the full analysis set (FAS).

1. Primary variable

Descriptive statistics will be used to summarize the proportion of days without symptoms during the treatment period 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.

2. Secondary variable

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).

3. Additional variable

The same analysis used for primary efficacy variable will be performed for mean severity of symptoms over the treatment period.

(2) Secondary analyses

For sensitivity analysis, the same analyses to those conducted in the primary analyses will be performed on the per-protocol set (PPS) to evaluate the stability of the results.

[Analyses for secondary endpoints]

Analyses for secondary endpoint will be performed similarly to the primary analyses on the FAS

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.

Response (improved or not improved) at Week 2 will be assessed in accordance with the following criteria.

Criteria 1:

Improved: the subject experiences heartburn on less than 2 days of the 7 days prior to Week 2 (Day 8 through Day 14).
Not improved: the subject experiences heartburn on 2 days or more of the 7 days prior to Week 2 (Day 8 through Day 14).

Criteria 2:

Improved: the proportion of days the subject experiences heartburn during the treatment period up to Week 2 (Day 14) is lower than that during the run-in period.

Not improved: the proportion of days the subject experiences heartburn during the treatment period up to Week 2 (Day 14) is equal to or larger than that during the run-in period.

Subjects are to be stratified by the following response to acid suppressants:

Improved: those whose heartburn has been resolved, or whose heartburn has not been resolved but relieved.

Not improved: those whose heartburn has remained unchanged, or whose heartburn has been worsened.

Sample Size Justification:

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 10mg group.

Assuming that, based on these results and assessment method of heartburn in this study, the difference between the TAK-438 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, around 3%, after randomization.

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
<i>H. pylori</i>	<i>Helicobacter pylori</i>
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
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 INTRODUCTION

4.1 Background

Non-erosive gastroesophageal reflux disease (NERD) is characterized by uncomfortable symptoms due to reflux of gastric content, including gastric acid, into the esophagus without the mucosal breaks [1]. The most common symptoms of NERD are acid reflux symptoms including heartburn and regurgitation [2]. Recurrence of such symptoms can deteriorate the patient's quality of life (QOL) [3]. Therefore, the clinically relevant goal of NERD treatment is to relieve acid reflux symptoms.

The first-line treatment for NERD is proton pump inhibitors (PPIs), such as lansoprazole, which are widely used in Japan as well as other parts of the world [4].

PPIs exert potent therapeutic effects through strong and continuous suppression of gastric acid secretion by inhibiting the proton pump (H^+ , K^+ -adenosine triphosphatase [ATPase]) in the final step of acid secretion by gastric mucosal parietal cells.

However, conventional PPIs have some characteristics, which mean that their effect is not always satisfactory in terms of extent and onset of symptom relief [5]. The following are some of the deficiencies of conventional PPIs that need to be improved: (1) conventional PPIs are relatively acid-labile and in enteric-coated dosage form [6], meaning the time to onset of their effect may vary widely between individuals; (2) conventional PPIs require about 3 to 5 days to exert their maximum acid-inhibitory effects [6, 7, 8]; (3) the acid-inhibitory effects of conventional PPIs are satisfactory during the day, but their effect on acid regurgitation during the night (nocturnal acid breakthrough) is inadequate in some individuals [8]; and (4) since conventional PPIs are metabolized by polymorphic cytochrome P450 (CYP) 2C19, plasma drug concentrations and acid-inhibitory effects may differ between extensive metabolizers (EMs) and poor metabolizers (PMs) [7, 9].

Vonoprazan fumarate (TAK-438) is a novel class of acid suppressants, referred to as a potassium-competitive acid blocker (P-CAB), which was developed by Takeda Pharmaceutical Company Limited. TAK-438 inhibits H^+ , K^+ -ATPase in the final step of acid secretion from gastric parietal cells. Unlike conventional PPIs, TAK-438 inhibits H^+ , K^+ -ATPase competitively with potassium ions without activation by acid. Acid-stability and water-solubility of TAK-438 enable a smaller variability in time-of-onset of action compared to conventional PPIs and consequently, a pharmaceutical dosage form such as enteric-coated formulation is not required. TAK-438 is predominantly metabolized by CYP3A4, and the contribution of polymorphic CYP2C19 is considered to be limited [10,11,12]. Whereas conventional PPIs require 3 to 5 days to exert their maximum acid-inhibitory effects [6,7,8], TAK-438 is expected to exhibit its maximum acid-inhibitory effects more quickly compared with conventional PPIs, and to exert potent and sustained acid-inhibitory effects, which may translate into better treatment outcomes.

The efficacy and safety of TAK-438 were established in the clinical studies in patients with acid-related diseases. TAK-438 was approved in December 2014 in Japan, indicated for erosive esophagitis (including a maintenance treatment of erosive esophagitis), gastric ulcer, duodenal ulcer, prevention of recurrent gastric or duodenal ulcer during low-dose aspirin therapy,

prevention of recurrent gastric or duodenal ulcer during non-steroidal anti-inflammatory drug (NSAID) therapy, and adjunct to *Helicobacter pylori* (*H. pylori*) eradication. For the treatment of NERD, a randomized, double-blind, parallel-group, phase 3 study (TAK-438/CCT-201) failed to verify the superiority of TAK-438 to placebo and thus NERD was not included in the TAK-438 indications.

4.2 Rationale for the Proposed Study

The past, randomized, double-blind, parallel-group, phase 3 study (TAK-438/CCT-201) was conducted to verify the superiority of TAK-438 (TAK-438 10 mg or 20 mg once daily) to placebo (TAK-438 placebo) in the treatment of NERD. The median proportion of days without heartburn during the treatment period in the full analysis set (FAS) was 7.40% in the placebo group, 10.30% in the TAK-438 10 mg group, and 12.00% in the TAK-438 20 mg group. Although there were no statistically significant differences between the TAK-438 treatment groups and the placebo group ($p=0.2310$ for the TAK-438 10 mg group, $p=0.0504$ for the TAK-438 20 mg group using the Wilcoxon rank-sum test). The reasons why TAK-438 was not superior to placebo in the study TAK-438/CCT-201 was considered to be the change in the symptom scale of heartburn from that used in the previous studies of PPIs, and possible enrollment of patients with heartburn unrelated to acid reflux. In the study TAK-438/CCT-201, the heartburn was categorized into 6 levels [no symptom, very mild, mild, moderate, severe, and very severe], while heartburn had been evaluated using 4 levels [none, mild, moderate, severe] in previous studies using PPIs in patients with NERD in Japan [13,14,15]. The Evidence-based Clinical Practice Guidelines for GERD 2015 (2nd Edition) [16] provides an explanation on different responses to PPI treatment between erosive esophagitis and NERD by stating that “especially, since patients with heartburn due to non-acid GER¹ or functional heartburn unrelated to GER are often included in those diagnosed with NERD, treatment of NERD patients with PPI may result in lower proportion of symptom-free patients compared to patients with erosive GERD².” In the study TAK-438/CCT-201, some patients whose heartburn had not been caused by acid reflux were possibly enrolled. Therefore, based on these reasons, this study has been planned to evaluate the efficacy and safety of TAK-438 in patients with NERD.

Pharmacogenomic analysis may be conducted to evaluate the contribution of genetic variance and/or gene expression on drug response, for example, its efficacy and safety. Participation of study subjects in pharmacogenomic sample collection is optional.

As pharmacogenomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response, which may lead to additional hypothesis-generating exploratory research on stored samples.

¹ gastroesophageal reflux

² gastroesophageal reflux disease

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

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

5.1.2 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.

5.2 Endpoints

5.2.1 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.

5.2.2 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 H₂-receptor antagonists [H₂RAs], or other agents [anticholinergics or anti-gastrin drugs]) in subjects who had a medication history of any of these drugs.

5.2.3 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 STUDY DESIGN AND DESCRIPTION

6.1 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 [17]. 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.

