Title: A Randomized, Double-Blind, Proof-of-Concept, Phase 2 Study to Evaluate the Efficacy and Safety of Once Daily Oral Vonoprazan 20 mg or Vonoprazan 40 mg Compared to Esomeprazole 40 mg for the Treatment of Subjects With Symptomatic Gastro-Esophageal Reflux Disease Who have a Partial Response Following Treatment with a High Dose of Proton Pump Inhibitor

NCT Number: NCT02743949

Protocol Approve Date: 29 March 2016

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL AMENDMENT

A Randomized, Double-Blind, Proof-of-Concept, Phase 2 Study to Evaluate the Efficacy and Safety of Once Daily Oral Vonoprazan 20 mg or Vonoprazan 40 mg Compared to Esomeprazole 40 mg for the Treatment of Subjects With Symptomatic Gastro-Esophageal Reflux Disease Who have a Partial Response Following Treatment with a High Dose of Proton Pump Inhibitor

Comparison of Vonoprazan to Esomeprazole in Subjects with Symptomatic GERD Who Responded Partially to a High Dose of PPI

Sponsor: **Takeda Development Centre Europe Ltd.**
61 Aldwych
London, WC2B 4AE, UK

Study Number: **Vonoprazan-2001**

IND Number: NA **EudraCT Number:** 2015-001154-14

Compound: Vonoprazan (TAK-438)

Date: 29 March 2016 **Amendment Number:** 02

Amendment History:

Date	Amendment Number	Amendment Type	Region
25 November 2015	Initial Protocol	Not applicable	Global*
15 February 2016	01	Non-substantial amendment	Global*
29 March 2016	02	Non-substantial amendment	Global*

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

TDC sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

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

Contact Type/Role	
Serious adverse event and pregnancy reporting	PPD
Medical Monitor (medical advice on protocol and compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

The signature of the responsible Takeda medical officer and other signatories, as applicable can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

1.3 Protocol Amendment 02 Summary of Changes

This document describes the changes in reference to the Protocol Incorporating Amendment No. 02.

The primary purpose of this amendment is to update the protocol to provide minor changes and clarification of study procedures.

Full details on changes of text are given in Appendix G. The following is a summary of the changes made in the amendment:

1. Addition of additional endpoint of heartburn. This analysis has been included as it includes components of both reduction in the number as well as severity of symptoms.
2. Clarification of inclusion criteria No 5 to include patients who have predominant heartburn symptoms in the presence of regurgitation. This confirms the patient has GERD and also has the appropriate symptoms to perform the required proposed data analysis
3. Correction of schedule of Subject reported Outcome Questionnaires(PSQI and PGIC).
4. Inclusion of blind reporting of serum gastrin and pepsinogen I and II values during double blind treatment period to avoid potential unblinding.
5. Clarification of barrier methods for contraception.
6. Clarification of unscheduled visits if necessary.
7. Correction of the condition of storage and shipping of CYP2C19 DNA samples.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Centre Europe Ltd.</td><td colspan="2">Compound:
Vonoprazan (TAK-438)</td></tr>
<tr><td>Title of Protocol:
A Randomized, Double-Blind, Proof-of-Concept, Phase 2 Study to Evaluate the Efficacy and Safety of Once Daily Oral Vonoprazan 20 mg or Vonoprazan 40 mg Compared to Esomeprazole 40 mg for the Treatment of Subjects With Symptomatic Gastro-Esophageal Reflux Disease Who have a Partial Response Following Treatment with a High Dose of Proton Pump Inhibitor</td><td>IND No.: N/A</td><td>EudraCT No.:
2015-001154-14</td></tr>
<tr><td colspan="2">Study Number: Vonoprazan-2001</td><td colspan="2">Phase: 2</td></tr>
<tr><td colspan="4">Study Design:
Vonoprazan-2001 is a Phase 2 proof-of-concept (POC) study to compare vonoprazan 20 mg or 40 mg once daily (QD) with esomeprazole 40 mg QD in subjects who have a history of predominant heartburn symptoms in the presence of regurgitation that are troublesome despite an adequate course of proton pump inhibitor (PPI) treatment and who are then confirmed to have a partial response to a 4-week treatment course with esomeprazole 40 mg QD.</td></tr>
<tr><td colspan="4">Primary Objectives:
To determine the effect of vonoprazan compared to esomeprazole for preventing heartburn symptoms over a 4-week treatment period in subjects who have a partial response to treatment with esomeprazole</td></tr>
<tr><td colspan="4">Secondary Objectives:
To determine the effect of vonoprazan treatment on sustained resolution of heartburn symptoms over a 4-week treatment period (at least one 7-day symptom-free period)</td></tr>
<tr><td colspan="4">Subject Population: Subjects aged 18 years or older who have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study and of not responding fully to their PPI treatment (at least 8 weeks of predominant heartburn symptoms in the presence of regurgitation that are troublesome after treatment at the standard doses of PPI). Subjects must also have a partial response to treatment with a high dose of esomeprazole 40 mg QD (defined as having heartburn on 2 to 5 days and regurgitation on at least one day of the last week (Week 4) of a 4 week PPI Assessment Period with esomeprazole 40 mg and an increase of at least 2 symptom days of heartburn in the last week of a 2 week Off-PPI Assessment Period (4 to 7 symptom days) and at least one symptom day with regurgitation compared with the last week of the PPI Assessment Period.</td></tr>
<tr><td colspan="2">Number of Subjects:
Estimated total: 213 randomized
Per treatment group: Vonoprazan 40 mg:Vonoprazan 20 mg: Esomeprazole 40 mg =1:1:1 (71 subjects in each treatment arm)</td><td colspan="2">Number of Sites:
Estimated total: Up to 50 sites in Europe</td></tr>
<tr><td colspan="2">Dose Level(s):
Vonoprazan 20 mg QD
Vonoprazan 40 mg QD
Esomeprazole 40 mg QD</td><td colspan="2">Route of Administration:
Oral</td></tr>
</table>

Duration of Treatment:	**Period of Evaluation:**
4 weeks double-blind treatment	Approximate total study duration: 12 weeks The study consists of 3 periods: a 7-week Run-in period (initial 1 week screen period and a 6-week single-blind Run-in), a 4-week double blind Treatment Period, and a 1-week Safety Follow-up.

Main Criteria for Inclusion:

Subjects will be eligible for participation in the study if they; have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study; have a history of predominant heartburn symptoms in the presence of regurgitation that are troublesome despite an adequate course of PPI treatment; continue to have symptoms of heartburn (and regurgitation) following 4 weeks treatment with a high dose of esomeprazole 40 mg QD during the Run-in Period; have symptoms of heartburn which increases following a 2-week Washout Period in the presence of regurgitation prior to randomization. Patients with mild (LA grade A) esophagitis are permitted to enter the study.

Main Criteria for Exclusion:

Subjects who have hypersensitivity to vonoprazan or related compounds; a history or any coexisting diseases affecting the esophagus; 'alarm features' in symptomatology pointing to a possible malignant disease of the GI tract; current or historical chest pain due to cardiac disease; a history of surgical treatment for GERD; dilation of an esophageal stricture or gastric or duodenal surgery. Subjects who have a documented history of functional dyspepsia or irritable bowel syndrome or other gastrointestinal diseases which are not acid-related, and therefore, are nonresponsive to gastric acid-blocking treatment. Subjects who have levels of AST, ALT or total bilirubin > ULN. In addition, the following subjects should be excluded: those who have a documented history of familial adenomatous polyposis, active gastric or duodenal ulcers or acute upper gastrointestinal hemorrhage within 30 days prior to screening and any other co-morbidities or any significant results from physical examinations, or clinical laboratory results as deemed by the investigator.

Main Criteria for Evaluation and Analyses:

The primary endpoint for this study is the percentage of heartburn free 24 hour periods (day and night) during 4 weeks of randomized double-blind treatment.

The secondary endpoint for this study is the proportion of subjects with ≥1 sustained resolution of heartburn (defined as ≥7 consecutive days without both daytime and nighttime heartburn any time during the 4-week randomized double-blind Treatment Period).

Statistical Considerations:

Analysis Sets:

Full Analysis Set (FAS): This analysis set will include all subjects randomized. Subjects in this set will be analyzed according to the original randomization.

Per Protocol Set (PPS): This analysis set is a subset of the FAS. The PPS consists of all subjects who do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects from the PPS dataset will be made prior to the unblinding of the study. Analyses using the PPS may be provided as a sensitivity analysis.

Safety Set: This analysis set will include all subjects who have received at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment they actually received.

Efficacy Analysis:

For the assessment of the percentage of heartburn-free days, the Wilcoxon-Mann-Whitney Odds estimator with the 97.5% CI and the Wilcoxon rank-sum test will be used at the 2.5% level of significance for each vonoprazan treatment comparison with esomeprazole to control for multiplicity. The Wilcoxon rank-sum test will be used because data from a previous vonoprazan trial (TAK-438/CCT-201) showed that the data is unlikely to be normally distributed.

To assess the secondary endpoint, the proportion of subjects with ≥1 sustained resolution of heartburn, a Pearson Chi-square test will be used at the 2.5% level of significance for each vonoprazan treatment comparison with esomeprazole to control for multiplicity. All subjects with missing data for determination of endpoint status will be considered as a non-responder in the analysis.

Multiplicity will not be adjusted across the remaining additional endpoints.

The time to sustained resolution of heartburn is defined as the time from the first dose of study drug to the first day of the 7 consecutive days free of heartburn and will be analyzed using a product-limit survival analysis with treatment group as the stratum. The survivor function will be estimated using the Kaplan-Meier method and the survivor functions between vonoprazan and esomeprazole treatment groups will be compared using log-rank tests. The median time to sustained resolution of heartburn from the survivor function will be presented by treatment group, along with the 95% confidence interval.

If the assumptions underlying planned inferential methods are not adequately met, methods will be amended as needed for appropriate analysis.

Other analysis

All data collected in this study will, where applicable, be summarized by treatment regimen using descriptive statistics. For continuous variables mean values, standard deviations, median and lower and upper percentiles will be calculated. For categorical variables frequencies and percent will be calculated.

Adverse events (AEs) will be summarized using the safety analysis set. Adverse events collected during the trial will be summarized by System Organ Class, treatment regimen and stage of trial (eg, screening and treatment emergent) and reported.

Sample Size Justification:

A total of 213 subjects (71 patients per treatment arm) who have a partial response to treatment with a high dose of esomeprazole (40 mg QD for 4 weeks) are planned to be randomized into the study with the expectation that 180 subjects will complete the study (assuming a 15% drop out rate). The sample size of 60 subjects completing the study per treatment group will provide at least 80% power at the 2-sided 0.025 level of significance to detect an absolute 20% difference between each Vonoprazan dose and esomeprazole in the percentage of heartburn-free 24 hour periods (day and night) during 4 weeks of randomized double-blind treatment. The pooled standard deviation was estimated as 33.61 from prior Dexlansoprazole studies.

With the expectation that 180 subjects will complete the study, the secondary endpoint; proportion of subjects with ≥1 sustained resolution of heartburn (defined as ≥7 consecutive days without both daytime and nighttime heartburn any time during the 4-week randomized double-blind Treatment Period) has 80% power at the 2-sided 0.025 level of significance to detect an absolute 30% difference between each vonoprazan dose and esomeprazole, assuming a response rate of 33% for esomeprazole.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory coordinating investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CK/CPK	Creatine Phosphokinase
Cl	Chloride
C_{max}	Maximum observed plasma concentration
CNS	Central nerve system
COX-2	Cyclooxygenase 2
eCRF	Electronic case report form
CRO	contract research organization
CSR	clinical study report
CYP	Cytochrome P450 enzyme
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
EDC	electronic data capture
EE	Erosive esophagitis
EM	Extensive metabolizers
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCDT	Global Clinical Development Team
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GERD	gastro-esophageal reflux disease
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
H. pylori	Helicobacter pylori
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IEC	independent ethics committee
INN	International Nonproprietary Name

INR	international normalized ratio
IRB	institutional review board
IWRS	interactive web response system
LA classification	Los Angeles classification
LDH	Lactate dehydrogenase
LFT	liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
NERD	Non-erosive reflux disease
NSAIDs	Non-steroidal anti-inflammatory drugs
P-CAB	Potassium-competitive acid blockers
PGx	Pharmacogenomics
pH4 HTR	pH4 holding time ratio
PM	Poor metabolizers
PPI	Proton Pump Inhibitor
PPS	Per-protocol analysis set
PTE	pretreatment event
QD	Once daily
QTc	corrected QT interval
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
SNRI	selective norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor.
UGI	upper gastrointestinal
ULN	upper limit of normal
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

Failure of proton pump inhibitor (PPI) treatment is very common, affecting approximately 30% of gastro-esophageal reflux disease (GERD) patients [1] and PPI failure is the most common presentation of GERD in gastrointestinal practice [2]. Most of the GERD patients who are not responsive to PPIs have non-erosive reflux disease (NERD), primarily due to their relatively large numbers in the GERD population (up to 70%) and low response rate to once daily (QD) PPI [2]. Bytzer *et al* reported that in a *post hoc* analysis of 5796 patients, partial response to PPI therapy occurred in 14% to 20% of GERD patients, more commonly in NERD than in reflux esophagitis [3] and El-Serag *et al* reported that 17–32% of the patients assessed in interventional primary care trials continue to experience reflux symptoms despite PPI treatment [4]. More recently (2011-2012), a survey was performed in Asia-Pacific (GERD in Asia Pacific Survey, GAPS) [5]. A total of 450 patients with GERD participated in the GAPS. Although the respondents generally complied with treatment, response to therapy was only partially successful. Most respondents indicated that PPIs eliminated pain (72%), took effect within 30 minutes (76%), provided sustained relief (73%), and provided nocturnal relief (77%). However, 45% of respondents reported limited improvement in nocturnal symptoms and 49% continued to take adjunctive therapy to manage their symptoms. After treatment, respondents' 'well-being' had improved. However, GERD still had a negative impact on well-being for 76% of respondents after treatment, compared with 94% before treatment. Asian patients reported a negative impact of GERD on their daily lives. Many respondents continued to experience symptoms despite reporting good compliance with PPI therapy, emphasizing the shortcomings of currently available therapy for GERD.

The European Medicines Agency (EMA) has recognized partial response to a PPI as a medical issue. The 2011 revision of the "Guideline on the evaluation of drugs for the treatment of Gastro-oesophageal reflux disease" includes recommendations on how to assess PPI partial responders (patients with an insufficient response to a PPI) [6]. Although it is likely that the majority of patients entered into the proposed study will be NERD patients [2], mild (LA grade A) erosive esophagitis (EE) patients will also be included as this is accepted in the EMA guidelines when the indication is for the treatment of symptomatic GERD [6].