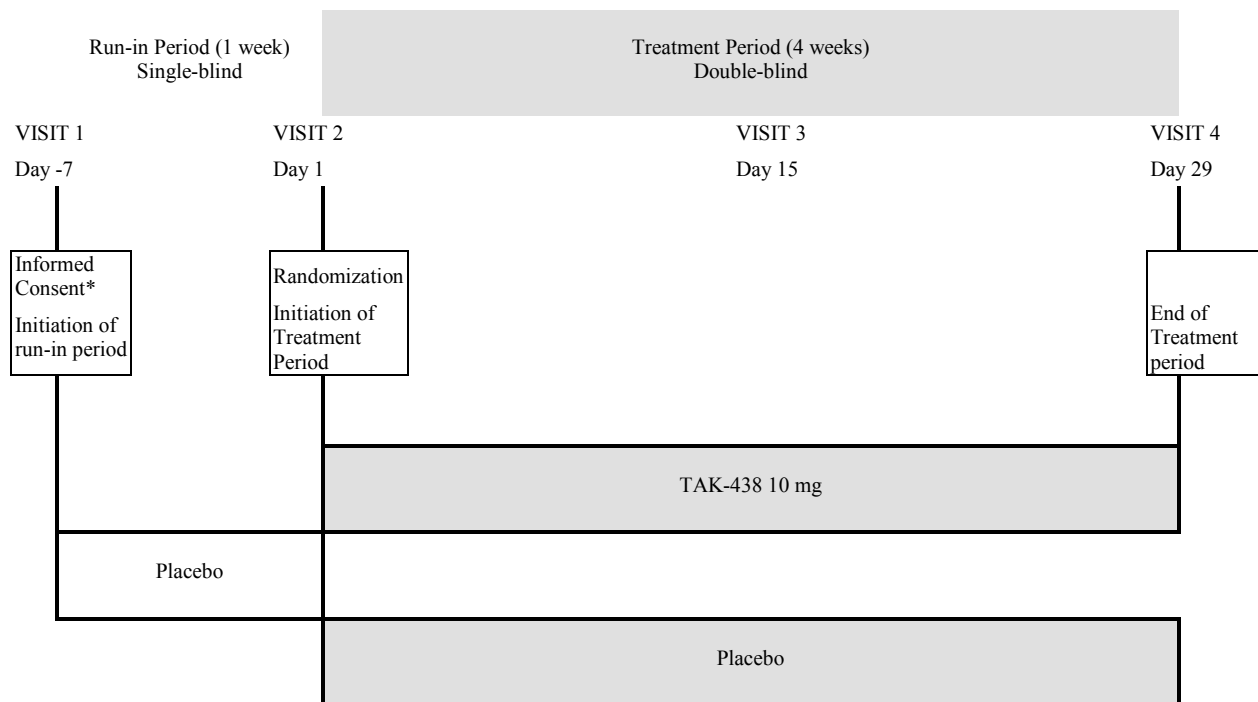
The subjects are required to visit the sites 4 times in total: at the start of the run-in period (Visit 1), at the start of the treatment period (Visit 2), after 2 weeks of treatment (Visit 3), and after 4 weeks of treatment (Visit 4).

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 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design



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

6.2 Justification for Study Design, Dose, and Endpoints

(1) Justification for Subject Population Studied

NERD is characterized by uncomfortable symptoms due to reflux of gastric content, including gastric acid, into the esophagus without the mucosal breaks [1]. The LA Classification, first presented at the World Congress of Gastroenterology in 1994, has been used widely in Japan for the diagnosis of erosive esophagitis in recent years. This study will employ the modified LA Classification for assessment of NERD patients, in which the absence of mucosal breaks is divided to Grades N and M based on mucosal decoloration [17]. This study will enroll patients with NERD of Grade N or M.

The most common acid reflux symptom of NERD is heartburn, followed by regurgitation [2]. Patients with recurrent heartburn will be eligible for this study since the clinically relevant goal of NERD treatment is relief of such acid reflux symptoms.

The basic pathology of NERD is acid reflux symptoms such as heartburn, and NERD is included in GERD. According to Rome III criteria [18], functional heartburn should be diagnosed when patients complain of heartburn likely due to any factor other than reflux. In the more recent Rome IV criteria [19], the current diagnosis of functional heartburn remains focused on a lack of conclusive evidence for GERD, no evidence of a symptom reflux correlation, and a negative response to acid suppressive therapy because this should alert the physician to the potential of a functional disorder. The Evidence-based Clinical Practice Guidelines for GERD 2015 (2nd Edition) [16] provides an explanation on different responses to PPI treatment between erosive esophagitis and NERD by stating that “since patients with heartburn due to non-acid GER or functional heartburn unrelated to gastroesophageal reflux are often included in those diagnosed with NERD, treatment of NERD patients with PPI may result in lower proportion of symptom-free patients compared to patients with erosive GERD”. Therefore, the patients with functional heartburn caused by factors other than acid reflux will be excluded from this study.

In clinical practice, dyspeptic symptoms such as epigastric pain, stomach upset, and nausea are sometime reported as heartburn because patients do not exactly know what heartburn is, and patients with dyspeptic symptom but no heartburn respond poorly to PPIs [20,21]. According to Rome IV criteria for gastroduodenal disorders [22], functional dyspepsia is defined as a medical condition that significantly impacts on the usual activities of a patient and is characterized by one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain, and epigastric burning that are unexplained after a routine clinical evaluation. Therefore, the patients with functional dyspepsia will be excluded from this study.

The patients with any concurrent conditions or any medical history that may affect gastric acid secretion will be excluded from this study to eliminate the potential effects on the efficacy evaluation of the study drug.

(2) Justification for Study Design

While it seems rational to confirm the efficacy of TAK-438 in an active-controlled study using a PPI as a comparator, the standard treatment for NERD, this study will employ a placebo-controlled design for the following reasons. Since large variability between subjects is predicted in the

primary endpoint of this study, ie, heartburn recorded in the patient's diary during treatment period, the number of subjects required in an active-controlled study is considered to be unrealistic, and setting a non-inferiority margin will also be difficult. In fact, ICH E10 Guideline (Choice of Control Group and Related Issues in Clinical Trials) lists symptomatic gastroesophageal reflux as a condition in which the minimum effect a drug will have in the setting of a specific trial cannot be reliably determined. The large variability in evaluation of NERD will make the sensitivity of this study unreliable, if conducted with an active-controlled, non-inferiority design. The placebo-controlled design is thus selected in view of study feasibility. The randomized, double-blind design is used to minimize possible biases in the selection of subjects and the evaluation of symptoms.

(3) Justification for Sample Size

Refer to Section 13.3.

(4) Justification for Selection of Dose

PPIs have been approved and indicated for the treatment of NERD, and the therapeutic dose for NERD is half the maximum dose allowed for the treatment of erosive esophagitis. Therefore, since TAK-438 is also expected to be effective at half the dose of erosive esophagitis treatment, and previous study of TAK-438 (TAK-438/CCT-201) investigated 20 mg once daily, the dose proposed for erosive esophagitis, and its half dose of 10 mg were considered. Consequently, the p-value for superiority to placebo was smaller in the TAK-438 20 mg group than that in the TAK-438 10 mg, meanwhile the proportion of days without heartburn in the treatment period (median) was almost the same in the responders with possibly acid-related heartburn between the TAK-438 10 mg and 20 mg groups when stratified by the response (improved or not improved) at Week 2. Based on the study results, TAK-438 10 mg once daily is selected as the clinical dose for NERD treatment and will be investigated in this study.

(5) Justification for Route and Mode of Administration of Study Drug

Effect of food on the TAK-438 pharmacokinetics was investigated at 10 mg and 40 mg doses in the phase 1, single-dose study in healthy male subjects in Japan (TAK-438/CPH-001). The AUC_{0-48} and C_{max} of TAK-438F were slightly higher under fed than under fasted conditions; the relative increases in AUC_{0-48} and C_{max} were 1.32 (90% confidence interval [CI], 1.18 to 1.48) and 1.21 (90% CI, 0.951 to 1.54), respectively, at the 10 mg dose, and 1.15 (90% CI, 1.05 to 1.27) and 1.08 (90% CI, 0.944 to 1.23), respectively, at the 40 mg dose. Also, in the pharmacodynamic results, once-daily administration of TAK-438 inhibited acid secretion for over 24 hours. Effect of food was also investigated using a 20 mg dose of the final TAK-438 formulation in the single-dose study in healthy male subjects in Japan (TAK-438/CPH-007). The relative increases in AUC_{0-48} and C_{max} of TAK-438F were 1.088 (90% CI, 0.942 to 1.256) and 1.077 (90% CI, 1.014 to 1.145). No clinically meaningful effect was noted between under fed and fasted conditions.

In light of the study results above and the timing of medication (usually postprandial), TAK-438 will be administered once daily after breakfast in this study.

(6) Justification for Treatment Period

In this study, the duration of the treatment period is set at 4 weeks because the approved duration of NERD treatment with PPIs, the standard treatment for NERD, is maximum of 4 weeks in Japan.

(7) Justification for Run-in Period

In the study TAK-438/CCT-201, antacids were used during the run-in period to exclude the responders. However, use of antacids is not required for the run-in period of this study in view of NERD treatment in clinical practice. In addition, the results of the previous studies has suggested that some subjects had a placebo effect [13,14,15], this study will therefore have the run-in period, where subjects will receive a placebo in a single-blind manner, to exclude placebo-responders. During the run-in period, treatment compliance will be investigated and the patient diaries will be checked to ensure proper entries.

(8) Justification for Primary and Secondary Endpoints

1) Primary Endpoint

Heartburn is a characteristic symptom of NERD [2], and its resolution is the most important goal in the treatment of NERD. Following the phase 3, double-blind, comparative studies of lansoprazole in NERD patients conducted in Japan (AG-1749/CCT-206) and the phase 3, double-blind, comparative study (TAK-438/CCT-201), the primary endpoint of this study is heartburn during treatment period, and the proportion of days without heartburn is selected as the primary variable. As sustained relief from the symptom and the time to relief are also important in NERD treatment in terms of therapeutic benefit, cumulative symptom improvement rate (using Kaplan-Meier method) is selected as the secondary variable. To evaluate the improvement in the severity of symptoms as well as its disappearance, the severity of symptoms is investigated as additional variable.

2) Secondary Endpoints

The post-hoc analysis for the phase 3, double-blind, comparative study (AG-1749/CCT-206) indicated that response after 2-week treatment was useful for guiding appropriate use of lansoprazole. The package insert of lansoprazole accordingly recommends that response be assessed after a 2-week treatment with lansoprazole, and if symptoms do not improve, consider changing to another treatment as acid reflux may not be the cause. The primary endpoint in subjects receiving TAK-438, stratified by the response at Week 2, is therefore investigated in this study.

While the subject population in the phase 3, double-blind, comparative study of lansoprazole (AG-1749/CCT-206) was limited to NERD patients with the modified LA Classification Grade M at the start of the run-in period, lansoprazole proved to be effective for NERD patients with either Grade N or M in its postmarketing study (AG-1749/CCT-971). Hence, the primary endpoint will be also investigated in subjects stratified by endoscopic finding in this study. In addition, the primary endpoint in subject subgroups stratified by the combination of response at Week 2 and endoscopic finding will be investigated.

The primary endpoint will also be investigated in subjects stratified by positive or negative response to acid suppressants in subjects who has a medication history of any of these drugs to ensure that efficacy of TAK-438 is evaluated in subjects with heartburn caused by acid reflux, the possible target disease of TAK-438.

3) Additonal Endpoints

The improvement in QOL associated with the relief of NERD symptoms was investigated as an additional endpoint using the acute (1-week recall) version of the SF-8 Health Survey questionnaire to further characterize the therapeutic benefit of TAK-438 treatment.

Since regurgitation is also one of the most common acid reflux symptoms of NERD [2], the same variables as those used in heartburn will be applied.

Increases in serum gastrin and pepsinogen I/II levels will also be measured as safety endpoints since TAK-438 administration may elevate the levels of these parameters.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

Primary inclusion criteria:

Subjects are eligible to enter the run-in period if they meet all of the following criteria:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written informed consent form prior to the initiation of any study procedures.
3. The subject with NERD.
4. The subject is endoscopically confirmed to have the modified LA Classification Grade N or M at the start of the run-in period (Visit 1).³

To allow efficacy evaluation in the subjects with Grade N as well as in those with Grade M, the target number of subjects in each grade is at least 30% of the total number of subjects.

Enrollment of patients with either Grade N or M will end when the number of enrolled subjects with each grade exceeds 332, or 70% of the total planned number of subjects.

5. The subject experiences recurrent heartburn*** on at least 2 days a week over the last 3 weeks prior to the start of the run-in period (Visit 1).

*Heartburn is defined as a burning sensation arising from the stomach or behind the breastbone, and the symptoms commonly appear or is exacerbated postprandially, or through forward-bending position and abdominal compression.

**Based on the result of hearing from the subjects, their severity is categorized as follows:

Without symptoms: no symptoms, no hindrance to daily activities.

With symptoms: mild (not very painful), moderate (rather painful), severe (painful).

6. The subject is either a male or female outpatient with a minimum age of 20 years at the time of informed consent signing. However, subjects who are hospitalized only for examination purposes are also allowed to participate.
7. A female subject of childbearing potential* agrees to use routinely adequate contraception from signing of informed consent throughout the duration of the study, and for 4 weeks after the last dose of study drug.

³ Any endoscopic confirmation within 7 days prior to the start of the run-in period (before signing of informed consent), if available, is acceptable instead of the endoscopic examination at Visit 1, given the invasive nature of the procedure.

*A female of childbearing potential are defined in Section 9.1.12 and reporting responsibilities are defined in Section 9.1.13.

Secondary inclusion criteria:

Subjects are eligible to enter the treatment period if they meet all of the following criteria:

8. The subject's compliance to the study drug has been good (75% or better)⁴ in the run-in period.
9. The subject has experienced heartburn on at least 2 days in the last 1 week prior to randomization.
10. The subject has appropriately provided in the patient's diary all the required information during the run-in period.

Justification of Inclusion Criteria

Criteria 1 and 2 were set as basic matters to conduct clinical studies.

Criterion 3 was set because the defined patients are the target patients for this study.

Criteria 4, 5, 8, 9 and 10 were set to select subjects appropriate for efficacy evaluation of the study.

Criterion 6 was set because it was appropriate to conduct this study and allow the subject's voluntary participation in the study.

Criterion 7 was set because the safety of TAK-438 in pregnant women and fetuses has not yet been established.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. The subject has received any investigational compound within 84 days prior to the first dose of study drug.
2. The subject has received TAK-438 in a previous clinical study or as a therapeutic agent, except one with experience of receiving TAK-438 as an adjunct therapy for *H. pylori* eradication, who can be enrolled in this study.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has donated at least 400 mL of blood within the 90 days prior to the start of the run-in period (Visit 1).
5. Endoscopic examination for entering this study fails to diagnose NERD within 84 days before the start of the run-in period (Visit 1).

⁴ Treatment compliance rate=number of drug administrations/[(Visit 2 date–Visit 1 date)]×100

6. The subject has any complications affecting the esophagus, including Barrett's esophagus (3 cm or more, long segment Barrett's esophagus [LSBE]), eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, and esophageal stenosis; a history of radiation therapy or cryotherapy for the esophagus; or caustic or physiochemical trauma (eg, esophageal sclerotherapy). However, subjects with Barrett's mucosa (less than 3 cm, short segment Barrett's esophagus [SSBE]) or Schatzki's ring (a mucosal tissue ring lining the inferior esophageal sphincter) are permitted to participate.
7. The subject has a history of surgery or treatment affecting gastroesophageal reflux, including fundoplication and mechanical dilatation for esophageal stenosis (except Schatzki's ring), or a history of gastric or duodenal surgery (except endoscopic removal of benign polyps).
8. The subject has acute upper gastrointestinal bleeding or gastric or duodenal ulcer, characterized by a defective mucosa with white coating, within 30 days prior to the start of the run-in period (Visit 1). However, subjects with gastric or duodenal erosion are permitted to participate.
9. The subject has acute gastritis or acute exacerbation of chronic gastritis.
10. The subject has, or has a history of, Zollinger-Ellison syndrome or gastric acid hypersecretion disorders.
11. The subject has, or has a history of chest pain due to cardiac disease, or has chest pain suspectedly caused by cardiac disease within 1 year prior to the start of the run-in period (Visit 1).
12. The subject has any other concurrent upper gastrointestinal symptoms more severe than heartburn.
13. The subject has depression.
14. The subject has, has a history of, or is suspected of functional upper gastrointestinal disorders, such as functional dyspepsia and functional heartburn diagnosed by the Rome IV criteria.
15. The subject has a history of hypersensitivity or allergies to TAK-438 (including the formulation excipients⁵).
16. The subject has a history or complication of drug abuse (defined as any illicit drug use) or of alcohol abuse within 1 years prior to the start of the run-in period (Visit 1).
17. The subject requires any excluded medications or treatments as listed in Section 7.3.
18. The female subject who is pregnant, is lactating, or is intending to become pregnant or to donate ova any time between the informed consent signing and 4 weeks after the last dose of study drug.
19. The subject has any serious neurological, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, endocrinological, or hematologic diseases.

⁵ mannitol, microcrystalline cellulose, hydroxypropyl cellulose, fumaric acid, croscarmellose sodium, magnesium stearate, hypromellose 2910, macrogol 6000, titanium oxide, ferric oxide, yellow and ferric oxide, red

20. The subject needs surgery requiring hospitalization during the course of the study, or surgery requiring hospitalization is scheduled for the subject during the course of the study.
21. The subject has a history of malignancy or is treated for malignancy within 5 years prior to the start of the run-in period (Visit 1). However, subjects who have recovered completely from cutaneous basal cell carcinoma or from cervical carcinoma in situ are permitted to participate.
22. The subject has acquired immunodeficiency syndrome (AIDS) or hepatitis, is a human immunodeficiency virus (HIV) carrier, or tested positive for the hepatitis B virus surface antigen (HBsAg) or the hepatitis C virus (HCV) antibody. However, subjects who tested negative for HCV antigen or HCV-RNA are permitted to participate.
23. The subject has any of the following abnormal clinical laboratory test values at the start of the run-in period (Visit 1):
 - Creatinine > 2 mg/dL.
 - ALT or AST > ULN.
 - Bilirubin (Total bilirubin) > ULN.