Varying underlying mechanisms have been proposed for a partial response to PPI treatment including residual acid, weakly acidic reflux, and weakly alkaline reflux in GERD patients [7]. This may be due to the pharmacodynamic profile of PPIs as therapeutic oral doses of some PPIs have a slow, cumulative onset of effect, and achieve maximal acid suppression only after 4 to 5 days of daily dosing [8].

Vonoprazan is a novel, orally active small-molecule potassium-competitive acid blocker (PCAB). Vonoprazan at doses ≥20 mg has been shown in both single and multiple repeat-dosing studies to have a rapid onset of action after the first dose and near maximal effect on pH holding time within 24 hours of dosing, which is maintained with chronic dosing [9].

Phase 2 clinical data in Japanese subjects with EE demonstrated that vonoprazan was effective at healing EE after 4 weeks of treatment and was non-inferior to lansoprazole 30 mg. In addition, EE healing rates with the higher doses of vonoprazan (20 and 40 mg) were higher than lansoprazole 30 mg at Week 2 and higher for more severe grades of EE at Week 4 [8]. Recently, vonoprazan at a dose of 20 mg has been shown in large phase 3 studies to be effective for the treatment of erosive EE [10], maintenance of EE healing [11], Gastric and Duodenal ulcer treatment [data on file], prevention of aspirin-induced and non-steroidal anti-inflammatory-induced peptic ulcers [12.13] and the eradication of *H pylori* in conjunction with antibiotics [14].

An extensive pre-clinical program has been conducted with vonoprazan including PK and PD studies in rats and dogs as well as single/repeat-dose toxicology studies, genotoxicity studies, carcinogenicity studies (rata/mice) and reproductive toxicity studies (rats and rabbits) [15].

In addition, the safety of vonoprazan has been closely monitored in an extensive clinical program. In 14 completed phase 3 studies conducted in Japan across multiple indications, 3397 patients were exposed to vonoprazan 5 to 40 mg once daily (QD) for up to 104 weeks (actual maximum exposure: 684 days). Vonoprazan treatment was generally well tolerated, with a similar safety profile to that of lansoprazole. Incidences of drug-related TEAEs were similar between the vonoprazan and lansoprazole treatment groups [15].

In phase 3 clinical studies with vonoprazan, a dose dependent increase of mean levels of serum gastrin to vonoprazan was observed and these elevations in serum gastrin were shown to be higher compared with lansoprazole. Changes in serum gastrin did not translate to gastric mucosal changes as evidenced by biopsies performed in EE studies of up to 52 weeks duration.

There was no pre-clinical safety data and nothing in the safety/tolerability profile observed to date that precludes continued clinical investigation of vonoprazan. The overall risk: benefit remains positive in both non-Japanese and Japanese healthy subjects and in Japanese patients with acid-related diseases. Non-Japanese patients are currently being recruited into EE healing/maintenance studies in a number of countries outside Japan. In addition, Takeda received approval for vonoprazan in Japan for the treatment of acid-related diseases in December 2014. Vonoprazan (TAKECAB®) is currently available in 2 dose strengths of 10 and 20 mg, as film-coated tablets, for oral dosing. The indications approved are as follows: treatment of gastric and duodenal ulcer; reflux esophagitis; prevention of ulcer recurrence during low-dose aspirin or NSAID administration and as an adjunct to *H pylori* eradication.

Agents that can increase gastric pH faster, to a greater extent, and for longer than is achievable with PPIs may offer a clinical advantage for the treatment of patients who have a partial response to PPIs and still have GERD symptoms after treatment with a PPI.

Vonoprazan-2001 is a Phase 2 proof-of-concept (POC) study comparing vonoprazan with esomeprazole in subjects who have a history of persistent heartburn and regurgitation GERD symptoms despite an adequate course of PPI treatment and who are then confirmed to have a partial response to a 4-week treatment course with esomeprazole 40 mg QD[16,17]. As vonoprazan is a strong gastric acid inhibitor, it is considered that esomeprazole 40 mg, which is

commonly used in patients not responding to their initial dose of PPI, is an appropriate comparator for this indication.

4.2 Rationale for the Proposed Study

Despite PPI treatment with an adapted dosing regimen, defined as use outside the approved labels, there is a significant patient population who do not achieve adequate symptom relief.

Upon once daily PPI treatment, it has been observed that the majority of GERD patients (70–75%) also have nighttime heartburn at least once a week and approximately 40% of these individuals reported that nighttime heartburn disrupted their sleep [18]. It is therefore possible that once daily PPI use may not alleviate all of the nighttime symptoms experienced by GERD patients.

Varying underlying mechanisms have been proposed for a partial response to PPI treatment, including their short duration of pharmacological activity [19], which leaves GERD patients exposed to residual acid and increase their susceptibility to weakly acidic reflux, and weakly alkaline reflux [7]. This may be due to the PD profile of PPIs, as therapeutic oral doses of some PPIs have a short half life (1–2 hours) and require an intermediate complex formation prior to acting on the parietal cells. Consequently, these PPIs have a slow, cumulative onset of effect, and achieve maximal acid suppression only after 4–5 days of daily dosing [8].

Unlike PPIs, Vonoprazan has a long-half-life (9 hours) and does not require intermediate complex formation, thus achieving a faster onset of action with greater duration of effect to control both daytime and nighttime symptoms [15].

This study is therefore designed to test the hypothesis that the fast onset, potency and long duration of action of Vonoprazan will provide superior symptom control compared with esomeprazole, during both daytime and nighttime, in a population of patients with a partial acid-related symptom response to a PPI.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

To determine the effect of vonoprazan compared to esomeprazole for preventing heartburn symptoms over a 4-week treatment period in subjects who have a partial response to treatment with esomeprazole.

5.1.2 Secondary Objectives

To determine the effect of vonoprazan treatment on sustained resolution of heartburn symptoms over a 4 week treatment period (at least one 7-day symptom-free period).

5.1.3 Additional Objectives

- To determine the effect of vonoprazan compared with esomeprazole on GERD-related endpoints, including:
  - Preventing heartburn at night over a 4 week treatment period.
  - Sustained resolution of heartburn during the final week of treatment.
  - Preventing regurgitation during 24-hour periods, over a 4 week treatment period.
  - Preventing regurgitation at night over a 4 week treatment period.
  - Preventing heartburn and/or regurgitation during 24-hour periods over a 4 week treatment period.
  - Complete prevention of regurgitation (response rate) during the final week of treatment.
  - Evaluation of the effect of vonoprazan on the use of rescue medication over 4 weeks of treatment.
  - Evaluation of the effect of vonoprazan on GERD quality of sleep over 4 weeks of treatment.
  - Evaluation of the effect of vonoprazan on Health Related Quality of Life (HRQL) over 4 weeks of treatment.
- To evaluate the pharmacokinetics of vonoprazan in patients.
- To determine the safety and tolerability of vonoprazan in this population.
- To evaluate the pharmacokinetics and clinical efficacy of vonoprazan in patients identified as CYP2C19 poor or extensive metabolizers (PM/EM).
- CCI [redacted]

CCI

5.2 Endpoints

5.2.1 Primary Endpoints

- Percentage of heartburn-free 24 hour periods (day and night) during 4 weeks of randomized double-blind treatment.

5.2.2 Secondary Endpoints

- Proportion of subjects with ≥1 sustained resolution of heartburn (defined as ≥7 consecutive days without both daytime and nighttime heartburn any time during the 4-week randomized double-blind Treatment Period).

5.2.3 Additional Endpoints

Heartburn Endpoint

- Change from baseline in percentage of heartburn-free 24 hour periods (day and night) during 4 weeks of randomized double-blind treatment, where baseline is defined as the 4 weeks run-in period on esomeprazole.
- Change from baseline in proportion of subjects with ≥1 sustained resolution of heartburn, where baseline is defined as the 4 weeks run-in period on esomeprazole
- Percentage of heartburn-free nights during 4 weeks of randomized double-blind treatment.
- Percentage of heartburn-free days after 4 weeks of randomized double-blind treatment.
- Proportion of patients with no nighttime heartburn symptoms during the last week of treatment.
- Proportion of patients with no daytime heartburn symptoms during the last week of treatment.
- Proportion of patients with no daytime and nighttime heartburn symptoms during the last week of treatment.
- Percentage of subjects with ≥80% heartburn free days and nights during 4 weeks of randomized double-blind treatment.
- Percentage of subjects with ≥80% heartburn free nights during 4 weeks of randomized double-blind treatment.
- Percentage of subjects with ≥80% heartburn free days during 4 weeks of randomized double-blind treatment.

- Percentage of heartburn free 24 hour periods (day and night) during weeks 1, 2 and week 3 of randomized double-blind treatment.
- Time to first sustained resolution (defined as 7 consecutive days without daytime and nighttime heartburn).
- Proportion of subjects who achieve sustained resolution of heartburn (defined as ≥7 consecutive days without daytime and nighttime heartburn) with an onset within 3 days of starting randomized double-blind treatment.
- Proportion of subjects with resolution of symptoms with an onset within 3 days of starting randomized double-blind treatment and continuing out to the end of week 2 and end of week 4.
- Maintenance of heartburn-free period – duration of heartburn symptom-free days and nights (24-hour periods) following the first 24-hour period when no symptoms were recorded until the next time symptoms were recorded.
- Heartburn severity (severity of the most intense episode will be assessed for daytime and nighttime).
- Percentage of responders, where a responder is defined as having at least 3 more days of not more than mild heartburn symptoms on average per week during the whole double blind treatment period compared to baseline, where baseline is defined as the 1 week run-in period on placebo prior to randomization.

<u>Regurgitation Endpoint</u>

- Percentage of regurgitation-free nights during 4 weeks of randomized double-blind treatment.
- Percentage of regurgitation-free days after 4 weeks of randomized double-blind treatment.
- Percentage of regurgitation-free 24 hour periods during 4 weeks of randomized double-blind treatment.
- Percentage of subjects with ≥80% regurgitation-free days and nights during 4 weeks of randomized double-blind treatment.
- Percentage of subjects free from regurgitation ("no regurgitation") during week 1, 2 and 3 of randomized double-blind treatment.
- Time to first sustained resolution (defined as 7 consecutive days without daytime and nighttime regurgitation).
- Proportion of subjects who achieve sustained resolution of regurgitation (defined as ≥7 consecutive days without daytime and nighttime heartburn) with an onset within 3 days of starting randomized double-blind treatment.

- Proportion of subjects with resolution of regurgitation symptoms with an onset within 3 days of starting randomized double-blind treatment and continuing out to the end of week 2 and the end of week 4.
- Proportion of patients with no daytime and nighttime regurgitation symptoms during the last week of treatment.
- Maintenance of regurgitation-free period – duration of regurgitation symptom-free days and nights (24-hour periods) following the first 24-hour period when no symptoms were recorded.
- Regurgitation severity (severity of the most intense episode and will be assessed for daytime and nighttime).

Heartburn and Regurgitation Endpoint

- Percentage of heartburn and/or regurgitation-free 24 hour periods (day and night) during 4 weeks of randomized double-blind treatment.

Rescue medication Endpoint

- Percentage of days without using rescue medication.
- Percentage of nights without using rescue medication.
- Percentage of days and nights without using rescue medication.

GERD Sleep quality measure

- Change from baseline in measured scores.
- Proportion of subjects with clinically significant improvement on sleep disturbance measures.

HRQoL

- HRQoL will be assessed using patient reported outcome questionnaires at patient visit and the following endpoints will be used for analysis:
  - Change from baseline in HRQoL scores.
  - Proportion of subjects with clinically significant improvement on HRQoL measures.

Other Additional Endpoints

- Summary statistics of plasma concentrations of Vonoprazan at the Week 2 and 4 visit and summary pharmacokinetic parameters where available: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to tau (AUC_{τ}).
- Summary statistics of plasma concentrations of Vonoprazan at the Week 2 and 4 visit for CYP2C19 poor or extensive metabolizers (PM/EM) and summary pharmacokinetic parameters where available: maximum observed plasma concentration (C_{max}), time to reach C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to tau (AUC_{τ}).

- Summary statistics of plasma concentrations of esomeprazole at the Week 4 visit.
- Safety parameters examined will include AEs, serious adverse events (SAEs), vital signs, results of standard laboratory tests.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2, randomized, double-blind, parallel-group, 3-arm PoC study with a 4-week active Treatment Period. This study will evaluate the safety and efficacy of vonoprazan 20 mg QD and 40 mg QD compared with esomeprazole 40 mg QD when administered as an oral daily dose in the morning, at least 1 hour before the first meal of the day, for 4 weeks of treatment in subjects with symptomatic GERD who have a partial response to treatment with a high dose of esomeprazole. This study will be conducted at a total of up to 50 sites in Europe. A total of 213 subjects will be randomized in a 1:1:1 ratio of Vonoprazan 40 mg to Vonoprazan 20 mg to Esomeprazole 40 mg (71 per treatment arm).

Subjects will be eligible for participation in the study if they: have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study; have a history of predominant heartburn symptoms in the presence of regurgitation that are troublesome despite an adequate course of PPI treatment; continue to have symptoms of heartburn and regurgitation following 4 weeks treatment with a high dose of esomeprazole 40 mg QD during the Run-in Period; have symptoms of heartburn which increases following a 2-week Washout Period in the presence of regurgitation prior to randomization; and meet all of the inclusion criteria and none of the exclusion criteria. Patients with mild (LA grade A) esophagitis are also permitted to enter the study. To confirm LA grade, endoscopy will be performed at screening, or historical data of endoscopy up to one year prior to screening may be permitted. The study will consist of 3 periods: a 7-week Run-in period (initial 1 week screening period and a 6-week single-blind Run-in), a 4-week double blind Treatment Period, and a 1-week Safety Follow-up. The Run-in includes a 1-week general Screening Period during which the subject will remain on their prescribed PPI (Day-49 to Day -42); followed by a 4-week single-blind PPI assessment period with blinded esomeprazole 40 mg QD (Day -42 to Day -14); and then a 2-week single-blind placebo Off-PPI Assessment period (Day -14 to Day-1). Subjects who remain symptomatic and compliant will be randomized to the 4-week Treatment Period followed by a one week safety Follow-up Call. Certain medications will require washout prior to entry into the study and will not be permitted during the study as outlined in Table 7.a.

The Screening Period will take up to 49 days. After providing informed consent and meeting the appropriate study entry criteria during the Initial Screening Visit (Visit 1), subjects will be taken off their prescribed PPI and be given esomeprazole 40 mg QD, be provided with an electronic diary (Visit 2), and trained in how to complete it. They will return 4 weeks later to assess treatment compliance, completion of the e-Diary and assessment of the PPI Treatment Period (Day -21 to -14). If the subject is still symptomatic, he or she will receive single-blinded placebo medication for a 2-week PPI Washout Period and their Off-PPI Baseline will be assessed during the week prior to randomization (Day -8 to -1).