Justification of Exclusion Criteria

Criteria 1, 2, 3, and 5 were set as basic matters to conduct clinical studies.

Criteria 6, 7, 8, 10, 11, 12, 13, 14 and 17 were set because it could influence the evaluation of efficacy in this study.

Criteria 4, 9, 15, 16, 18, 19, 20, 21, 22 and 23 were set with respect to the safety of the subjects.

7.3 Excluded Medications, Restricted Medications and Prohibited Treatments

The subjects must be instructed not to take any medications, including over-the-counter (OTC) medications, without consulting the investigator. However, on-demand medications for endoscopic examination and topical medications, including liniments, ophthalmic drops, nasal drops, ear drops, inhaled drugs, adhesive skin patches, and gargle (mouthwash), are allowed, whether or not they are excluded or restricted.

(1) Excluded Medications

A list of excluded concomitant medications is provided below.

Excluded medications		Excluded period
(1) Medications for gastrointestinal tract*	PPIs [including TAK-438 (vonoprazan fumarate)]	From 14 days before the start of the run-in period to completion of the study
	H ₂ RAs	From 7 days before the start of the run-in period to completion of the study
	Prokinetics Anticholinergic drugs Prostaglandins Antacids Anti-gastrin drugs Mucosal protective agents	From the start of the run-in period to completion of the study
	(2) <i>H. pylori</i> eradication	Triple therapy with PPI+2 antibiotics
(3) Concomitant use is contraindicated for TAK-438 (vonoprazan fumarate)	Atazanavir sulfate Rilpivirine hydrochloride	From the start of the run-in period to completion of the study
(4) Antidepressants	Medications with the indication of antidepressants on the label (eg, tricyclic antidepressant, tetracyclic antidepressant, SSRI, SNRI, NaSSA)	From 14 days before the start of the run-in period to completion of the study
(5) Anxiolytics	Medications with the indication of anti-anxiety on the label (eg, benzodiazepine anxiolytic, serotonin 1A receptor partial agonist)	From 42 days before the start of the run-in period to completion of the study
(6) Other investigational products	Other investigational products and postmarketing study products	From 84 days before the start of the run-in period to completion of the study

* Use of agents for gastrointestinal tract not listed here (eg, herbal medicines) is permitted. Use of drugs with no gastrointestinal indications is also permitted.

Justification of Excluded Medications

Excluded concomitant medications (1), (2), (4), and (5) were set because they may affect the evaluation of efficacy.

Excluded concomitant medication (3) was set because concomitant use with acid suppressants could reduce solubility and then effects of atazanavir sulfate; and also could reduce absorption and then effects of rilpivirine hydrochloride.

Excluded concomitant medication (6) was set in consideration of safety assurance for subjects.

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(2) Restricted Medications

Restricted medications	Conditions for concomitant use
Bisphosphonates	<p>After informed consent signing, the dosage was not changed in subjects who met the following criteria (however, switching between once-daily weekly and monthly regimens was permitted for drugs containing the same active ingredient):</p> <p>Subjects who had been treated with a bisphosphonate before informed consent signing, who had no bisphosphonate-associated gastrointestinal inflammation or a history of gastrointestinal inflammation before the start of the run-in period, and who were compliant with the dosage as instructed by the bisphosphonate package insert.</p>

Justification of Restricted Medications

The restricted medications listed above were set because they could affect the evaluation of efficacy, but the expected impact could be low under a restricted condition for dosage.

(3) Prohibited Treatments

The following concomitant therapies are prohibited from the start of the run-in period through the end of study.

- Surgical treatment of EE and NERD (eg, fundoplication).
- Any surgery affecting gastric acid secretion (eg, resection of upper gastrointestinal tract and vagotomy).

Justification of Prohibited Treatments

The treatments above were set because they could affect the evaluation of efficacy.

7.4 Diet, Fluid and Activity Control

The investigator, or study collaborator gives the following instructions to the subjects prior to and during the study and asks the subjects at each visit if they have followed the instructions.

- The subjects are to visit the sites as scheduled and undergo all examinations and assessments scheduled for the visit. In cases where the subjects are unable to visit the sites as scheduled, they are to promptly inform the investigator, or study collaborator.
- The subjects are required to be compliant with the study treatment, which includes adhering to the daily dose and timing (in principle, after breakfast). In the event that a subject misses a dose of study drug, the subject is to inform the investigator of the duration of noncompliance with the study treatment. The subject is also required to bring the study drug packages (including the empty blister packs after use) and any unused study drug at every visit.
- The subjects are instructed to daily record any acid reflux symptoms (heartburn and regurgitation) experienced during the day before bedtime throughout the study. The subjects are also instructed to record their compliance with the study treatment. The subjects are instructed to bring their diaries at every visit.

- The subjects are required to fast before any visit to the study site for endoscopic examination, for blood sampling to obtain serum gastrin and pepsinogen I/II levels, or for clinical laboratory tests (triglycerides and glucose).
- The subjects are to visit the sites in the morning, in principle, at the start of the treatment period (Visit 2). At Weeks 2 and 4 (Visits 3 and 4), the subjects are to visit the sites in the morning, in principle, without taking the study drug. On the day of the start of the run-in period (Visit 1), at the start of the treatment period (Visit 2), and the day after 2 weeks of treatment (Visit 3), the subjects are to take the study drugs given for the day of site visit after completion of all scheduled examinations and assessments, but before leaving the site.
- On the days the subjects do not have breakfast, they are to take the study drugs at the same time of the day as they are to usually do; exceptions are to be made on the days of the endoscopic examination, blood testing for serum gastrin and pepsinogen I/II levels, or for clinical laboratory tests.
- The subjects are to consult the investigator, or study collaborator before receiving any therapy from other physicians or before taking any medications, including OTC products, other than the prescribed study drugs. The subjects are required to inform the investigator of any therapy they have received from other physicians and any medication they have taken, including OTC products.
- At every visit, the subjects are to report any symptoms or signs they have experienced, with the onset date, severity, outcome, and outcome date of the episode. In the event of an emergency, including occurrence of a serious adverse event (SAE), either the subject or the subject's family member is to inform the investigator immediately.
- Female subjects with childbearing potential are to adhere to acceptable contraception methods from signing of informed consent to 4 weeks after the last dose. Any pregnancy is to be immediately reported to the sponsor.
- Blood donation is not permitted during the study. If the subjects have donated blood, they are to inform the investigator immediately.
- The subjects are instructed to avoid, throughout the study, excessive eating and drinking, any drastic change in diet (eg, change to excessively fat-rich diet), and excessive exercising.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the case report form (eCRF) using the following categories. For subject failure, refer to Section 9.1.18.

1. Death. The subject died on study.

Note: If the subject dies on study, the event will be considered as SAE. See Section 10.2.2 for the reporting procedures.

2. Adverse event (AE). The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
 - Liver Function Test (LFT) Abnormalities.

Study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status), if the following circumstances occur at any time during study drug treatment:

 - ALT or AST or bilirubin (total bilirubin) > 2×ULN.
3. Protocol deviation. The discovery post-randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Withdrawal by subject. The subject wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE).
6. Study terminated by sponsor. The sponsor terminates the study.
7. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.13.
8. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.
9. Lack of treatment compliance. The subject's treatment compliance is poor, and improvement in compliance is not expected. Treatment compliance is described in Section 9.2.
10. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by

the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all medication and materials provided directly by the sponsor, and/or sourced by other means, that are required by the study protocol, including important sections describing the management of clinical trial material.

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 Study Drug

(1) Dosage Form and Manufacturing

Drugs being studied in the current protocol are as follow:

- 1) Study drug for the treatment period (TAK-438 DB tablet)

Study drug code: TAK-438

Chemical name:

1-[5-(2-Fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanamine monofumarate

Non-proprietary name: Vonoprazan Fumarate (JAN)

Study drug	Ingredients
TAK-438 10 mg tablet	A tablet, coated by pale-yellow film, contains 10 mg of TAK-438 (as the free base) as active ingredient.
TAK-438 placebo tablet	A tablet, coated by pale-yellow film, contains no active ingredient, TAK-438.

TAK-438 10 mg tablets and TAK-438 placebo tablets are manufactured by Takeda Pharmaceutical Company Limited. Appearance of TAK-438 DB tablets is indistinguishable from that of TAK-438 placebo tablets.

- 2) Study drug for the run-in period (TAK-438 placebo tablet)

Study drug	Ingredients
TAK-438 placebo tablet	A tablet, coated by pale-yellow film, contains no active ingredient, TAK-438.

TAK-438 placebo tablets are manufactured by Takeda Pharmaceutical Company Limited. Appearance of TAK-438 DB tablets is indistinguishable from that of TAK-438 placebo tablets.