It is estimated that approximately 426 subjects will be screened to ensure that a total of 213 subjects who meet the symptomatic GERD entry criteria for a partial response to PPI (defined as having heartburn following 4 weeks of treatment with esomeprazole 40 mg and an increase of at

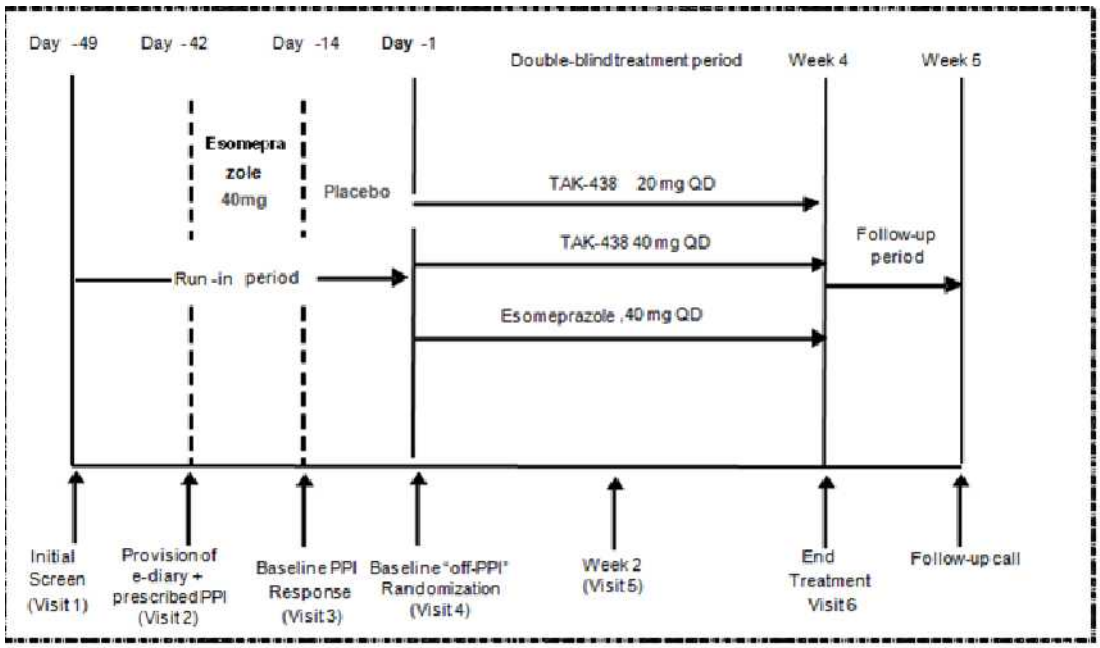
least 2 symptom days of heartburn (and/or regurgitation) in the last week of the Off-PPI assessment period compared with the last week of esomeprazole treatment) are randomized equally to 1 of 3 treatments at Visit 4 (vonoprazan 20 mg QD, vonoprazan 40 mg QD or esomeprazole 40 mg QD for 4 weeks). A 50% screen failure rate is higher than for standard GERD studies and has been estimated based on the duration of the run-in, inclusion of a 2 week placebo washout period and the symptom criteria to be met prior to randomization. Patients will take their first dose of study drug on the morning after Visit 4 and be treated on an outpatient basis, complete their e-Diary twice daily and will return to the clinic at Weeks 2 (Visit 5) and Week 4 (Visit 6) of the Treatment Period.

A Safety Follow-up call will be made approximately 1 week after completion of the 4-week Treatment Period. If possible, subjects who prematurely withdraw from the study will be seen for a withdrawal visit as soon as possible after discontinuation, and also will be contacted for Safety Follow-up approximately 1 week after withdrawal.

Rescue antacid medication will be provided for all subjects at the Initial Screening Visit and as required throughout the study.

From the Initial Screening Visit to the End-of-Treatment Visit, there will be 6 subject visits and a phone call during the Follow-up period. 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



6.2 Justification for Study Design, Dose, and Endpoints

Vonoprazan-2001 is a phase 2, randomized, double-blind, parallel-group, 3-arm PoC study with a 4-week Treatment Period. The study is designed to assess a maximum clinical dose of vonoprazan (40 mg QD) and a lower clinical dose (20 mg QD) vs. the maximum approved dose of esomeprazole (40 mg QD for the treatment of erosive esophagitis), to identify if vonoprazan offers a clinically meaningful benefit for the treatment of symptomatic GERD in patients who have a partial response to a high dose of PPI. A total of 213 subjects will be randomized in the study, in a 1:1:1 ratio of Vonoprazan 40 mg to Vonoprazan 20 mg to Esomeprazole 40 mg.

This study aims to recruit subjects who have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study and of not responding fully to their PPI treatment (at least 8 weeks of predominant heartburn symptoms in the presence of regurgitation that are troublesome after treatment at the standard doses of PPI) and who have a partial response to treatment with a high dose of esomeprazole 40 mg QD (defined as having heartburn on 2 to 5 days and regurgitation on at least one day of the last week [Week 4] of a 4 week Run-in with esomeprazole 40 mg). To further confirm that their heartburn is acid-related, subjects also have to have an increase of at least 2 symptom days of heartburn) in the last week of a 2-week Off-PPI Assessment Period (4 to 7 symptom days) and at least one symptom day with regurgitation compared with the last week of the PPI Assessment Period. Having the Washout after PPI treatment will result in a higher pre-randomization baseline heartburn frequency allowing the effects of both treatments as well as the treatment difference to be estimated. Symptomatic patients with mild EE (LA Grade A) will be permitted to enter the study as the presence of EE is a good indicator of the patient suffering from an acid-related problem and the study treatments are being used at doses which have been shown to effectively treat EE. Two doses of vonoprazan (20 mg and 40 mg) have been selected for this study. Vonoprazan 20 mg has been included, as this is the clinical dose recommended in Japan for the treatment of EE. Experience with PPIs indicate that for patients with a partial response to approved once daily therapy, tailored therapy is often given off-label with adjustment of dose, dose timing and/or twice daily dosing [20]. Therefore, vonoprazan 20 mg may be expected to be a minimally effective clinical dose in this difficult to treat population. As such, a higher dose of vonoprazan 40 mg has also been selected as a potentially appropriate dose for this population of patients. Using vonoprazan 20 mg and 40 mg therefore allows for a comparison of dose effect and to select the appropriate dose of vonoprazan to take forward in to Phase 3. Esomeprazole is considered as the current gold standard PPI for the treatment of GERD and 40 mg is the most appropriate dose for this difficult to treat population.

All subjects will receive blinded esomeprazole 40 mg QD for 4 weeks during the PPI assessment Run-in Period at the licensed dose for the treatment of erosive esophagitis in the EU and US [16,17]. This standard 4-week PPI assessment Run-in Period allows for PPI exposure to be consistent across subjects. Subjects having heartburn symptoms on 2 to 5 days and regurgitation on at least one day of the last week of the PPI Assessment Run-in Period (Week 4 of this period) are therefore having a partial response to their PPI treatment. A Washout of 2 weeks prior to Randomization, where subjects receive blinded placebo, will be of sufficient duration to observe an increase in the frequency of heartburn of 2 or more symptom-days off-PPI and together with at

least one symptom day of regurgitation will confirm that subjects have symptomatic acid-related disease. In addition, 2 weeks should be an acceptable length of time for subjects to stop PPI treatment without risking their withdrawal from the study. Compliance with taking medication and completing their e-Diary also will be monitored during the Run-in Period and has been set at ≥85% for both ensuring that the subject's historical partial response to a PPI is not due to lack of treatment compliance.

Vonoprazan has been given at doses of up to 40 mg QD for 7 days in both healthy Caucasian and Japanese subjects and its pharmacodynamic (PD) profile suggests that it has a quick onset of action, strong PD effect, and a long (> 24 hours) duration of action [21]. In addition, vonoprazan at doses up to 40 mg QD for 8 weeks has been shown to be beneficial for the treatment of EE in Japanese subjects with EE [9] and more recently, vonoprazan 20 mg has been shown in large phase 3 studies to be effective for the treatment of EE [10], maintenance of EE healing [11], aspirin-induced and non-steroidal anti-inflammatory induced peptic ulcers [12,13] and the eradication of *H. pylori* in conjunction with antibiotics [14].

Vonoprazan can increase gastric pH faster, to a greater extent, and for a longer duration than that achievable with PPIs and therefore may offer a clinical advantage for the treatment of acid-related diseases. As heartburn is often considered the most frequent and troublesome symptom for subjects and the goal of treatment is to prevent heartburn throughout the whole day and night, the percentage of heartburn-free days and nights (in 24-hour periods) during 4 weeks of randomized double-blind treatment has been selected as the primary endpoint. The secondary endpoint will be the percentage of subjects with ≥1 sustained resolution of heartburn (defined as ≥7 consecutive days without daytime and nighttime heartburn any time during the 4-week randomized double-blind Treatment Period). Other additional endpoints include the following: Percentage of heartburn -free nights during 4 weeks of randomized double-blind treatment; Percentage of regurgitation-free nights during 4 weeks of randomized double-blind treatment; Percentage of patients with no daytime and nighttime heartburn symptoms during the last week of treatment; Percentage of patients with no daytime and nighttime regurgitation symptoms during the last week of treatment and change from baseline in the primary and secondary endpoints, where baseline is defined as the 4 week run-in period on esomeprazole. These endpoints are believed to be appropriate for an effective and long-acting gastric acid blocker and are also goals for treatment in this difficult to treat population of patients who have a partial response to a PPI.

A 4-week Treatment Period has been proposed for this Phase 2 proof-of-concept study as it will allow both vonoprazan and esomeprazole to have reached steady-state in plasma and to have plateaued in terms of their respective efficacy. The cardinal symptom of interest in this study is heartburn as the presence of this symptom suggests there is a gastric acid related issue and we are comparing two gastric-acid blocking treatments. A number of other symptom-based endpoints also will be investigated at Week 4.

Although the influence of 2C19 PM/EM status is expected to have minimal impact on the exposure to vonoprazan, the effect of metabolizer status on vonoprazan pharmacokinetics/clinical efficacy will be evaluated in this study.

The general study design, subject number, dose selection, choice of active comparator, treatment period, and endpoints are believed to be appropriate to determine if there is a clinically meaningful treatment difference between vonoprazan (vonoprazan 20 mg and 40 mg QD) and esomeprazole (40 mg QD) in subjects with a partial response to PPI treatment.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

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

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

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

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is a man or a woman and ≥18 years of age, at the time of the Screening visit.
4. The subject has a documented history of symptoms of both heartburn (burning pain) and acid regurgitation prior to entry into the study.
5. The subject has a medical history of ≥ 8 weeks of persistent heartburn symptoms in the presence of regurgitation symptoms (persistent heartburn symptoms defined as heartburn symptoms on ≥ 2 days a week) that are troublesome despite appropriate and correctly performed treatment with a PPI at standard doses.
6. The subject is ≥85% compliant at taking their Run-in medication and completing their e-Diary.

   Compliance for taking the Run-in medication is defined as the medication provided (esomeprazole and placebo) taken for 85% of the 6 weeks Run-in Period (or on 36 of 42 days of the Run-in Period).

   Compliance for the e-Diary is defined as the percentage of scheduled assessments that are completed based on 2 assessments per day (daytime and nighttime). For randomization, 85% compliance is required and is defined as 12 of 14 assessments completed over the 7-day period (Day -21 to Day-14) prior to the single blind Placebo Run-in Period.
7. The subject has a partial response to a PPI defined as having heartburn on 2 to 5 days and regurgitation on at least one day of the last week (Week 4) of a 4 week PPI Run-In Period with esomeprazole 40 mg and an increase of at least 2 symptom days of heartburn in the last week of a 2 week Placebo Run-In Period (4 to 7 symptom days) and at least one symptom day with regurgitation compared with the last week of the PPI Run-In Period.
8. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use routinely adequate contraception* from signing of informed consent throughout the duration of the study and for 4 weeks after last dose of the study medication.

*Definitions and acceptable methods of contraception are defined in Section 9.1.10 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.11 Pregnancy.

7.2 Exclusion Criteria

A 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 30 days prior to the Screening Visit.
2. The subject has received vonoprazan in a previous clinical study.
3. The subject is an immediate family member, study site employee, 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 have consented under duress.
4. The subject has, in the judgment of the investigator, clinically significant abnormal hematological parameters of hemoglobin, hematocrit, or erythrocytes at Screening**.**
5. The subject has a history of erosive esophagitis of Los Angeles (LA) Classification Grade B severity or worse prior to screening or at Screening endoscopy.
6. The subject has a history of or any coexisting diseases affecting the esophagus (eg, Barrett's esophagus, eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, or esophageal stricture), history of radiation therapy or cryotherapy to the esophagus, caustic trauma, or physiochemical trauma such as sclerotherapy to the esophagus.
7. The subject has "alarm features" in symptomatology, including odynophagia, severe dysphagia, bleeding, weight loss, anemia, and blood in stool, pointing to a possible malignant disease of the GI tract. Patients displaying "alarm symptoms" in addition to the "typical" GERD symptoms may be included based on endoscopic exclusion of malignancy.
8. The subject has current or historical chest pain due to cardiac diseases (eg, within one year).
9. The subject has had surgical treatment for GERD (eg, cardioplasty), dilation of an esophageal stricture (other than Schatzki ring) or gastric or duodenal surgery, except simple oversew of an ulcer or endoscopic polypectomy of benign polyps.
10. The subject has active gastric or duodenal ulcers which have been confirmed by endoscopy within 30 days prior to Screening. Gastric or duodenal erosions are not exclusionary, unless considered severe and symptomatic by the investigator.
11. The subject has had an acute upper gastrointestinal hemorrhage within 30 days prior to Screening.
12. The subject has current or historical evidence of Zollinger-Ellison syndrome or other hypersecretory condition.
13. The subject has current or historical evidence of eosinophilic esophagitis (evidence may be based on the following: missing response to acid suppressive therapy, the presence of eosinophilia in histological probes of the esophageal mucosa, a normal pH profile of the distal esophagus, symptoms of dysphagia and food impaction). The exclusion of patients based on a predominance of the "typical" eosinophilic esophagitis symptoms only (as above) is

considered acceptable. However, in patients with a predominance of "typical" symptoms and co-existing significant dysphagia and food impaction, the syndrome should be excluded by endoscopy with biopsy.

14. The subject has a documented history (within 6 months prior to screening) of functional dyspepsia (suggested by the presence of one or more of the following symptoms: epigastric pain, postprandial fullness or early satiety), or irritable bowel syndrome or other gastrointestinal diseases which are not acid-related, and therefore, are nonresponsive to gastric acid-blocking treatment.
15. The patient has a documented history of familial adenomatous polyposis.
16. The subject has known intolerance, hypersensitivity or allergies to any PPI or their components (including lansoprazole, dexlansoprazole, omeprazole, rabeprazole, pantoprazole, or esomeprazole), any component of vonoprazan, or antacid(s) selected as rescue medication for this study.
17. The subject has a history of alcohol abuse, illegal drug use, or drug addiction within the 12 months prior to Screening, or regularly consumes >21 units of alcohol (1 unit = 12 oz/300 mL beer, 1.5 oz/25 mL hard liquor/spirits, or 5 oz/100 mL wine) per week. Subjects must have a negative drug screen at Screening.
18. The subject has evidence of a serious uncontrolled concomitant disease including: clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, systemic, or endocrine disease or other abnormality (other than the disease being studied), which may impact the ability of the subject to participate or potentially confound the study results.
19. The subject has planned, or is likely to require, in-patient surgery during the course of the study.
20. The subject has a history of cancer (except basal cell carcinoma of the skin) within 3 years prior to Screening.
21. The subject is known to have acquired immunodeficiency syndrome or chronic hepatitis due to any etiology.
22. The subject has abnormal laboratory values at Screening that suggest a clinically significant underlying disease or condition that may prevent the subject from completing the study.
23. The subject has an ALT, AST or T-bilirubin level which exceeds ULN set by the testing laboratory at the Screening.
24. If female, the subject is pregnant or lactating or intending to become pregnant before, during, or within 1 month after participating in this study; or intending to donate ova during such time period.

25. The subject is required to take excluded medications or it is anticipated that the subject will require treatment with at least 1 of the disallowed concomitant medications during the study please refer to Excluded Medication listed in Section 7.3).
26. The subject who, in the opinion of the investigator, is unable to comply with the requirements of the study or is unsuitable for any reason.

7.3 Excluded Medications, Procedures, and Treatments

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

Table 7.a Excluded Medication

	Pre-screening (Days)		Run-In Period (Days)			Randomization (Day)	Treatment (Days)
Excluded Medication	**-90**	**-60**	**-49**	**-42**	**-14**	**-1**	**1-28**
Drugs that may be affected by increase in stomach pH (eg itraconazole)			X	X	X	X	X
High dose methotrexate	X	X	X	X	X	X	X
Bisphosphonates			X	X	X	X	X
Antacids (a)			X	X	X	X	X
Strong CYP3A4 inhibitors (eg, clarithromycin)			X	X	X	X	X
Strong CYP2C19 inhibitors (eg, fluconazole)			X	X	X	X	X
CYP2C19 or CYP3A4 inducers (eg, Rifampin, St. John's Wort, Phenytoin, Mephenytoin)			X	X	X	X	X
CYP2C19 substrates (eg, S-mephenytoin)			X	X	X	X	X
PPIs (b)					X	X	X
Histamine 2 receptor antagonists			X	X	X	X	X
Anticoagulant therapy (c) including, but not limited to: Warfarin, Heparin, Clopidogrel, Prasugrel				X	X	X	X
Other agents affecting digestive organs including: muscarinic M_3 receptor antagonists, prokinetics (eg, metoclopramide, cisapride, tegaserod), anticholinergic agents, prostaglandins, anti-gastrin agents or mucosal-protective (eg, sucralfate) agents				X	X	X	X
Oral corticosteroids (d)				X	X	X	X
Drugs with a narrow therapeutic range (eg, Digoxin, Warfarin)				X	X	X	X

(a) Study antacid medication provided may be used during the Screening and Treatment Periods.
(b) Subjects will change their prescribed PPI to esomeprazole 40 mg QD for the 4 week PPI Run-in period. Subjects are not allowed to take any other PPIs other than study drug during the Run-in and Treatment Periods.
(c) Aspirin up to 325 mg per day is allowed as anticoagulant therapy.
(d) A short course taper for the treatment of asthma exacerbations and inhaled corticosteroids are permitted.

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. The investigator should review any additions or changes in medications at all visits. All medications should be recorded in the source documents or equivalent and then transcribed onto the appropriate electronic case report forms (eCRFs).

Concomitant medications should remain at a stable dose during the study unless a change in dosage is medically indicated.

7.4 Diet, Fluid, Activity Control

The subject should refrain from excessive drinking and eating, an extreme diet change (eg, Change to an extremely high-fat diet) or excessive exercise throughout the study. Vonoprazan 20 mg, vonoprazan 40 mg and esomeprazole 40 mg will be administered as an oral daily dose in the morning, at least 1 hour before the first meal of the day.

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 medication should be recorded in the case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.17.

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

   - Liver Function Test (LFT) Abnormalities

     Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.9), if the following circumstances occur at any time during study medication treatment:

     – alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or total bilirubin > 2 × upper limit of normal (ULN)

2. Significant 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.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy).
5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.

8. Other.

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

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. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, study medication refers to vonoprazan (20 mg and 40 mg) active, esomeprazole (40 mg) active and matching placebo capsules defined below. Study medication will be packaged in blinded fashion.

8.1.1.1 Investigational drug

Vonoprazan 20 mg and 40 mg Capsules

Vonoprazan study medication will be supplied as 20 mg and 40 mg capsules. The drug product will be over-encapsulated into DBAAel Swedish Orange capsules at the contract manufacturing organization, Almac UK. Takeda Pharmaceutical Company Ltd., Osaka, Japan, manufactures the vonoprazan drug substance and vonoprazan drug product.

The over-encapsulated vonoprazan 20 mg and 40 mg strengths will be identical in appearance. They will be foil/foil blister packaged into 10-day (1 week plus 3 extra days) child-resistant blister cards, containing a total of 10 capsules. Dosing consists of 1 capsule daily.

Each wallet of vonoprazan 20 mg or 40 mg capsules will bear a multilingual booklet or a single language label that includes pertinent study information along with caution statement.

Labels will be in the appropriate language where the study medication is being dispensed.

Esomeprazole (40 mg) active and Placebo Capsules

Commercially available 40 mg esomeprazole tablets will be over-encapsulated by Almac, UK, hence the product is considered investigational material and Almac Clinical Services becomes the manufacturer of active over-encapsulated esomeprazole 40 mg and matching placebo capsules.

The esomeprazole and placebo will be identical in appearance to the vonoprazan 20 mg and 40 mg over encapsulated drug product as DBAAel Swedish Orange Capsules, which will be foil/foil blister packaged into 10-day (1 week plus 3 extra days) child-resistant blister cards, containing a total of 10 capsules. Dosing consists of 1 capsule daily.

Each wallet of either esomeprazole or placebo capsules will bear a multilingual booklet or a single language label that includes pertinent study information along with caution statement.

Labels will be in the appropriate language where the study medication is being dispensed.

8.1.1.2 Rescue Medication

During the study period including the screening period, antacids such as Gelusil (main ingredients are aluminium hydroxide, magnesium hydroxide and simethicone) or other bicarbonate based medication, if available in the participating countries, can be used as the rescue medication if the symptoms caused by acid reflux cannot be tolerated by the subjects.

A guideline of commonly used medications which may be used as rescue medications in each of the countries will be provided. If the listed rescue medications in the guideline are not available, CRO/Takeda medical monitor may provide guidance of available brand to investigators. The administration of rescue medication shall be in accordance to the package insert approved in the corresponding countries. For aluminum based medications, an interval of at least 2 hours must be maintained between administration of study medication (Vonoprazan or esomeprazole) and rescue medication. Subjects shall contact the investigators if they would like to take the rescue medication at a dose higher than the approved ones in the local insert package.

When rescue medication has been taken for more than 7 consecutive days in the randomization treatment period, the investigator should discuss the case with the CRO/sponsor medical monitor and consider whether to withdraw the subject.

The use of rescue medication shall be recorded in the subject electronic diary. The sponsor will reimburse the investigational sites for the cost of supplying rescue medication drugs to subjects.

8.1.1.3 Sponsor-Supplied Drug

Over-encapsulated vonoprazan (20 mg and 40 mg) active as well as over-encapsulated esomeprazole (40 mg) active and matching placebo capsules will be supplied by the sponsor.

8.1.2 Storage

Vonoprazan, esomeprazole and matching placebo capsules should be stored in blister at or below 25°C. Investigational drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Investigational 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.

Temperature excursion must be reported to the sponsor or designee.

8.1.3 Dose and Regimen

PPI Run-In period (Days -42 to -14)

Subjects will be dispensed 4 blister cards containing 10 capsules of esomeprazole 40 mg.

Subjects will be instructed to take one capsule at least 1 hour before the first meal of the day. The subject will also be reminded to bring the study medication blister cards (including any unused study medication) to the following study visit.

Single blind Placebo Run-In period (Days -14 to -1)

Subjects will be dispensed two blister cards containing 10 capsules of Placebo.

Subjects will be instructed to take one capsule at least 1 hour before the first meal of the day. The subject will also be reminded to bring the study medication blister card (including any unused study medication) to the following study visit.

Treatment Day 1 – Randomization and Treatment Period visits

Each subject who meets all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive either once daily vonoprazan or esomeprazole via the IWRS.

After randomization subjects will be dispensed two blister cards containing 10 capsules of either vonoprazan 20 mg or 40 mg or esomeprazole 40 mg.

Subjects will be instructed to take one capsule at least 1 hour before the first meal of the day. The subject will also be reminded to bring the study medication blister card (including any unused study medication) to the following study visit. A further two blister cards will be dispensed at visit 5 (week 2) so that the subjects will receive study drug for 4 weeks of treatment, thereafter they will move into the follow-up phase (with a phone call follow-up completed 1 week after the last dose).

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

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	Treatment Dose
	PPI Run-in QD	Esomeprazole 40 mg capsule	One 40 mg esomeprazole capsule
	Placebo Run-in QD	Zero active capsule	One placebo capsule
A	20 mg vonoprazan QD	Vonoprazan 20 mg capsule	One capsule from vonoprazan 20 mg blister card
B	40 mg vonoprazan QD	Vonoprazan 40 mg capsule	One capsule from vonoprazan 40 mg blister card
C	40 mg esomeprazole QD	Esomeprazole 40 mg capsule	One capsule from esomeprazole 40 mg blister card

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational 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, Pretreatment Events and Adverse Events.

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

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

8.2 Investigational drug Assignment and Dispensing Procedures

Subjects will be assigned to receive their treatment according to the schedule allocated to each study site.

The investigator or investigator's designee will access the IWRS to obtain the subject number at screening. The IWRS will be accessed at Day -42 (Visit 2) to enroll the subject into the PPI Run-in period of the study and at Day -14 (Visit 3) to enroll them into single-blind placebo run-in period of the study. The investigator or the investigator's designee will utilize the IWRS to randomize the subject into the study (visit 4). During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. At subsequent drug-dispensing visits (visit 5), the investigator or designee will again contact the IWRS to request additional investigational drug for a subject. The medication identification (Med ID) number of the investigational drug to be dispensed will then be provided by the IWRS.

If sponsor-supplied drug (vonoprazan 20 mg or 40 mg capsule or esomeprazole 40 mg capsule or placebo capsule) is lost or damaged, the site can request a replacement from IWRS. (Refer to IWRS manual provided separately.)

The subject will take the first dose of study medication at Visit 2 after completion of all assessments but before leaving the clinic. At all subsequent study visits during the Treatment phase the subject should be instructed to present to the clinic for the study visit without taking the study medication. The daily dose of the study medication on those days will be taken by the subject after completion of assessments.

Subjects should be instructed that all doses of study medication (vonoprazan, esomeprazole or placebo) should be taken 1 hour before breakfast except on study visit dates where it will be taken after completion of the visit assessments. Study drug is to be kept in the blister cards provided until the dose is to be taken. Subjects should also be instructed that if any dose is missed inadvertently it is acceptable for that dose to be taken within 12 hours of the time that it was due. If longer than 12 hours have passed since the dose was due, it should not be taken but noted instead in the subject's diary that the dose was missed.

8.3 Randomization Code Creation and Storage

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

At the Randomization Visit, Day 1 (Visit 4), all qualified subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio to vonoprazan 20 mg, 40 mg and esomeprazole 40 mg using the IWRS.

8.4 Investigational Drug Blind Maintenance

The investigational drug blind will be maintained using the IWRS.

8.5 Unblinding Procedure

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, the investigator will be able to access the IWRS to determine the patient's treatment group assignment. The investigator will, whenever possible, discuss options with the medical monitor before unblinding. The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, investigational drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or, where appropriate destroyed at the site according to local procedures

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, vonoprazan (20 mg and 40 mg), esomeprazole 40 mg and placebo, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by recording in IWRS. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the Med ID number used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IWRS will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs (vonoprazan 20 mg and 40 mg, esomeprazole 40 mg and placebo) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry and/or retest date, date and amount dispensed including initials or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drugs that was not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

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

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

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

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

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

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

9.1.1.1 Pharmacogenomic Informed Consent Procedure

The sampling of whole blood for CYP2C19 genotyping analysis is mandatory; every subject must sign the informed consent in order to participate in this study. The informed consent for the CYP2C19 genotyping analysis is a component of the overall study informed consent.

A separate PGx informed consent form pertaining to storage of the sample must be obtained in order to store the sample after the study related PGx analysis described in the protocol is completed. The provision of consent to store the sample for future analysis is independent of consent to the other aspects of the study. The requirements are described in Section 15.2.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth (or age for the countries which don't allow to collect the date of birth), sex, race as described by the subject, and employment status, smoking status, history of use alcohol and history of caffeine-containing drinks, night sweats within the past 1 month, weight change within the past 1 year, history of *H. pylori* eradication therapy (eg, triple therapy with PPI + amoxicillin + clarithromycin) and date of completion of such therapy (within the past 1 year/more than 1 year) of the subject at Screening.

Medical history including inflammatory disorder, chronic pain conditions and diabetes mellitus to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8).

Medication history information to be obtained includes any medication relevant to eligibility criteria and efficacy/safety evaluation stopped at or within 90 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment prior to first dose of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment from the baseline examination.

9.1.4 Weight and Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off.

Height will be collected at Visit 1 in centimeters without decimal places.

Weight will be measured at Visit 1, Visit 4 (Randomization) and Visit 6 (or early withdrawal).

Weight will be collected in kilograms to 1 decimal place. BMI is calculated by sponsor or its designee using metric units with the formula provided below.

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

9.1.5 Vital Sign Procedure

Vital signs will include body temperature (oral or tympanic measurement), sitting blood pressure (resting more than 5 minutes), and pulse (bpm).

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

Vital signs will be measured at Visit 1, Visit 4 (Randomization) and Visit 6 (or early termination).

9.1.6 Efficacy Measurement

9.1.6.1 Reflux Symptom Questionnaire Electronic Diary (RESQ-eD)

RESQ-eD is an electronic diary that Astra Zeneca developed and validated in patients with partial response to PPI [22]. Subjects will be given and trained on the use of the study e-Diary at Visit 2 and re-trained at Visit 3 if necessary once initial eligibility criteria have been confirmed at Visit 3. Subjects will be instructed to complete the e-Diary every morning upon waking and every evening before going to sleep.