(2) Packaging and Labeling

Study drugs are packaged by Takeda Pharmaceutical Company Limited.

TAK-438 placebo tablets will be used as study drugs for the run-in period and provided in blister packs. Each blister pack contains 7 tablets of TAK-438 placebo (each pack last for 7 days), and 12

blister packs are placed into one box.

TAK-438 DB tablets will be used as study drugs for the treatment period and provided in blister packs. Each blister pack contains 7 tablets of TAK-438 DB (each pack last for 7 days), and 5 blister packs (including extra 7-day supply) are placed into one box for one subject.

A label for study drug is placed on the box. The label includes a clear indication of investigational use, name of study drug, quantity of study drugs, name and address of the sponsor, lot number and storage.

8.1.2 Storage

Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Even in the event that a subject misses a dose of study drug during the run-in period or the treatment period, the subject is required to comply with the next dosing scheduled and thereafter. The subject should not take any study drugs that he/she has failed to use on the scheduled day. Any unused study drugs should be collected.

Run-in Period

Each subject will remove 1 tablet of TAK-438 placebo as the study drug for the run-in period from the blister pack once a day and take it orally after breakfast in principle for 1 week. The run-in period (Visit 1) begins after completion of all scheduled examinations and assessments.

The study drugs for the run-in period will be prescribed after all scheduled examinations and assessments (Visit 1) are completed. The subject will receive their first dose of study drug for the run-in period before leaving the site.

Treatment Period

Each subject will remove either 1 tablet of TAK-438 10 mg or 1 tablet of TAK-438 placebo for the treatment period from the TAK-438 DB blister pack once a day and take it orally after breakfast in principle for 4 weeks. Treatment period begins from the day of the randomization (at the start of the treatment period [Visit 2]) after completion of all scheduled examinations and assessments.

The study drugs for the treatment period will be prescribed after all scheduled examinations and assessments (Visit 2) are completed. The subject will receive their first dose of study drug for the treatment period before leaving the site. After 2 weeks and 4 weeks of treatment (Visits 3 and 4), the subject is required to visit the site without taking the study drug. After 2 weeks of treatment (Visit 3), the subject will receive the study drug given for the day of site visit after completing all scheduled examinations and assessments, but before leaving the site.

Table 8.a describes the dose and regimen for each group.

Table 8.a Dose and Regimen

Run-in Period

Dose	Treatment Description (TAK-438 placebo tablet)
TAK-438 placebo once daily	One TAK-438 placebo tablet

Treatment Period

Treatment group	Dose	Treatment Description (TAK-438 DB tablet)
TAK-438 10 mg	10 mg TAK-438 once daily	One 10 mg TAK-438 tablet
Placebo	TAK-438 placebo once daily	One TAK-438 placebo tablet

8.1.4 Overdose

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

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

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

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

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will be assigned to receive the study drugs in order of medication ID number allocated to each study site. The investigator or the investigator's designated representatives will enter the medication ID number on the eCRF.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The principal investigator will not receive information on the study drug key code. To maintain blinding of the study, the Emergency Key Control Center will keep the emergency keys until emergency code-breaking or when all the subjects data are fixed. During regularly scheduled, the sponsor or the sponsor's designee will perform an inventory of the number of unused blinded study

drugs and used study drug packages. All unused study drug packages are to be returned to the sponsor or the sponsor's designee before study closure.

As knowledge of serum gastrin and pepsinogen I/II levels may affect the integrity of blinding, the final results of these measurements, in principle, will be kept undisclosed until unblinding at each laboratory that performs the clinical laboratory tests. The sponsor should be notified when unblinding is permitted. Disclosure of the result to the sponsor, if ever necessary, before unblinding, is only permitted by the randomization personnel and only after appropriate masking that prevents the laboratory staff from identifying the subject.

8.5 Unblinding Procedure

The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the study drug blind can be obtained by contacting the Emergency Key Control Center (contact information is described in the procedure).

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the document called Record of Early Blind-Breaking and the same information (except the time) must be recorded on the eCRF.

If subject's blind is broken, the investigator should stop administering of study drug to the subject immediately, and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The site designee will receive the procedures for handling, storage and management of study drugs created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

The site designee will immediately return unused medications to the sponsor after the study is closed at the site.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

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

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

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

After the subject sign the informed consent form, the informed consent will be reported to the subject registration center.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

A separate informed consent form pertaining to storage of the sample must be obtained prior to collecting a blood sample for Pharmacogenomic Research for this study. The provision of consent to collect and analyze the pharmacogenomic sample is independent of consent to the other aspects of the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, race as described by the subject, smoking classification, use of alcohol or caffeine-containing drinks, treatment history of *H. pylori* eradication (eg, triple therapy with PPI + amoxicillin + clarithromycin) of the subject, and if treated, when the treatment was completed (within the last year or more than one year before) at the start of the run-in period (Visit 1).

Medical history to be obtained will include whether the subject has any significant conditions or diseases relevant to the disease under study that stopped prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.10). Any significant conditions or diseases relevant to the proposed indication include NERD and other diseases or procedures related to upper gastrointestinal tract.⁶ Extent of medical history for NERD should be just prior to signing of informed consent, while for other diseases or procedures related to upper gastrointestinal tract it should be for 3 years prior to signing of informed consent.

The investigator will inquire subjects with possible case of heartburn, and identify and document causative factors in the eCRF according to the following categories. Subjects will also be asked whether they will voluntarily change their lifestyle to manage their heartburn.

⁶ Erosive esophagitis, gastric ulcer, duodenal ulcer, gastritis, and other.

- Physical factors: kyphosis, evident obesity.
- Movement: forward flexion, lying in bed, etc.
- Diet: fatty foods (eg, fried food), carbohydrates (eg, grains, potatoes), sweet foods (eg, chocolate), acidic foods (eg, citrus fruits, carbonated beverages), spices (eg, pepper, curry), etc.
- Habits: smoking, caffeine ingestion, drinking alcohol.
- The above factors are not applicable.

Medication history information to be obtained will include any medication relevant to eligibility criteria and efficacy evaluation stopped at or within 90 days prior to signing of informed consent. These records include the medication's trade or generic names and the routes of administration. The investigation of the subject's medication history will cover the following agents: that are stopped within 28 days prior to signing of informed consent, except PPIs and H₂RAs.

- PPIs.
- H₂RAs.
- Any other medications for gastrointestinal tract.
- Antidepressants
- Anxiolytics

9.1.3 Acid Suppressants

Subjects are to be asked whether they have taken any acid suppressants (PPIs, H₂RAs, or other agents [anticholinergics or anti-gastrin drugs]) within 180 days prior to informed consent. For subjects who have been treated with these drugs, the investigator will ask them to identify which type of acid suppressants they have taken and categorize them according to a response to any of these drugs using 4 scales: 'heartburn has been resolved', 'heartburn has not been resolved but relieved', 'heartburn has remained unchanged', or 'heartburn has been worsened'.

9.1.4 Physical Examination Procedure

A physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

All physical examinations after the start of the study drug administration will assess clinically significant changes from before the start of the study drug administration.

9.1.5 Patient Diary

Subjects are to record any heartburn and regurgitation, most common acid reflux symptoms of NERD, in the patient diary for assessment.

The subjects will receive their diary at each visit and be instructed on how to record acid reflux symptoms (heartburn and regurgitation) in their diary.

The subjects are to start the diary before bedtime from the start of the run-in period (Visit 1) and then continue daily to record the severity of acid reflux symptom (heartburn or regurgitation) throughout the study, according to Table 9.a. Compliance with the study treatment will also need to be recorded throughout the study.

The patient diary will be reviewed at each visit and the subjects will be inquired for any missing entries, inconsistencies or questions. After the required entries are recorded by the subjects, the investigators are to collect the patient diary. The principal investigator will store the patient diary.

Table 9.a Severity of Acid Reflux Symptoms

Without symptom	No symptom
	No hindrance to daily activities
With symptom	Mild (not very painful)
	Moderate (rather painful)
	Severe (painful)

9.1.6 Weight, Height and BMI

A subject should have weight and height measured according to the study procedures (Appendix A). The BMI is calculated by the sponsor using weight and height recorded on the eCRF with the formula provided below:

$$\text{Metric: BMI} = \text{weight (kg)} / \text{height (m)}^2$$

Standard used by the sponsor for collecting height is in centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place.

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height=176 cm (1.76 meters) and weight=79.2 kg, then $\text{BMI} = 79.2 / 1.76^2 = 25.56818 \text{ kg/m}^2$

9.1.7 Vital Sign Procedure

Vital signs will include body temperature (axilla measurement), sitting blood pressure (systolic and diastolic, after at least 5 minutes of rest [mm Hg]), and pulse (beats per minute). Vital signs are to be measured according to the study procedures (Appendix A).