Throughout the Run-in Period and Treatment Period, subjects will document the presence of daytime and nighttime heartburn and regurgitation, as well as the use of rescue medication. Any subjective symptoms experienced should be entered in accordance with the descriptions given in Table 9.a, throughout the study, describing in the diary the severity of all heartburn or regurgitation symptoms.

Subjects will complete the e-Diary during the Run-in Period for at least 42 days prior to Randomization and during the 4-week Treatment Period.

Table 9.a Requirements for Subject Diary Entries Regarding Subjective Symptoms

Subjective symptom	Description of symptom	Entry requirements
Heartburn	A burning feeling behind your breastbone, pain behind your breastbone, a burning feeling in the center of the upper stomach, a pain in the center of the upper stomach	Since waking today/ During the nighttime, how would you rate the intensity of…?
Regurgitation	An acid or sour taste in your mouth, A bitter taste in your mouth, Unpleasant movement of material upwards from the stomach or stomach contents (liquid or food) moving upwards to your throat or mouth	Since waking today/ During the nighttime, how would you rate the intensity of…?

Items are scored for intensity on a 6-point scale (0=did not have; 1=very mild; 2=mild; 3=moderate; 4=moderately severe; 5=severe).

9.1.6.2 Subject Reported Outcome Questionnaires

Sleep

Nighttime awakenings (eDiary)

Question that will be included in the morning evaluation of the eDiary are tabulated as follows:

Did you wake up during night (=usual sleeping time)?
1 Yes
2 No

Fatigue (eDiary)

Questions that will be included in the evening evaluation of the eDiary are tabulated as follows (both rated on 5-point Likert scale):

1. How much physical fatigue have you experienced today? 0 = none, 1 = slight, 2 = medium, 3 = a lot, 4 = severe
2. How much intellectual fatigue have you experienced today? 0 = none, 1 = slight, 2 = medium, 3 = a lot, 4 = severe

Quality of Sleep

Quality of sleep will be assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire [23]. The PSQI questionnaire is a 19-item validated questionnaire completed by patients regarding the previous 1-month period. Items are grouped into seven component scores: subjective sleep

quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component score is weighted equally on a 0–3 scale, with 3 representing the worse effect, then summed to yield a global PSQI score, which could range from 0 to 21. Patients with a global score >5 are considered to have poor sleep quality. Patients will complete the questionnaire at the Visit 2, Visit 3, Visit4 and Visit 6 (or early termination).

HRQoL

Health-Related Quality of Life (HRQL) will be assessed at Visit 2, Visit 3, Visit 4 and Visit 6 (or early termination) using generic and disease specific PRO instruments.

The EuroQol-5 dimensions (EQ-5D-5L) is a validated and reliable generic instrument [24,25] that was developed as a standardized non-disease-specific instrument describing and evaluating HRQL. It was intended to complement other forms of HRQL measures and have the capacity to generate cross-national comparisons for health care evaluations. EQ-5D-5L is used to calculate quality-adjusted life years (QALYs) for pharmaco-economic studies [26,27,28]. The questionnaire includes 5 domain items: mobility, self-care, usual activities (UA), pain/discomfort (P/D), and anxiety/depression (A/D). Subjects choose the level of health problems they currently have on each item as “None”, “Slightly”, “Moderate”, “Severe”, or “Unable” and are scored a 1, 2, or 3, respectively. The 5 items allow the calculation of a utility index ranging between 0 (the worst) and 1 (the best). The questionnaire also uses a Visual Analog Scale (VAS). The EQ-5D-5L VAS score is a self-assigned rating of overall health using a 20 cm visual, vertical scale, with a score of 0 as the worst and 100 as best possible health. A decrease of ≥0.08 points in the EQ-5D-5L index score represents a meaningful improvement in patient’s HRQoL [25]. The EQ-5D-5L has a recall period of one day and will be provided in the Study Manual.

An upper-GI (UGI)-disorder specific questionnaire PAGI-QOL (Patient Assessment of Upper Gastrointestinal Disorders Quality-of-Life Index) will be used in order to evaluate with more sensitivity the treatment-induced changes in HRQoL. The PAGI-QOL is a validated and reliable instrument used to measure QOL in patients with UGI disorders including GERD, dyspepsia, and gastroparesis [29].

Changes in UGI symptoms

Changes in UGI symptoms will be measured with the PAGI-SYM (Patient Assessment of Upper Gastrointestinal Disorders Symptom Severity Index), a validated and reliable instrument used to measure symptom severity in patients with UGI disorders including GERD, dyspepsia, and gastro paresis [30,27]. The PAGI-SYM measures UGI symptom severity over the 2 weeks preceding the visit. PAGI-SYM will be used to identify patient that are more likely to be functional patients. PAGI-SYM will also be used to identify meaningful change in RESQ-eD. Patients will complete the questionnaire at the Visit 2, Visit 3, Visit 4 and Visit 6 (or early termination).

Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is a patient-rated instrument that measures change in patient’s GERD-related symptoms on a 7-point scale ranging from 1 (very much

improved) to 7 (very much worse) [31]. Higher scores indicate a change for the worse. For this study, subjects will be asked to rate their symptoms relative to their previous past 4-weeks or 2-weeks. The PGIC item will be assessed at visit 3, visit 4 and visit 6 (Early termination). The PGIC will be used to further document the ability RESQ-eD to detect change as well as clinical meaningfulness of change.

Mood

Studies showed that in patients who are referred for a diagnostic work-up for GERD, increased anxiety levels were observed most often in patients in whom complaints were owing to a functional disorder such as functional heartburn or functional dyspepsia [32,33]. High ratings suggestive of depression or an anxiety disorder measured with the Hospital Depression and Anxiety scale (HADS) have been shown to be associated with poorer PPI response [34].

The presence of anxiety levels and depression levels will be assessed using the HADS and treatment group efficacy outcomes and HADS scores will be assessed [35]. The HADS is a widely used scale that was designed for detecting depression and anxiety in an out-patient clinic setting, HADS part A (HADS-A) focuses on anxiety and HADS part D (HADS-D) focuses on depression. HADS-A and HADS-D are 7-item subscales that measure the presence and severity of anxiety and depression symptoms, respectively, on a scale of 0 to 3. Total scores ≤ 7 indicate no clinically relevant symptoms, 8 to 10 mild symptoms, 11 to 14 moderate symptoms, and ≥15 (maximum 21) indicate more severe symptoms. HADS will be assessed at visit 2, visit 3, visit 4 and visit 6(or early termination).

Questionnaires should be completed by the subject prior to dosing at appropriate clinic visits and questionnaires completeness should be checked prior to the subject leaving the site.

9.1.7 Documentation of Concomitant Medications

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

9.1.8 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, electrocardiogram (ECG), or physical examination abnormalities noted at baseline examination. The condition (ie, diagnosis) should be described.

9.1.9 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 55 mL, and the approximate total volume of blood for the study is 100 ml or 125 mL depending on the assigned PK assessment group. Details of these procedures and required safety monitoring will be given in the laboratory manual. Table 9.b lists the laboratory tests that will be required by the protocol. Laboratory samples will be taken at the time points stipulated in the Schedule of Study Procedures (Appendix A).

Table 9.b Clinical Laboratory Tests

Hematology	**Serum Chemistry**	**Urinalysis**
Hematocrit Hemoglobin Platelet count RBC count Reticulocyte count WBC count (with differential) Erythrocyte indices (MCV, MCH, MCHC) **Coagulation Tests** Prothrombin time Partial thromboplastin time International normalized ratio	ALT Albumin Alkaline phosphatase Amylase AST Blood urea nitrogen Calcium Chloride Cholesterol CK C-reactive protein (CRP) (a) Gastrin tests (b) γ-Glutamyl transferase Glucose Lactate dehydrogenase Magnesium Pepsinogen I/II(c) Potassium Phosphate Serum creatinine Sodium Standard iron panel (serum iron, TIBC, serum ferritin) (d) Total bilirubin Direct bilirubin (e) Total protein Triglycerides Uric acid	Appearance Color Bilirubin Glucose Hemoglobin Ketones Leucocytes Nitrites pH Protein Specific gravity Urobilinogen **Microscopy** for abnormal urinalysis result (RBCs, WBCs, casts, crystals, organisms, and epithelial cells)

Table 9.b Clinical Laboratory Tests (continued)

Other:		
Serum	**Urine**	**Breath**
Hepatitis panel, including HBsAg and anti-HCV Thyroid-stimulating hormones (TSH)(f) Female subjects only Beta hCG (for pregnancy, female subjects of childbearing potential) Follicle-stimulating hormone (FSH) if menopause is suspected (g)	Female subjects only hCCGI (for pregnancy, female subjects of childbearing potential) All subjects Drug screen including: amphetamines (including methamphetamine), barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, methadone and phencyclidine (h)	Helicobacter pylori (i)

MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV= mean corpuscular volume, RBC=red blood cell, TIBC= total iron binding capacity, WBC=white blood cell.
(a) CRP will be collected at Visit 4 and Visit 6(or Early termination).
(b) Gastrin and Gastrin-17 will be performed.
(c) This includes pepsinogen I, pepsinogen II and pepsinogen I/II ratio.
(d) Standard iron panel will be collected at Visit 1 and Visit 6(or Early termination).
(e) Assess direct bilirubin only if total bilirubin >1.5×ULN.
(f) TSH will be checked at Visit 4 and Visit 6(or Early termination).
(g) Follicle-stimulating hormone will be conducted at investigator's discretion to determine the postmenopausal status of women whose duration of (consecutive) amenorrhea is borderline or open to doubt and where the investigator believes the subject to be menopausal by history.
(h) The central laboratory will confirm any positive drug screen results.
(i) *Helicobacter pylori* breath test will be performed at Randomization via a urea breath test (C13 or C14 urea test) at a local laboratory. A stool test may be performed at those centers which do not have the facilities to perform a *H. pylori* breath test procedure.

The central laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

If subjects experience an increase in any one of either ALT, AST or total bilirubin >2×ULN then trial medication should be stopped due to the criteria for discontinuation has been met (please refer to section 7.5 for discontinuation criteria). Follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) to monitor recovery should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was noted.

Please refer to Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests.

CCI

CCI

The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

To obtain information on *H. pylori* infection that reportedly could affect the onset of erosive esophagitis, *H. pylori* infection status will be measured at Randomization. To establish *H. pylori* infection status a 13C or 14C urea breath test will be performed. Exhaled air samples will be taken in accordance with instructions for use of locally available testing kits for *H. pylori* infection status determination. A stool test to measure the infection of *H. pylori* may be performed at those centers which do not have the facilities to perform a *H. pylori* breath test procedure.

9.1.10 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 4 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

- Cap (plus spermicidal cream or jelly) PLUS male condom.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom.

Intrauterine devices (IUDs):

- Copper T.

*Barrier methods is only applicable in countries where spermicide is commercially available.

Subjects can continue to use contraceptive medications and/or devices as long as they use additional contraceptive precautions as highlighted above. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova during the course of the study.

During the course of the study, regular serum or urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (Appendix A). In addition to a negative hCG pregnancy test at Screening, subjects also must have a negative hCG pregnancy test at Randomization prior to receiving first dose of double blind investigational drug.

9.1.11 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug (vonoprazan active and placebo tablets, esomeprazole and matching placebo) should be immediately discontinued.

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

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

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

All pregnancies in subjects on active study drug including comparator will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, PR interval, QT interval and QRS interval.

ECG will be recorded at Visit 1(screening), Visit 4(Randomization) and Visit 6(or early termination). A copy of the ECG trace should be kept with the subject's notes. For ECG results printed on thermal paper, non-thermal paper copies should be made to avoid degradation of trace over time.

9.1.13 Endoscopy

Endoscopy to check the stomach and esophagus will be performed at screening, or historical data of endoscopy checking stomach and esophagus up to one year prior to screening may be permitted. Subjects are fasted for 10 hours according to the usual practice of the institution (ie, in regards to pre-medications or concomitant therapies as long as they are not prohibited in Section 7.3 of this protocol) prior to the endoscopy. The purpose of the endoscopy is to confirm erosive esophagitis status and exclude esophageal and gastric malignancies. During endoscopy, the investigator or designee should ensure that gastric and esophageal mucosa is observed for a sufficient duration that the subject's eligibility is confirmed and/or ensure that accurate classification of the grade of any erosive esophagitis observed can be made. Digital images of the current esophageal erosions will be captured and stored at the investigational site which has a method of storage.

Table 9.c Los Angeles (LA) classification for diagnosis and grading of erosive esophagitis

Grade	Description
Grade 0	No mucosal breaks
Grade A	One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
Grade B	One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds
Grade C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of esophageal circumference
Grade D	Mucosal breaks which involve at least 75% of esophageal circumference

Source : [36]

9.1.14 Pharmacogenetic Sample Collection For Genotyping (Mandatory)

The sampling of whole blood for CYP2C19 genotyping analysis is mandatory; every subject must sign the informed consent in order to participate in this study.

One 6 mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected before dosing on visit 4 (randomization) from each subject in the study, into plastic K2 ethylenediamine-tetraacetic acid (EDTA) spray-coated tubes, and stored under frozen conditions. If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible.

The DNA sample collected from each subject will be used for CYP2C19 genotyping analysis. Genetic variation in the CYP2C19 gene may lead to changes in metabolic activity of the CYP2C19 enzyme that may contribute to the variability in the PK/clinical efficacy of Vonoprazan.

Investigators will be blinded to CYP2C19 metabolic status to ensure that assessments of efficacy and tolerability are unbiased by knowledge of metabolic status. After the study ends, the CYP2C19 metabolic status information may be provided to investigators and the subject based on subject or the legal representative request.

9.1.15 Pharmacogenomic Sample Collection For Storage (Optional)

A separate PGx informed consent form must be obtained in order to store the remaining DNA sample from the CYP2C19 genotyping and to collect additional blood samples for ribonucleic acid (RNA) isolation. The provision of consent to store the sample for future analysis is independent of consent to the other aspects of the study.

Two whole blood samples (2.5 mL per sample) for ribonucleic acid (RNA) isolation will be collected from each subject predose at visit 4 (randomization), into a PaxGene TM tube and stored under frozen conditions.

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "Pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to vonoprazan.
- Finding out more information about how vonoprazan works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to vonoprazan.
- Identifying variations in genes related to the biological target of vonoprazan.

This information may be used, for example, to develop a better understanding of the safety and efficacy of vonoprazan and other study medications, understanding of disease/condition being studied and for improving the efficiency, design and study methods of future research studies.

Each pharmacogenomic sample for a study subject should be identifiable on the requisition form with a subject ID.

The samples will be stored for no longer than 15 years after completion of the study and/or until the drug development of vonoprazan is no longer actively pursued by Takeda or its collaborators. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from Takeda. "Stored samples" are defined as samples that are key-coded (the samples are stripped of all personal identifying information but a key links the samples to the clinical data collected from the sample donor) and are used in the analysis of investigational drug or related drugs.

Detailed instructions for the handling and shipping of samples are provided in Appendix E.

9.1.16 Pharmacokinetic Sample Collection and Analysis

Subjects will be assigned to one of two sub PK groups.

Subjects in Group 1 (minimum 15 subjects per treatment arm) will be asked to arrive at the clinic prior to taking the daily dose at Visit 5 (Week 2) and Visit 6 (Week 4). A predose sample will be collected, followed by drug administration. One post dose sample will be taken at a time after

1 hour post dose at Visit 5 and 5 post-dose plasma samples will be taken at time point 0.5, 2, 5, 6 and 8 hours post dose at Visit 6.

The remaining subjects in each treatment arm will be assigned to Group 2 (minimum 45 subjects per treatment arm). Subjects will be asked to arrive at the clinic prior to taking the daily dose at Visit 5 (Week 2) and Visit 6 (Week 4). A predose sample will be collected, followed by drug administration. Additional plasma samples will be taken at a time after 1 hour post dose.

Table 9.d Schedule of Pharmacokinetic Sample Collection

Group	Sample collection time	
	Visit 5	**Visit 6**
Group 1	Predose / >1 hr post dose	Predose / 0.5, 2, 5, 6 and 8 hr post dose
Group 2	Predose / >1 hr post dose	Predose / >1 hr post dose

All subjects will provide a blood sample in order to maintain the blind; however, only samples from subjects receiving vonoprazan will be analyzed for all groups and visits. Samples from subjects receiving esomeprazole may be analyzed, but will be reported separately. The plasma samples will be analyzed for plasma concentration of vonoprazan and esomeprazole (if required) by validated methods.

For the final pharmacokinetic analysis, it is important that the date and time of administration of the previous study drug dose before collection of the pharmacokinetic sample (PK dose), and the dose before that, be accurately recorded in the source documents and eCRF at Visit 5 and Visit 6. Similarly, it is important that the date and time that each blood sample is drawn is accurately recorded in the eCRF.

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9.1.16.1 Bioanlytical Methods

Plasma concentrations of Vonoprazan and esomeprazole (if required) will be analyzed using separate validated LC/MS/MS methods.

9.1.17 Documentation of Screen Failure and Run-In Failure

Investigators must account for all subjects who sign informed consent.

If the subject is found to be not eligible at the screening visit or prior to Run-in period, the investigator should complete the eCRF. The IWRS should be contacted as a notification of screen failure.

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

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

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

If the subject has begun the PPI Run-in study medication or single-blind placebo Run-in study medication and they are found to not be eligible for randomization, they are considered a run-in failure. The investigator or designee should complete appropriate eCRFs and register the subjects as a run-in failure in the IWRS.

9.1.18 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 phase. IWRS will be contacted for treatment assignment and this information should be captured on the appropriate eCRF.

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

9.2 Monitoring Subject Treatment Compliance

Subjects will be required to bring study medication containers/unused medications to each dispensing site visit regardless of whether the study medication container is empty. Compliance with the study drug regimen will be documented throughout the study and must be calculated from counts of returned tablets and capsules.

If a subject is persistently noncompliant with the study medication (< 75% or >133% of the allocated medication for 2 consecutive 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 evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

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

9.4 Post Study Care

Unless required by law, the study medication 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.

9.5 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.14 . The genetic material will be stored initially at CCI and then if consent has been provided to store the samples for future analysis, the samples will be preserved and retained at the designated laboratory for up to but not longer than 15 years or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to personal health information with code numbers. This link means that the subject may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the sponsor.

Subjects who consented and provided a pharmacogenomic samples for DNA analysis can withdraw their consent and request disposal of a stored sample at any time. Notify sponsor of consent withdrawal.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Laboratory values and ECG findings:

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

intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.

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

- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

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

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 Severity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

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

10.1.6 Causality of AEs

The relationship of each AE to study medication(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 cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs 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 drugs and concurrent treatments.

10.1.7 Relationship to Study Procedures

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

The relationship 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 relationship should be assessed as Not Related.

10.1.8 Start Date

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

10.1.9 Stop Date

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

10.1.10 Frequency

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

10.1.11 Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose 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/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Visit 2, Day -42) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Visit 2, Day -42). Routine collection of AEs will continue until 1 week after completion or withdrawal from the study (safety follow-up call).

10.2.1.2 PTE and AE Reporting

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

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

1. Event term.
2. Start and stop date.
3. Severity.

4. Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
5. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
6. Action concerning study medication (not applicable for PTEs).
7. Outcome of event.
8. Seriousness.

Patient diary and questionnaire 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 patient 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.

10.2.2 Collection and Reporting of SAEs

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

A Takeda SAE form must be completed, in English and signed by the investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

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

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.1.

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

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests as an SAE

If a subject is noted to have ALT or AST >3 ×ULN and total bilirubin >2 ×ULN for which an alternative etiology has not been identified, the event should be recorded as an SAE 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 9.1.9 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and transmit it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

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

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the European Medicines Agency (EMA), investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted 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 an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 CRFs

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, 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, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to

retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

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

13.1.1 Analysis Sets

Full Analysis Set: this analysis set will include all subjects randomized. Subjects in this set will be analyzed according to the original randomization.

Per Protocol Set: this analysis set is a subset of the FAS. The PPS consists of all subjects who do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects from the PPS dataset will be made prior to the unblinding of the study. Analyses using the PPS may be provided as a sensitivity analysis.

Safety Set: this analysis set will include all subjects who have received at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment they actually received.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by each treatment group and overall. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristics data will be listed.

13.1.3 Efficacy Analysis

For the assessment of the percentage of heartburn-free days, the Wilcoxon-Mann-Whitney Odds estimator with the 97.5% CI and the Wilcoxon rank-sum test will be used at the 2.5% level of significance for each vonoprazan treatment comparison with esomeprazole to control for multiplicity. The Wilcoxon rank-sum test will be used because data from a previous Vonoprazan trial (TAK-438/CCT-201 [37]) showed that the data is unlikely to be normally distributed. This endpoint will be analyzed for both the FAS and PPS. The FAS analysis will be considered the primary analysis and the PPS analysis as a sensitivity analysis.

The percentage of days with neither daytime nor nighttime heartburn will be calculated for each subject who has at least one daytime or nighttime heartburn result (yes or no) during treatment by calculating the days that are heartburn-free out of the total number of days for which either a

daytime or nighttime result is marked. Thus, days missing diary results for both daytime and nighttime will be excluded from the numerator and denominator.

To assess the secondary endpoint, proportion of subjects with ≥1 sustained resolution of heartburn (defined as ≥7 consecutive days without both daytime and nighttime heartburn any time during the 4-week randomized double-blind Treatment Period) a Pearson Chi-square test will be used at the 2.5% level of significance for each Vonoprazan treatment comparison with esomeprazole to control for multiplicity. All subjects with missing data for determination of endpoint status will be considered as a non-responder in the analysis. The difference in proportion and odds ratio for each Vonoprazan treatment comparison with esomeprazole will be estimated and presented with 97.5% confidence intervals. This endpoint will be analyzed for both the FAS and PPS. The FAS analysis will be considered the primary analysis and the PPS analysis as a sensitivity analysis.

Additional Endpoints

All additional endpoints will be analyzed for the FAS only and tested at the 5% level of significance for each Vonoprazan treatment comparison with esomeprazole. 95% confidence levels will also be presented. Multiplicity will not be adjusted across the remaining endpoints.

If the assumptions underlying planned inferential methods are not adequately met, methods will be amended as needed for appropriate analysis.

The time to first sustained resolution of heartburn is defined as the time from the first dose of study drug to the first day of the 7 consecutive days free of heartburn and will be analyzed using a product-limit survival analysis with treatment group as the stratum. The survivor function will be estimated using the Kaplan-Meier method and the survivor functions between Vonoprazan and Esomeprazole treatment groups will be compared using log-rank tests. The median time to sustained resolution of heartburn from the survivor function will be presented by treatment group, along with the 95% confidence interval. Time to first sustained resolution of regurgitation will be similarly analyzed.

The analysis of the remaining additional endpoints will be described in the SAP.

13.1.4 Pharmacokinetic Analysis

Vonoprazan

Listings of all Vonoprazan concentration data will be provided in the clinical study report. The plasma concentration-time data for Vonoprazan will be summarized using descriptive statistics including geometric mean and CV%. Full details of the analysis will be included in the study SAP.

Data from the subset of patients with full PK sampling will be performed by traditional NCA as outlined in the CPAP and results of this analysis will be reported in the CSR.

Concentration-time data will be analyzed using population PK approach. A detailed description of the pharmacokinetic analysis methodology to be followed will be given in the population PK/PD analysis plan. This will be a standalone document and will not be included in the CSR.

Esomeprazole

If esomeprazole concentration data is required, listings of all esomeprazole concentration data will be provided in a separate report to this clinical study report. The plasma concentration-time data for esomeprazole will be summarized using descriptive statistics including geometric mean and CV%.

13.1.5 Patient Reported Outcomes Analysis

The scores of the PRO questionnaires will be summarized descriptively at each visit including changes from baseline "off-PPI" (visit 4) and changes from baseline PPI response (visit 3) by each treatment group. Absolute values and changes from baseline will be summarized per treatment arm. CCI [redacted]

13.1.6 Other Analysis

All data collected in this study will, where applicable, be summarised by treatment regimen using descriptive statistics. For continuous variables mean values, standard deviations, median and lower and upper percentiles will be calculated. For categorical variables frequencies and percent will be calculated.

13.1.7 Safety Analysis

Adverse events (AEs) will be summarized using the safety analysis set.

Adverse events collected during the trial will be summarised by System Organ Class, treatment regimen and stage of trial (eg, screening and treatment emergent) and reported.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

It is estimated that approximately 426 subjects will be screened from which a total of 213 subjects (71 per treatment arm) who have a partial response to treatment with a high dose of esomeprazole (40 mg QD for 4 weeks) are planned to be randomised into the study with the expectation that 180 subjects will complete the study (assuming a 15% dropout rate). The sample size of 60 subjects per treatment group will provide at least 80% power at the 2-sided 0.025 level of significance to detect an absolute 20% difference between each vonoprazan dose and esomeprazole 40 mg for the percentage of heartburn free 24 hour periods (day and night) during 4 weeks of randomized double-blind treatment. The pooled standard deviation was estimated as 33.61 from prior Dexlansoprazole (T-GD04-082, T-GD04-083, T-EE04-084, T-EE04-085) and vonoprazan (CCT-201) studies (Data on file). The sample size was calculated using the Wilcoxon rank-sum test in EAST version 6.0.

With the expectation that 180 subjects will complete the study, the secondary endpoint; proportion of subjects with ≥1 sustained resolution of heartburn (defined as ≥7 consecutive days without both daytime and nighttime heartburn any time during the 4-week randomized double-blind Treatment Period) has 80% power at the 2-sided 0.025 level of significance to detect an absolute 30% difference between each vonoprazan dose and esomeprazole, assuming a response rate of 33% for esomeprazole. The sample size was calculated using the Fisher's exact test in EAST version 6.0.

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 or IEC.

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). 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. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

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

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During 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, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

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

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or 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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Appendix A Schedule of Study Procedures

	Run-In Period			Treatment Period			
		PPI Run-In Period 4 weeks	Placebo Run-In Period 2 weeks (a)			Week 4 End of Treatment Visit or Early Termination Visit (b)	Safety Follow-up (c) Week 5
Visit:	**Screen Visit**	PPI assessment	Off-PPI assessment	**Randomization**	**Week 2**		
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day:	**Max Day -49**	**Day -42**	**Day -14**	**Day 1**	**Day 14**	**Day 28**	**Day 35**
Visit Windows:	**-**	**± 3 days**	**± 3 days**	**0**	**±3 days**	**±3 days**	**±3 days**
Informed consent	X						
Inclusion/exclusion criteria	X	X	X	X			
Demographics, medical history, smoking status, alcohol and caffeine consumption and medication history	X						
Physical examination	X			X		X	
Vital signs, height and weight (d)	X			X		X	
Clinical laboratory tests and urinalysis(e)	X (e)			X (e)	X	X (e)	
Fasting serum gastrin, Pepsinogen I/II(f)				X	X	X	
Mandatory Pgx sample for genotyping (g)				X			
Optional Pgx sample for storage (h)				X			
PK sampling (i)					X	X	
12-lead ECG	X			X		X	
Pregnancy test (j) – Serum/Urine	X			X		X	
Endoscopy (k)	X						
H. pylori breath test (l)				X			
Dispense e-Diary/Review compliance (m)		X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X
AE/PTE assessment	X	X	X	X	X	X	X
Contact IWRS	X	X	X	X	X	X	
Dispense PPI Run-in medication		X					
Dispense Single blind Placebo Run-in			X				
Dispense Double blind study medication				X (n)	X		
Drug accountability			X	X	X	X	

Appendix A Schedule of Study Procedures (continued)

	Run-In Period			Treatment Period			
Visit:	**Screen Visit**	**PPI Run-In Period 4 weeks** PPI assessment	**Placebo Run-In Period 2 weeks (a)** Off-PPI assessment	**Randomization**	**Week 2**	**Week 4 End of Treatment Visit or Early Termination Visit (b)**	**Safety Follow-up (c) Week 5**
Visit Number:	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day:	**Max Day -49**	**Day -42**	**Day -14**	**Day 1**	**Day 14**	**Day 28**	**Day 35**
Visit Windows:	**-**	**± 3 days**	**± 3 days**	**0**	**±3 days**	**±3 days**	**±3 days**
Dispense rescue (antacid) medication	X			X	X		
Accountability of rescue medication (o)				X	X	X	
Questionnaires(p): PSQI/ HADS/ PGIC(q)/ EQ-5D-5L/ PAGI-QOL/ PAGI-SYM		X	X	X		X	

Footnotes are on the following page.