9.1.8 QOL Survey

QOL survey will be conducted using the acute (1-week recall) version of the SF-8 Health Survey questionnaire according to the study procedures (Appendix A). Subjects are instructed on how to fill out a QOL survey form, which will be handed out at the time of informed consent. The subjects

will be required to fill out the questionnaire on how they have felt in the previous week at the start of the run-in period (Visit 1) and at every visit during the study period.

9.1.9 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

Information on the following concomitant medications is not mandatory: infusions, rehydrants, medications used for endoscopy (eg, analgesics, local anesthetics, anticholinergics, sedatives, antagonists, antifoaming agents, and pigments), internal/external diagnostic products, and test drugs (eg, pregnancy test agents).

9.1.10 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the first examination after signing of informed consent. The condition (ie, diagnosis) should be described.

9.1.11 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 10 mL, and the approximate total volume of blood for the study is approximately 40 mL. Clinical laboratory tests are listed in Table 9.b.

Table 9.b Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Red blood cells (RBC)	ALT	Protein (qualitative)
White blood cells (WBC)	ALP	Glucose (qualitative)
Hemoglobin	AST	
Hematocrit	GGT	
Platelets	Bilirubin (Total bilirubin)	
White blood cell differentials (neutrophils, eosinophils, basophils, monocytes, lymphocytes)	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	
Other: Urine human chorionic gonadotropin (hCG) (for pregnancy test in female subjects with childbearing potential)		

*blood sampling under fasted condition.

The central laboratory will perform laboratory tests for hematology, chemistries, and urinalysis. The hCG test will be performed at the study site. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience ALT or AST $> 2 \times \text{ULN}$ or bilirubin (total bilirubin) level $> 2 \times \text{ULN}$, follow-up laboratory tests (at a minimum, serum ALP, ALT, AST, bilirubin (total bilirubin), GGT, and international normalized ratio [INR]) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was noted. For more detail refer to Section 10.2.1.3.

Refer to Section 7.5 if ALT or AST or bilirubin (total bilirubin) $> 2 \times \text{ULN}$.

In addition, refer to Section 10.2.3 in relation to ALT or AST $> 3 \times \text{ULN}$ in conjunction with bilirubin (total bilirubin) $> 2 \times \text{ULN}$ when a decision is made that these abnormalities in the liver function test cannot reasonably be explained by other factors.

9.1.12 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, and throughout the duration of the study, and for 4 weeks after last dose of study drug, female subjects of childbearing potential (ie, nonsterilized, premenopausal female subjects) who are sexually active must use acceptable methods of contraception.

Such subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process, and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study. During the course of the study, regular urine hCG pregnancy tests will be performed, and subjects will receive continued guidance with respect to avoiding pregnancy as part of the study procedures (Appendix A).

In addition to a negative urine hCG pregnancy at the start of the run-in period (Visit 1) and the start of the treatment period (Visit 2), subjects also must have a negative urine hCG pregnancy test at each visit throughout the study.

9.1.13 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug for the run-in period and the treatment period should be immediately discontinued.

If the pregnancy occurs during administration of study drug for the treatment period, eg, after Visit 2 or within 4 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to Emergency Reception Center for Safety Information listed in the annex.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time she became pregnant and provide details of treatment the subject received (blinded or unblinded, as applicable).

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. Postnatal evaluation will also be conducted.

9.1.14 ECG Procedure

A standard 12-lead ECG will be recorded as part of the study procedures (Appendix A). The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: normal or abnormal. The investigator (or a qualified observer at the study site) will judge if it is clinically significant.

The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QT interval, and QRS interval.

9.1.15 Pharmacogenomic Sample Collection

When sampling of whole blood for pharmacogenomic analysis occurs, every subject must sign informed consent in order to participate in the study and to collect, storage and analyze of the pharmacogenomic sample.

One 5-mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected after 2 weeks of treatment (Visit 3) from each subject in the study, into plastic tubes with K2 ethylenediamine-tetraacetic acid (EDTA).

Pharmacogenomic sample should not be collected from any subject who has received comparable bone marrow transplant or whole blood transfusion within 6 months of any sample collection.

See the separately created procedure for directions on collecting, handling, and storage of pharmacogenomic samples.

9.1.16 Serum Gastrin and Pepsinogen I/II Levels

Serum gastrin and pepsinogen I/II levels (pepsinogen I, pepsinogen II and pepsinogen I/II ratio) will be measured since serum gastrin, pepsinogen I and pepsinogen II are expected to increase after TAK-438 administration. Blood samples for measurement of serum gastrin and pepsinogen I/II levels will be collected with clinical laboratory test samples according to the study procedures (Appendix A). Blood sample will be collected under fasted condition, and sampling is recommend at the same time period each time. Serum gastrin and pepsinogen I/II levels will be measured by the central laboratory.

Disclosure of the measurement results to the sites is not reported in principle.

9.1.17 Anti-*H. pylori* Antibody Titer

Blood samples for measurement of anti-*H. pylori* antibody titer will be collected with clinical laboratory test samples according to the study procedures (Appendix A).

Anti-*H. pylori* antibody titer will be measured by the central laboratory.

9.1.18 Documentation of Subjects Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible after signing of informed consent but prior to the randomization, the investigator should complete the eCRF. The following information are to be recorded in the eCRF: the date of signing of informed consent, date of birth, sex, self-reported race, conditions at the end of run-in period (including the date of study drug discontinuation, and reasons for premature discontinuation), and occurrence of an AE. Any case of occurrence of AEs should be documented on the eCRF in detail.

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

- Death
- Adverse Event
- Screen Failure (failed inclusion criteria or did meet exclusion criteria) <specify reason>.
- Protocol deviation.
- Lost to follow-up.
- Withdrawal by subject <specify reason>.
- Study terminated by sponsor.
- Pregnancy
- Other <specify reason>.

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

As for subjects who have received the study drug for the run-in period but fail before randomization, the eCRF should include the start and completion dates of the study drug for the run-in period and history of taking acid suppressants/response after taking the acid suppressants* (refer to Section 9.1.3) in addition to the above information. Any overdose should be documented on the eCRF.

* The record of the history of taking acid suppressants/response after taking the acid suppressants is required only for those who were determined ineligible for failing to meet the inclusion criterion 9.

9.1.19 Documentation of Randomization

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

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

9.1.20 Endoscopic Assessment

The investigator, or study collaborator (physician) should perform esophagus endoscopy in accordance with the schedule of the study procedures (Appendix A). For the esophagus endoscopy, the subjects should be asked to visit the site under fasted condition. The investigator, or study collaborator (physician) should capture clear photographs of the subject's esophagus for the assessment of the modified LA Classification grade. The endoscopic photographs will be classified according to the modified LA Classification [17] shown in Table 9.c.

Barrett's mucosa is classified according to the following criteria at the start of the run-in period (Visit 1): present (less than 3 cm), absent, or unknown.

Esophageal hiatal hernia at the start of the run-in period (Visit 1) is classified into the following: present (2 cm or more), present (less than 2 cm), absent, or unknown.

The investigator (with possible assistance by a study collaborator, if necessary) will provide the sponsor with the endoscopic findings at the start of the run-in period (Visit 1) using the modified LA Classification in the form of electronic media or of attached paper to the endoscopic test report.

The Central Adjudication Committee (CAC) will be established. Further information is provided in Section 11.1.

Table 9.c The Modified LA Classification

Grade N	Normal mucosa
Grade M	Minimal changes to the mucosa, such as erythema and/or whitish turbidity
Grade A	Nonconfluent mucosal breaks < 5 mm in length
Grade B	Nonconfluent mucosal breaks \geq 5mm in length
Grade C	Confluent mucosal breaks < 75% circumferential
Grade D	Confluent mucosal breaks > 75% circumferential

[17]

A 'mucosal break' is defined as 'an area of slough or erythema with a sharp line of demarcation from adjacent normal mucosa' [23].

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study drug containers/unused medications to the site at every visit. The investigator will investigate treatment compliance using the patient diaries and record the following information on the eCRF.

- Dates of the first and last doses of the study drug for the run-in period.
- Dates of the first and last doses of the study drug for the treatment period.

If a subject is persistently noncompliant with the study drug (eg, taking less than 50% of the allocated medication for 2 successive visits), it may be appropriate to withdraw the subject from the study. All subjects should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all examinations and assessments is shown in Appendix A. All examinations and assessments should be completed at the designated time points.

9.3.1 Start of Run-in Period (Visit 1)

The following procedures will be completed at the start of the run-in period (Visit 1). Subject eligibility will be confirmed in accordance with predefined primary inclusion and exclusion criteria as described in Section 7.0 and the eligibility will be reported to the subject registration center.

- Informed consent.

- Primary inclusion criteria and exclusion criteria.
- Demographics and medical history.
- Medication history.
- History of taking acid suppressants.
- Physical examination.
- Vital signs.
- Weight and height.
- Concomitant medications.
- Concurrent medical conditions.
- Clinical laboratory tests (hematology, chemistry, urinalysis).
- Anti-*H. pylori* antibody titer.
- Pregnancy test (only female subjects with childbearing potential).
- ECG procedure.
- Provision of a patient diary, instructions on how to record, and initiate entries in the patient diary.
- QOL survey.
- Endoscopy.
- Prescription of the study drug for the run-in period (only for subjects confirmed eligible).
- Assessment of AEs.

Subjects will be instructed on when to take the first dose of study drug for the run-in period as described in Section 6.1.

The procedure for documenting subject failures (before randomization) is provided in Section 9.1.18.

9.3.2 Start of Treatment Period (Visit 2)

Subject eligibility will be confirmed in accordance with predefined secondary inclusion and exclusion criteria as described in Section 7.0 and the final eligibility will be reported to the subject registration center.

If the subject satisfies all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized as described in Section 8.2.

The following procedures will be completed at the start of the treatment period (Visit 2).

The subjects will be instructed on when to take the first dose of study drug as described in Section 6.1. The procedure for documenting subject failures before start of study drug treatment is provided in Section 9.1.18.

- Secondary inclusion criteria and exclusion criteria.
- Physical examination.
- Vital signs.
- Concomitant medications.
- Clinical laboratory tests (hematology, chemistry, urinalysis).
- Serum gastrin and pepsinogen I/II levels.
- Pregnancy test (only female subjects with childbearing potential).
- Collection, review, and provision of a patient diary.
- QOL survey.
- Randomization.
- Prescription of the study drug for the treatment period (only for subjects confirmed eligible).
- Treatment compliance during the run-in period.
- Assessment of AEs.

9.3.3 After 2 Weeks of Treatment (Visits 3)

Procedures to be completed or documented after 2 weeks of treatment (Visit 3) include:

- Physical examination.
- Vital signs.
- Concomitant medications.
- Clinical laboratory tests (hematology, chemistry, urinalysis).
- Serum gastrin and pepsinogen I/II levels.
- Blood sampling for PGx (only from subjects who have given consent to PGx measurement; ideally, blood samples for PGx are to be obtained after 2 weeks of treatment; however, blood samples obtained anytime between the start of the study drug administration for the treatment period and after 4 weeks of treatment/early termination of the study treatment are acceptable).
- Pregnancy test (only female subjects with childbearing potential).
- Collection, review, and provision of a patient diary.
- QOL survey.

- Prescription of the study drug for the treatment period (only for subjects confirmed eligible).
- Treatment compliance during the treatment period.
- Assessment of AEs.

9.3.4 After 4 Weeks of Treatment (Visit 4)

Procedures to be completed or documented after 4 weeks of treatment (Visit 4) include:

- Physical examination.
- Vital signs.
- Concomitant medications.
- Clinical laboratory tests (hematology, chemistry, urinalysis).
- Serum gastrin and pepsinogen I/II levels.
- Pregnancy test (only female subjects with childbearing potential).
- ECG procedure.
- Collection and review of a patient diary.
- QOL survey.
- Treatment compliance during the treatment period.
- Assessment of AEs.

Study completion should be reported to the subject registration center.

For all subjects receiving study drug, the investigator must complete the Subject Status eCRF page.

9.3.5 Early Termination

Early termination should be reported to the subject registration center. Procedures to be completed or documented at early termination include:

- Physical examination.
- Vital signs.
- Concomitant medications.
- Clinical laboratory tests (hematology, chemistry, urinalysis).
- Serum gastrin and pepsinogen I/II levels.
- Blood sampling for PGx (only from subjects who have given consent to PGx measurements but have not yet finished blood sampling).
- Pregnancy test (only female subjects with childbearing potential).

- ECG procedure.
- Collection and review of a patient diary.
- QOL survey.
- Treatment compliance.
- Assessment of AEs.

For all subjects receiving study drug, the investigator must complete the Subject Status eCRF page.

9.3.6 Post Study Care

The study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

9.4 Biological Sample Retention and Destruction

Whole blood 5-mL samples for PGx analysis will be stored frozen at PPD (see the procedure).

The collected samples will be retained for no longer than 15 years after completion of the TAK-438 study or until the drug development of TAK-438 is no longer actively pursued by the sponsor.

When subjects request disposal of a stored sample during the retention period, the site will ask PPD to destroy the sample via the sponsor according to the procedure. PPD will destroy the sample in accordance with the procedure, and notify the site and sponsor. However, any samples should not be destroyed if all the documents (including medical records) have been destroyed which could identify the subject and it is impossible to link the sample to the subject.

Even if the sample can be linked to the subject, when pharmacogenomic investigation has been conducted, the remaining samples will be destroyed and the results of pharmacogenomic investigation of an anonymized subject will be retained by the sponsor.

The sponsor will build an appropriate management system required for protection of the subject's personal information, define standards for collecting store and destruction of samples, and prepare appropriate procedures.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with this treatment or study participation.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the study participation whether or not it is considered related to the drug or study procedures.

10.1.2 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions :

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

Worsening of AEs:

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

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE that are not related to starting the study drug or changing in the dose or regimen, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study:

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

Table 10.a Takeda Medically Significant AE List

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

10.1.4 AEs of Special Interest

An AE of Special Interest (treatment-emergent only, serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in Section 10.2.1.3 as to how and when they should be reported to the sponsor.

In this study, hepatic function abnormality*, *clostridium difficile* enteric infection, and hypersensitivity* are to be collected as AEs of special interest. Refer to Section 10.2.1.3 for criteria for AEs of special interest reporting.

*: Although both hepatic function abnormality and hypersensitivity are identified as risks of vonoprazan, these are treated as AEs of special interest in order to collect detail informations.

10.1.5 Severity of AEs

The different categories of severity are characterized as follows:

- Mild: The event is transient and easily tolerated by the subject.
- Moderate: The event causes the subject discomfort and interrupts the subject's usual activities.
- Severe: The event causes considerable interference with the subject's usual activities.

10.1.6 Causality of AEs to Study Drug(s)

The causality of each AE to study drug(s) will be assessed using the following categories:

- Related: An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug is at least a reasonable possibility, i.e., the relationship cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
- Not related: An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.7 Causality of AEs to Study Procedures

The causality of each AE to study procedures will be assessed.

The causality should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the causality should be assessed as Not Related.

10.1.8 Start Date

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

The start date of AEs will be determined using the following criteria;

AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when laboratory findings showed previous findings or the onset time can be estimated.
Worsening of concurrent medical conditions or any signs/symptoms/diseases before treatment from signing of informed consent	The date that a worsening of disease and symptom was noted first by the subject and/or the investigator should be recorded.
The first examination after signing of informed consent or the examination right before the start of the study drug showed abnormal findings.	The date of examination when an abnormal value that was judged to be clinically significant was noted should be recorded.

The first examination after signing of informed consent or the examination right before the study drug showed abnormal findings, and the subsequent examinations showed worsening of the symptoms.

The date of examination when apparent elevation, reduction, increase or decrease was confirmed in medical judgment according to the trends in laboratory values should be recorded.

10.1.9 End Date

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

10.1.10 Pattern of Adverse Event

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

10.1.11 Action Taken with Study Treatment

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE, the AE that occurred before the study drug administration.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Drug Interrupted – the dose was interrupted due to the particular AE.

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining “Not recovered/not resolved”.

- Recovered/Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of AEs will commence from the time the subject signs the informed consent. Routine collection of AEs will continue until Visit 4. AEs occurring after the first dose of study drug for the run-in period and before start of study drug administration for the treatment period are defined as AEs during the run-in period, and AEs occurring after start of study drug administration for the treatment period until end of the treatment period are defined as AEs during the treatment period.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious AE that occurs prior to the first exposure to study drug must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious AEs that occur prior to the first exposure to study drug, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

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

1. Event term.
2. Start and end date.
3. Pattern.
4. Severity.
5. Investigator's opinion of the causality between the event and administration of study drug(s).

6. Investigator's opinion of the causality to study procedure(s), including the details of the suspected procedure.
7. Action taken with study treatment.
8. Outcome of event.
9. Seriousness.
10. After administration of study drug.
11. Treatment emergent.

Patient diary/QOL survey form will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the subject for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.1.3 AEs of Special Interest Reporting

If this AE of special interest, which occurs during the treatment period or the follow-up period, is considered to be clinically significant based on the criteria below, it should be reported to the safety information center (contact information is described in the annex) immediately or within 1 business day of first onset or subject's notification of the event. Hepatic Function Abnormality Form, *Clostridium Difficile* enteric infection Form, Hypersensitivity Form or an SAE Form should be completed, signed and/or sealed by the principal investigator, and reported to appropriate personnel in the annex within 10 business days. In case if AE may be drug-induced liver function test abnormalities possibly leading to an SAE or a serious hepatic disorder, refer to Section 10.2.2.