(a) All subjects will receive esomeprazole 40 mg QD during the PPI Run-in period to assess their response to a high dose of PPI. The subject must have a partial response to a PPI defined as having heartburn on 2-5 days of the last week of a 4 week PPI Run-In Period with esomeprazole 40 mg and an increase of at least 2 symptom days of heartburn (and/or regurgitation) in the last week of a 2 week Off-PPI Assessment Period (4-7 symptom days) compared with the last week of the esomeprazole Treatment Period. Total screening including run-in period is max 49 days.
(b) Subjects who prematurely discontinue from the Treatment Period should undergo early termination Visit procedures.
(c) The subjects will be contacted for a safety follow up call approximately 1 week after last dose of study drug. Subjects who withdraw their consent should still be contacted for a Safety Follow-up but the contact should only be recorded in the medical records (and not in the eCRF), according to data protection regulations.
(d) Vital signs include body temperature. Vital sign, weight and height at Screening, vital signs and weight at Randomization and Visit 6(or early termination).
(e) Standard iron panel to be collected only at Visit 1 and Visit 6(or early termination). TSH and CRP samples to be collected at Visit 4 and Visit 6(or early termination).Urine drug screening and hepatitis test only at Visit 1.
(f) Subjects should be fasting for a minimum of 12 hours prior to the collection at Randomization, Visit 5 (Week 2) and Visit 6 (Week 4) or early termination. At the visits, subjects should be instructed to take their dose of study medication on the morning of their visit with a sip of water. Actual value of serum gastrin and serum pepsinogen I and II will be reported to investigators at Visit 4. In order to maintain blinding of study treatment, investigators will be blinded to serum gastrin and serum pepsinogen I and II values at Visit 5 and Visit 6. After the study ends, the level of serum gastrin and pepsinogen I and II at Visit 5 and Visit 6 may be provided to investigators.
(g) One 6 mL whole blood sample for DNA CYP2C19 genotyping collected at visit 4 prior to the dose administration (mandatory).
(h) Two whole blood samples (2.5 mL per sample) for ribonucleic acid (RNA) isolation to be collected at visit 4 prior to the dose administration (optional).
(i) For group 1 (a minimum of 15 subjects per treatment arm), plasma samples will be taken at time points 0 (predose) and 1 hour postdose at Visit 5 and 0 (predose), 0.5, 2, 5, 6, and 8 hours postdose at Visit 6. For group 2 (the remaining subjects in each treatment arm), plasma samples will be taken at predose and at 1 hour postdose at Visit 5 and Visit 6.
(j) Pregnancy test is only performed for women of child-bearing potential. In this group of women, the serum pregnancy testing must be done at Screening and at Week 4 (or early termination). A urine pregnancy test will be performed at Randomization.
(k) Endoscopy – For assessment of EE status and to exclude esophageal and gastric malignancies. Historical data up to one year prior to Screening is permitted. Only NERD or Grade A EE subjects are permitted to continue in the study.
(l) *Helicobacter pylori* breath test will be performed via a urea breath test (C13 or C14 urea test) at a local laboratory. A stool test may be performed at those centers which do not have the facilities to perform a H pylori breath test procedure.
(m) Subjects will complete the e-Diary during the Screening Period for at least 42 days prior to randomization and during the 4-week Treatment Period. Subjects should complete the diary every morning (for nighttime symptoms) and every evening (for daytime symptoms) on each day of the study. Instruct the subject to continue to complete the diary every morning upon waking and evening before bedtime.
(n) Study drug will be dispensed at randomization visit (Day 1) after the subject has completed all of the Screening Period procedures and subject has met all inclusion/exclusion criteria for the study including the baseline PPI insufficient responder criteria. Following randomization, the first dose of study medication will be administered at the clinic and be continued on a daily basis for 4 weeks. A 2 weeks supply of randomized treatment will be given at Visits 4 and Visit 5.
(o) Rescue medication will be dispensed at Screening and may be dispensed at Study Day 1, Week 2 and Week 4 if needed. Subjects should not take more doses than stipulated in the patient information leaflet.
(p) Questionnaires will be completed electronically on e-diary device by the subject prior to dosing and questionnaires completeness should be check prior to the subject leaving the site.
(q) PGIC questionnaire will be completed only at Visit 3, Visit 4 and Visit 6.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

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

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

Appendix C Elements of the Subject Informed Consent

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

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

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Collection, Shipment, and Storage of Pharmacogenomic Samples

Sample Collection

1. Mandatory Collection for CYP2C19 Genotyping:

   One 6 mL whole blood sample for DNA isolation and genotyping will be collected from each subject at Visit 4 after randomization and prior to dosing, into a plastic tube spray coated with K2 ethylenediamine-tetraacetic acid (EDTA).

2. Optional Collection for storage of the sample for future use:

   Two whole blood samples (2.5 mL per sample) for RNA isolation will be collected at Visit 4 prior to dose administration from each subject in the study, into a PaxGene TM tube.

Sample Shipment

1. CYP2C19 DNA samples will be shipped ambient after collection and RNA pharmacogenomic samples will be shipped frozen at -20°C after collection.
2. The laboratory must confirm arrival of the shipped samples. Store CYP2C19 samples at ambient and optional RNA samples at -20°C or colder at the site prior to shipping.
3. For instructions on shipping, both ambient and frozen, and packing follow the laboratory manual and shipping instructions provided by the central laboratory.
4. Before shipping, ensure the sample tubes are tightly sealed. Ship samples to the Central Laboratory Services. Shipping information can be found in the lab manual.

Sample Storage

CCI will initially store the DNA and RNA samples in a secure storage space with adequate measures to protect confidentiality. The samples that have consent for storage and future use will be retained at the designated laboratory for up to but not longer than 15 years or as required by applicable law.

Appendix F Collection, Shipment and Storage of Pharmacokinetic Samples

Vonoprazan and/or Esomeprazole (if required) Sample Collection and Processing

1. Using sample collection kits provided by the Central Laboratory, collect 6 mL of venous blood into a chilled Becton-Dickinson Vacutainer®. For all Vonoprazan or esomeprazole samples, blood samples should be collected into chilled vacutainers containing sodium heparin.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice or stored at room temperature.
3. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 (RCF) at room temperature or approximately 4°C in a refrigerated centrifuge. If using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
4. Immediately following centrifugation, gently remove plasma from the packed cells. To ensure a more homogeneous sample, all plasma should first be transferred into 1 aliquot. From there, split the plasma evenly between the 2 aliquots. A minimum of 1.0 mL needs to be obtained for each sample. Labeling will include protocol number, matrix (ie, plasma), analyte (vonoprazan or esomeprazole), subject number, visit number, accession number, PK blood draw [ie, Predose PK 1, Predose PK 2, PK (0.5-1 hr) Post, or PK(2-5 hr) Post] and either "SET 1" (for original sample) or "SET 2" (for duplicate sample). Refer to Central Laboratory Instruction manual for detailed sample collection, processing, packaging & shipping guidelines.
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower. No more than 60 minutes will elapse between blood collection and freezing the plasma sample.
6. Keep samples frozen at approximately -20°C or lower until shipment to Central laboratory. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the Central laboratory.

Sample Handling and Shipping

1. Biological samples (ie, plasma) should be shipped on dry ice to prevent thawing during transit. Ship samples only on Monday, Tuesday or Wednesday, and at least 2 days prior to a national holiday, to minimize the possibility of samples in transit over a weekend or holiday. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
2. Separate the duplicate SET 2 samples from the SET 1 samples.
3. Follow Central Laboratory Manual for shipping samples.

Appendix G Detailed Description of Amendments to Text

This document describes changes in reference to Protocol Incorporating Amendment No. 02.

Section 2.0 Study Summary, Page 11

Existing text

Study Design: Vonoprazan-2001 is a Phase 2 proof-of-concept (POC) study to compare vonoprazan 20 mg or 40 mg once daily (QD) with esomeprazole 40 mg QD in subjects who have a history of persistent heartburn and/or regurgitation symptoms that are troublesome despite an adequate course of proton pump inhibitor (PPI) treatment and who are then confirmed to have a partial response to a 4-week treatment course with esomeprazole 40 mg QD.

(…….)

Subject Population: Subjects aged 18 years or older who have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study and of not responding fully to their PPI treatment (at least 8 weeks of persistent heartburn and/or regurgitation symptoms that are troublesome after treatment at the standard doses of PPI).

(…….)

Main Criteria for Inclusion: Subjects will be eligible for participation in the study if they; have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study; have a history of persistent heartburn and/or regurgitation symptoms that are troublesome despite an adequate course of PPI treatment; continue to have symptoms of heartburn (and regurgitation) following 4 weeks treatment with a high dose of esomeprazole 40 mg QD during the Run-in Period; have symptoms of heartburn which increases following a 2-week Washout Period in the presence of regurgitation prior to randomization. Patients with mild (LA grade A) esophagitis are permitted to enter the study.

Revised text

Study Design: Vonoprazan-2001 is a Phase 2 proof-of-concept (POC) study to compare vonoprazan 20 mg or 40 mg once daily (QD) with esomeprazole 40 mg QD in subjects who have a history of **predominant heartburn symptoms in the presence of regurgitation** that are troublesome despite an adequate course of proton pump inhibitor (PPI) treatment and who are then confirmed to have a partial response to a 4-week treatment course with esomeprazole 40 mg QD.

(…….)

Subject Population: Subjects aged 18 years or older who have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study and of not responding fully to their PPI treatment (at least 8 weeks of **predominant heartburn symptoms in the presence of regurgitation** that are troublesome after treatment at the standard doses of PPI).

(……)

Main Criteria for Inclusion: Subjects will be eligible for participation in the study if they; have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study; have a history of **predominant heartburn symptoms in the presence of regurgitation** that are troublesome despite an adequate course of PPI treatment; continue to have symptoms of heartburn (and regurgitation) following 4 weeks treatment with a high dose of esomeprazole 40 mg QD during the Run-in Period; have symptoms of heartburn which increases following a 2-week Washout Period in the presence of regurgitation prior to randomization. Patients with mild (LA grade A) esophagitis are permitted to enter the study.

Rationale for Amendment

Updated to reflect the change of inclusion criteria No 5. The inclusion criteria has been clarified to include patients who have predominant heartburn symptoms in the presence of regurgitation.

Section 4.1 Background, Paragraph 7, Page 18

Existing Text

Vonoprazan-2001 is a Phase 2 proof-of-concept (POC) study comparing vonoprazan with esomeprazole in subjects who have a history of persistent heartburn and/or regurgitation GERD symptoms despite an adequate course of PPI treatment and who are then confirmed to have a partial response to a 4-week treatment course with esomeprazole 40 mg QD[16,17]. As vonoprazan is a strong gastric acid inhibitor, it is considered that esomeprazole 40 mg, which is commonly used in patients not responding to their initial dose of PPI, is an appropriate comparator for this indication.

Revised Text

Vonoprazan-2001 is a Phase 2 proof-of-concept (POC) study comparing vonoprazan with esomeprazole in subjects who have a history of persistent heartburn and regurgitation GERD symptoms despite an adequate course of PPI treatment and who are then confirmed to have a partial response to a 4-week treatment course with esomeprazole 40 mg QD[16,17]. As vonoprazan is a strong gastric acid inhibitor, it is considered that esomeprazole 40 mg, which is commonly used in patients not responding to their initial dose of PPI, is an appropriate comparator for this indication.

Rationale for Amendment

Updated to reflect the change of inclusion criteria No 5. The inclusion criteria has been clarified to include patients who have predominant heartburn symptoms in the presence of regurgitation.

Section 5.2.3 Additional Endpoints, Page 22

Existing Text

None

Revised Text

- **Percentage of responders, where a responder is defined as having at least 3 more days of not more than mild heartburn symptoms on average per week during the whole double blind treatment period compared to baseline, where baseline is defined as the 1 week run-in period on placebo prior to randomization.**

Rationale for Amendment

The additional analysis is being included as this was one of the primary endpoints derived from RESQ-eD data in a previous study which enrolled GERD Patients with partial response to PPI (NCT01005251). This analysis has been included as it includes components of both reduction in the number as well as severity of symptoms.

Section 6.1 Study Design, Paragraph 2, Page 25

Existing Text

Subjects will be eligible for participation in the study if they: have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study; have a history of persistent heartburn and/or regurgitation symptoms that are troublesome despite an adequate course of PPI treatment; continue to have symptoms of heartburn (and/or regurgitation) following 4 weeks treatment with a high dose of esomeprazole 40 mg QD during the Run-in Period; have symptoms of heartburn which increases following a 2-week Washout Period in the presence of regurgitation prior to randomization; and meet all of the inclusion criteria and none of the exclusion criteria. Patients with mild (LA grade A) esophagitis are also permitted to enter the study. To confirm LA grade, endoscopy will be performed at screening, or historical data of endoscopy up to one year prior to screening may be permitted. The study will consist of 3 periods: a 7-week Run-in period (initial 1 week screening period and a 6-week single-blind Run-in), a 4-week double blind Treatment Period, and a 1-week Safety Follow-up. The Run-in includes a 1-week general Screening Period during which the subject will remain on their prescribed PPI (Day-49 to Day -42); followed by a 4-week single-blind PPI assessment period with blinded esomeprazole 40 mg QD (Day -42 to Day -14); and then a 2-week single-blind placebo Off-PPI Assessment period (Day -14 to Day-1). Subjects who remain symptomatic and compliant will be randomized to the 4-week Treatment Period followed by a one week safety Follow-up Call. Certain medications will require washout prior to entry into the study and will not be permitted during the study as outlined in Table 7.a.

Revised Text

Subjects will be eligible for participation in the study if they: have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study; have a history of

predominant heartburn symptoms in the presence of regurgitation that are troublesome despite an adequate course of PPI treatment; continue to have symptoms of heartburn **and** regurgitation following 4 weeks treatment with a high dose of esomeprazole 40 mg QD during the Run-in Period; have symptoms of heartburn which increases following a 2-week Washout Period in the presence of regurgitation prior to randomization; and meet all of the inclusion criteria and none of the exclusion criteria. Patients with mild (LA grade A) esophagitis are also permitted to enter the study. To confirm LA grade, endoscopy will be performed at screening, or historical data of endoscopy up to one year prior to screening may be permitted. The study will consist of 3 periods: a 7-week Run-in period (initial 1 week screening period and a 6-week single-blind Run-in), a 4-week double blind Treatment Period, and a 1-week Safety Follow-up. The Run-in includes a 1-week general Screening Period during which the subject will remain on their prescribed PPI (Day-49 to Day -42); followed by a 4-week single-blind PPI assessment period with blinded esomeprazole 40 mg QD (Day -42 to Day -14); and then a 2-week single-blind placebo Off-PPI Assessment period (Day -14 to Day-1). Subjects who remain symptomatic and compliant will be randomized to the 4-week Treatment Period followed by a one week safety Follow-up Call. Certain medications will require washout prior to entry into the study and will not be permitted during the study as outlined in Table 7.a.

Rationale for Amendment

Updated to reflect the change of inclusion criteria No 5. The inclusion criteria has been clarified to include patients who have predominant heartburn symptoms in the presence of regurgitation.

Section 6.2 Justification for Study Design, Dose, and Endpoints, Paragraph 2, Page 27

Existing Text

This study aims to recruit subjects who have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study and of not responding fully to their PPI treatment (at least 8 weeks of persistent heartburn and/or regurgitations symptoms that are troublesome after treatment at the standard doses of PPI) and who have a partial response to treatment with a high dose of esomeprazole 40 mg QD (defined as having heartburn on 2 to 5 days and regurgitation on at least one day of the last week [Week 4] of a 4 week Run-in with esomeprazole 40 mg). To further confirm that their heartburn is acid-related, subjects also have to have an increase of at least 2 symptom days of heartburn) in the last week of a 2-week Off-PPI Assessment Period (4 to 7 symptom days) and at least one symptom day with regurgitation compared with the last week of the PPI Assessment Period. Having the Washout after PPI treatment will result in a higher pre-randomization baseline heartburn frequency allowing the effects of both treatments as well as the treatment difference to be estimated. Symptomatic patients with mild EE (LA Grade A) will be permitted to enter the study as the presence of EE is a good indicator of the patient suffering from an acid-related problem and the study treatments are being used at doses which have been shown to effectively treat EE. Two doses of vonoprazan (20 mg and 40 mg) have been selected for this study. Vonoprazan 20 mg has been included, as this is the clinical dose recommended in Japan for the treatment of EE. Experience with PPIs indicate that for

patients with a partial response to approved once daily therapy, tailored therapy is often given off-label with adjustment of dose, dose timing and/or twice daily dosing [20]. Therefore, vonoprazan 20 mg may be expected to be a minimally effective clinical dose in this difficult to treat population. As such, a higher dose of vonoprazan 40 mg has also been selected as a potentially appropriate dose for this population of patients. Using vonoprazan 20 mg and 40 mg therefore allows for a comparison of dose effect and to select the appropriate dose of vonoprazan to take forward in to Phase 3. Esomeprazole is considered as the current gold standard PPI for the treatment of GERD and 40 mg is the most appropriate dose for this difficult to treat population.

Revised Text

This study aims to recruit subjects who have a documented history of symptoms of both heartburn and acid regurgitation prior to entry into the study and of not responding fully to their PPI treatment (at least 8 weeks of **predominant heartburn symptoms in the presence of regurgitation** that are troublesome after treatment at the standard doses of PPI) and who have a partial response to treatment with a high dose of esomeprazole 40 mg QD (defined as having heartburn on 2 to 5 days and regurgitation on at least one day of the last week [Week 4] of a 4 week Run-in with esomeprazole 40 mg). To further confirm that their heartburn is acid-related, subjects also have to have an increase of at least 2 symptom days of heartburn) in the last week of a 2-week Off-PPI Assessment Period (4 to 7 symptom days) and at least one symptom day with regurgitation compared with the last week of the PPI Assessment Period. Having the Washout after PPI treatment will result in a higher pre-randomization baseline heartburn frequency allowing the effects of both treatments as well as the treatment difference to be estimated. Symptomatic patients with mild EE (LA Grade A) will be permitted to enter the study as the presence of EE is a good indicator of the patient suffering from an acid-related problem and the study treatments are being used at doses which have been shown to effectively treat EE. Two doses of vonoprazan (20 mg and 40 mg) have been selected for this study. Vonoprazan 20 mg has been included, as this is the clinical dose recommended in Japan for the treatment of EE. Experience with PPIs indicate that for patients with a partial response to approved once daily therapy, tailored therapy is often given off-label with adjustment of dose, dose timing and/or twice daily dosing [20]. Therefore, vonoprazan 20 mg may be expected to be a minimally effective clinical dose in this difficult to treat population. As such, a higher dose of vonoprazan 40 mg has also been selected as a potentially appropriate dose for this population of patients. Using vonoprazan 20 mg and 40 mg therefore allows for a comparison of dose effect and to select the appropriate dose of vonoprazan to take forward in to Phase 3. Esomeprazole is considered as the current gold standard PPI for the treatment of GERD and 40 mg is the most appropriate dose for this difficult to treat population.

Rationale for Amendment

Updated to reflect the change of inclusion criteria No 5. The inclusion criteria has been clarified to include patients who have predominant heartburn symptoms in the presence of regurgitation.

Section 7.1 Inclusion Criteria, Page 30

Existing Text

5. The subject has a medical history of ≥ 8 weeks of persistent heartburn and/or regurgitation symptoms (persistent heartburn and/or regurgitation symptoms defined as symptoms on ≥ 2 days a week) that are troublesome despite appropriate and correctly performed treatment with a PPI at standard doses.

Revised Text

5. The subject has a medical history of ≥ 8 weeks of persistent heartburn symptoms **in the presence of** regurgitation symptoms (persistent heartburn symptoms defined as **heartburn** symptoms on ≥ 2 days a week) that are troublesome despite appropriate and correctly performed treatment with a PPI at standard doses.

Rationale for Amendment

The inclusion criteria has been clarified to include patients who have predominant heartburn symptoms in the presence of regurgitation. This confirms the patient has GERD and also has the appropriate symptoms to perform the required proposed data analysis.

Section 8.1.1.2 Rescue Medication, Page 37

Existing Text

A guideline of commonly used medications which may be used as rescue medications in each of the countries will be provided. If the listed rescue medications in the guideline are not available, CRO/Takeda medical monitor may provide guidance of available brand to investigators. The administration of rescue medication shall be in accordance to the package insert approved in the corresponding countries. When rescue medication is administered, subjects should be instructed to take rescue medication only after consultation with the investigator. For aluminum based medications, an interval of at least 2 hours must be maintained between administration of study medication (Vonoprazan or esomeprazole) and rescue medication. Subjects shall contact the investigators if they would like to take the rescue medication at a dose higher than the approved ones in the local insert package.

Revised Text

A guideline of commonly used medications which may be used as rescue medications in each of the countries will be provided. If the listed rescue medications in the guideline are not available, CRO/Takeda medical monitor may provide guidance of available brand to investigators. The administration of rescue medication shall be in accordance to the package insert approved in the

corresponding countries. For aluminum based medications, an interval of at least 2 hours must be maintained between administration of study medication (Vonoprazan or esomeprazole) and rescue medication. Subjects shall contact the investigators if they would like to take the rescue medication at a dose higher than the approved ones in the local insert package.

Rationale for Amendment

Removal of the instruction for subjects to contact the investigators when rescue medication is administered as this is not practical.

Section 9.1.6.2 Subject Reported Outcome Questionnaires, Quality of Sleep, Page 45

Existing Text

Quality of sleep will be assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire [23]. The PSQI questionnaire is a 19-item validated questionnaire completed by patients regarding the previous 1-month period. Items are grouped into seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component score is weighted equally on a 0–3 scale, with 3 representing the worse effect, then summed to yield a global PSQI score, which could range from 0 to 21. Patients with a global score >5 are considered to have poor sleep quality. Patients will complete the questionnaire at the Visit 4 and Visit 6 (or early termination).

Revised Text

Quality of sleep will be assessed using the Pittsburgh Sleep Quality Index (PSQI) questionnaire [23]. The PSQI questionnaire is a 19-item validated questionnaire completed by patients regarding the previous 1-month period. Items are grouped into seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each component score is weighted equally on a 0–3 scale, with 3 representing the worse effect, then summed to yield a global PSQI score, which could range from 0 to 21. Patients with a global score >5 are considered to have poor sleep quality. Patients will complete the questionnaire at the **Visit 2, Visit 3,** Visit 4 and Visit 6 (or early termination).

Rationale for Amendment

Correction of inconsistencies with appendix A. schedule of study procedures.

Section 9.1.6.2 Subject Reported Outcome Questionnaires, Patient Global Impression of Change, Page 45

Existing Text

The Patient Global Impression of Change (PGIC) is a patient-rated instrument that measures change in patient's GERD-related symptoms on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) [31]. Higher scores indicate a change for the worse. For this study, subjects will be asked to rate their symptoms relative to their previous past 4-weeks or 2-weeks. The PGIC item will be assessed at visit 2, visit 3, visit 4 and visit 6 (Early termination).

The PGIC will be used to further document the ability RESQ-eD to detect change as well as clinical meaningfulness of change.

Revised Text

The Patient Global Impression of Change (PGIC) is a patient-rated instrument that measures change in patient's GERD-related symptoms on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse) [31]. Higher scores indicate a change for the worse. For this study, subjects will be asked to rate their symptoms relative to their previous past 4-weeks or 2-weeks. The PGIC item will be assessed at visit 3, visit 4 and visit 6 (Early termination). The PGIC will be used to further document the ability RESQ-eD to detect change as well as clinical meaningfulness of change.

Rationale for Amendment

Correction of schedule of PGIC assessment due to an error of the original protocol.

Section 9.1.9 Procedures for Clinical Laboratory Samples, Table 9.b, Page 47

Existing Text

Urinalysis
Bilirubin
Glucose
Hemoglobin
Ketones
Leucocytes
Nitrites
pH
Protein
Specific gravity
Urobilinogen

Revised Text

Urinalysis
Appearance
Color
Bilirubin
Glucose
Hemoglobin
Ketones
Leucocytes
Nitrites
pH
Protein
Specific gravity
Urobilinogen

Rationale for Amendment

Missing of urine appearance and color from the original protocol.

Section 9.1.9 Procedures for Clinical Laboratory Samples, Paragraph 5, Page 48

Existing Text

CCI [redacted]

Revised Text

CCI [redacted]

Rationale for Amendment

CCI [redacted]

Section 9.1.10 Contraception and Pregnancy Avoidance Procedure, Paragraph 4, Page 49

Existing Text

Barrier methods (each time the subject has intercourse):

- Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.

Intrauterine devices (IUDs):

- Copper T.

Revised Text

Barrier methods (each time the subject has intercourse):

- Cap (plus spermicidal cream or jelly) PLUS male condom.
- Diaphragm (plus spermicidal cream or jelly) PLUS male condom.

Intrauterine devices (IUDs):

- Copper T.

Rationale for Amendment

Duplication of spermicide is not required.

Section 9.3 Schedule of observations and Procedures, Page 55

Existing Text

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

Visit windows should be calculated from the day of randomization. Visit windows are listed in Appendix A.

Revised Text

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

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

Rationale for Amendment

Clarification of unscheduled non-study visits which may be held, if necessary.

Section Appendix A Schedule of Study Procedures, Page 81

Existing Text

Visit:	Screen Visit	**PPI Run-In Period 4 weeks** PPI assessment	**Placebo Run-In Period 2 weeks (a)** Off-PPI assessment
Visit Number:	**1**	**2**	**3**
Day:	**Max Day -49**	**Day -42**	**Day -14**
Visit Windows:	**-**	**± 3 days**	**± 3 days**
Questionnaires(p): PSQI/ HADS/ PGIC/ EQ-5D-5L/ PAGI-QOL/ PAGI-SYM		X	X

(a) All subjects will receive esomeprazole 40 mg QD during the PPI Run-in period to assess their response to a high dose of PPI. The subject must have a partial response to a PPI defined as having heartburn on 2-5 days of the last week of a 4 week PPI Run-In Period with esomeprazole 40 mg and an increase of at least 2 symptom days of heartburn (and/or regurgitation) in the last week of a 2 week Off-PPI Assessment Period (4-7 symptom days) compared with the last week of the esomeprazole Treatment Period.

(……..)

(f) Subjects should be fasting for a minimum of 12 hours prior to the collection at Randomization, Visit 5 (Week 2) and Visit 6 (Week 4) or early termination. At the visits, subjects should be instructed to take their dose of study medication on the morning of their visit with a sip of water.

(……..)

(p) Questionnaires should be completed by the subject prior to dosing and questionnaires completeness should be check prior to the subject leaving the site.

Revised Text

Visit:	Screen Visit	PPI Run-In Period 4 weeks PPI assessment	Placebo Run-In Period 2 weeks (a) Off-PPI assessment
Visit Number:	**1**	**2**	**3**
Day:	**Max Day -49**	**Day -42**	**Day -14**
Visit Windows:	**-**	**± 3 days**	**± 3 days**
Questionnaires(p): PSQI/ HADS/ PGIC**(q)**/ EQ-5D-5L/ PAGI-QOL/ PAGI-SYM		X	X

(a) All subjects will receive esomeprazole 40 mg QD during the PPI Run-in period to assess their response to a high dose of PPI. The subject must have a partial response to a PPI defined as having heartburn on 2-5 days of the last week of a 4 week PPI Run-In Period with esomeprazole 40 mg and an increase of at least 2 symptom days of heartburn (and/or regurgitation) in the last week of a 2 week Off-PPI Assessment Period (4-7 symptom days) compared with the last week of the esomeprazole Treatment Period.
Total screening including run-in period is max 49 days.

(……..)

(f) Subjects should be fasting for a minimum of 12 hours prior to the collection at Randomization, Visit 5 (Week 2) and Visit 6 (Week 4) or early termination. At the visits, subjects should be instructed to take their dose of study medication on the morning of their visit with a sip of water. **Actual value of serum gastrin and serum pepsinogen I and II will be reported to investigators at Visit 4. In order to maintain blinding of study treatment, investigators will be blinded to serum gastrin and serum pepsinogen I and II values at Visit 5 and Visit 6. After the study ends, the level of serum gastrin and pepsinogen I and II at Visit 5 and Visit 6 may be provided to investigators.**
(……..)

(p) Questionnaires **will** be completed **electronically on e-diary device** by the subject prior to dosing and questionnaires completeness should be check prior to the subject leaving the site.
(q) PGIC questionnaire will be completed only at Visit 3, Visit 4 and Visit 6.

Rationale for Amendment

Clarification of total screening period including PPI/Placebo run-in. Clarification of completion of questionnaires electronically. Correction of schedule of PGIC assessment due to error of the original protocol.

Section Appendix E Collection, Shipment, and Storage of Pharmacogenomic Samples, Page 89

Existing Text

Sample Shipment

1. DNA and RNA pharmacogenomic samples will be shipped frozen at -20°C after collection.
2. Ship samples only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, to minimize the possibility of samples in transit over a weekend or holiday.
3. The laboratory must confirm arrival of the shipped samples. Storage at the site prior to shipping must be at -20°C or colder.

6. For instructions on shipping, both ambient and refrigerated, and packing follow the laboratory manual and shipping instructions provided by the central laboratory.
7. Before shipping, ensure the sample tubes are tightly sealed. Ship samples to the Central Laboratory Services. Shipping information can be found in the pharmacogenomic lab manual.

Revised Text

Sample Shipment

1. **CYP2C19 DNA samples will be shipped ambient after collection** and RNA pharmacogenomic samples will be shipped frozen at -20°C after collection.
2. The laboratory must confirm arrival of the shipped samples. **Store CYP2C19 samples at ambient and optional RNA samples** at -20°C or colder at the site prior to shipping .
3. For instructions on shipping, both ambient and **frozen**, and packing follow the laboratory manual and shipping instructions provided by the central laboratory.
4. Before shipping, ensure the sample tubes are tightly sealed. Ship samples to the Central Laboratory Services. Shipping information can be found in the pharmacogenomic lab manual.

Rationale for Amendment

Correction of sample storage and shipping condition of CYP2C19 DNA samples.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical VP Approval	31-Mar-2016 12:35
	Clinical Science Approval	31-Mar-2016 14:12
	Biostatistics Approval	04-Apr-2016 08:08