(1) Hepatic Function Abnormality

In the clinical studies and postmarketing safety data of TAK-438, hepatic function abnormalities have been identified as a risk associated with TAK-438. Thus, hepatic function abnormalities are treated as AEs of special interest in this study in order to collect detail information.

Any hepatic function abnormality is to be reported based on the following criteria:

- ALT or AST > 2×ULN.
- bilirubin (total bilirubin) > 2×ULN.

A Hepatic Function Abnormality Form should include relevant subject details, possible alternative etiologies (eg, acute viral hepatitis A or B, other acute liver disease, medical history, concurrent medical conditions), clinical course and procedures taken for the event. For re-examination, refer to Section 9.1.11.

(2) Clostridium Difficile Enteric Infection

As the precautionary statement regarding *clostridium difficile* enteric infection is provided in the package inserts of PPIs which include TAK-438, AEs related to *clostridium difficile* enteric infection are to be collected as AEs of special interest.

The following AEs are defined as *clostridium difficile* enteric infection:

- Clostridial infection, clostridium bacteraemia, clostridium colitis, clostridium difficile colitis, clostridium difficile infection, clostridium difficile sepsis, clostridium test positive, gastroenteritis clostridial, or pseudomembranous colitis, according to AEs coded by Preferred Term (PT) in Medical Dictionary for Regulatory Activities (MedDRA)/Version 19.0.

Clostridium Difficile Enteric Infection Form should include details of the subject, possible factors other than the study drug (eg, concomitant use of antibacterials or immunosuppressive agents, medical history, concurrent medical conditions), clinical course and procedures taken for the event.

(3) Hypersensitivity

Since hypersensitivity events have been reported, and which the causality to TAK-438 can not be ruled out. Any hypersensitivity event is to be reported based on the following criterion:

- Hypersensitivity-related events leading to study discontinuation (eg, anaphylaxis, angioedema, erythema multiforme, urticarial, rash).

Hypersensitivity Form should include the details of the subject, possible factors other than the study drug, clinical course and procedures taken for the event.

The AE of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure.

An SAE should be reported to the Emergency Reception Center for Safety Information (contact information is described in the annex) within 1 business day of first onset or subject's notification of the event. The principal investigator should complete the SAE form within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the study drug(s)
- Causality assessment.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST $> 3 \times \text{ULN}$ and bilirubin (total bilirubin) $> 2 \times \text{ULN}$ for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.11 must also be performed.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should prepare an SAE form and fax it immediately. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs/the head of the study site, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

The Central Adjudication Committee (CAC) will be established in this study.

11.1 Central Adjudication Committee

The CAC will comprise independent experts with experience and training appropriate for reviews of the clinical endpoints. In response to the sponsor's request, the CAC will review all endoscopic assessments reported by the sites in a consistent manner.

The CAC will review endoscopic assessments at the start of the run-in period (Visit 1) reported by investigators, and the CAC review report will be documented. The CAC will submit the documented review report to the sponsor.

The sponsor will provide the site with the results of CAC review. Even if there are inconsistencies between the assessment of the investigator and the CAC review, the investigator should take into account the CAC report as a reference, but is not required to change the original assessment, in principle.

The sponsor should prepare the CAC Charter and the manual for the CAC secretariat prior to the start of the CAC review. The CAC Charter will define the purposes and the responsibilities of the committee.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs and medical history including concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic)

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

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

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

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

The following data will not be recorded into the eCRFs:

- Clinical laboratory test results measured at the central laboratory.
- Measurements of anti-*H. pylori* antibody titer.
- Measurements of serum gastrin and pepsinogen I/II levels.
- Endoscopic assessments provided by the CAC.

After the lock of the clinical study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, the investigator and the head of the institution are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the institution should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the clinical study.

In addition, the investigator and the head of the institution should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

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

Prior to the database lock, the sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, consulting a medical expert as needed, and then finalize the SAP.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group based on all the randomized subjects.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Endpoint and Analytical Methods

Primary Endpoint

Heartburn during the treatment period

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

Analytical Methods

(1) Primary Analyses

The primary analyses for primary endpoint will be performed based on the FAS.

1. Primary variable

Descriptive statistics will be used to summarize the proportion of days without symptoms during the treatment period 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.

2. Secondary variable

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).

3. Additional variable

The same analysis in Section 13.1.3.1(1) will be performed for mean severity of symptoms over the treatment period.

(2) Secondary Analyses

For sensitivity analysis, the same analyses to those conducted in Section 13.1.3.1(1) will be performed on the per-protocol set (PPS) to evaluate the stability of the results.

13.1.3.2 Secondary Endpoints and Analytical Methods

Secondary Endpoints

- 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 (PPIs, H₂RAs, or other agents [anticholinergics or anti-gastrin drugs]) in subjects who had a medication history of any of these drugs.

Analytical Methods

Analyses for secondary endpoint will be performed similarly Section 13.1.3.1(1) on the FAS.

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.

Response (improved or not improved) at Week 2 will be assessed in accordance with the following criteria.

Criteria 1:

Improved: the subject experiences heartburn on less than 2 days of the 7 days prior to Week 2 (Day 8 through Day 14).

Not improved: the subject experiences heartburn on 2 days or more of the 7 days prior to Week 2 (Day 8 through Day 14).

Criteria 2:

Improved: the proportion of days the subject experiences heartburn during the treatment period up to Week 2 (Day 14) is lower than that during the run-in period.

Not improved: the proportion of days the subject experiences heartburn during the treatment period up to Week 2 (Day 14) is equal to or larger than that during the run-in period.

Subjects are to be stratified by the following response to acid suppressants (exclude naïve subjects from this analysis):

Improved: those whose heartburn has been resolved, or whose heartburn has not been resolved but relieved.

Not improved: those whose heartburn has remained unchanged, or whose heartburn has been worsened.

13.1.3.3 Additional Efficacy Endpoints and Analytical Methods

Additional Efficacy Endpoints

- QOL.
- Regurgitation during the treatment period.

Analytical Methods

1. QOL

The following analyses will be performed by treatment group:

- 1) Summary statistics at each visit
 - 2) 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
- ##### 2. Regurgitation during the treatment period

The same analysis as the primary analysis described in Sections 13.1.3.1(1) will be performed using the FAS.

13.1.3.4 Data Conversion Method and Handling of Missing Data

Details will be described in the SAP.

13.1.3.5 Significance Level and Confidence Coefficient

- The significance level: 5% (2-sided test)
- Confidence coefficient: 95% (2-sided estimation)

13.1.4 Safety Analysis

The following analyses will be performed on the safety analysis set.

13.1.4.1 TEAE

A TEAE is defined as an AE occurring after receiving the study drug for the treatment period or an aggravation of an existing complication.

TEAEs will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The incidences of TEAEs will be summarized by treatment group.

- All TEAEs
- TEAEs by intensity
- TEAEs by period
- Drug-related TEAEs
- Drug-related TEAEs by intensity
- TEAEs leading to study drug discontinuation
- Serious TEAEs

In the tabulation of TEAE frequency, if a subject will have more than 1 episode of the same event, the subject should be counted only once for that event. If a subject will have more than 1 episode of the same PT, the subject should be counted only once for that PT. If a subject will have more than 1 TEAE within a SOC, the subject should be counted only once for that SOC. In the tabulation of TEAE frequency by intensity, a subject should be counted only once using the highest severity for either PT or SOC.

13.1.4.2 Clinical Laboratory Test Values, ECGs, Vital Signs, Serum Gastrin and Pepsinogen I/II Levels

For continuous variables, the observed values and the changes from the start of the study drug for the treatment period will be summarized by treatment group for each visit using descriptive statistics.

For categorical variables, shift tables (eg, assessment of laboratory measurements and qualitative test results) in each category before and after treatment for the treatment period post-baseline visit will be provided for each treatment group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB.

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

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reasons, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations. Significant deviations should be recorded on the eCRFs and then confirmed by the sponsor or its designee. Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB Approval

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

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

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

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

Regarding pharmacogenomic investigation using collected and stored specimens, analysis will be carried out at the time when detail is determined. The sponsor will create a research protocol for pharmacogenomics investigations.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the informed consent form. The informed consent form must be approved by both the IRB and the sponsor prior to use.

The informed consent form must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, determines he or she will participate in the study, then the informed consent form must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form shall be given to the subject.

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

The informed consent form for pharmacogenomic sample collection in the clinical study of TAK-438 will be used to explain pharmacogenomic analysis to only subjects who provided consent to study participation. Pharmacogenomic samples are to be collected from only subjects who provided consent to both study participation and pharmacogenomic sampling.

When subjects request disposal of a stored sample, follow the procedures described in Section 9.4.

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and other publicly accessible websites before start of study, as defined in Takeda Policy/Standard.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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