Title: A Phase 1, Randomized, Open-label, 2-way Cross-over Study to Evaluate the Bioequivalence Between a Single Oral Dose of Esomeprazole 40 mg Capsules and Esomeprazole 40 mg Tablets in Healthy Subjects

NCT Number: NCT03083639

Protocol Approve Date: 07 March 2017

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

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

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

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Randomized, Open-label, 2-way Cross-over Study to Evaluate the Bioequivalence Between a Single Oral Dose of Esomeprazole 40 mg Capsules and Esomeprazole 40 mg Tablets in Healthy Subjects

Esomeprazole Bioequivalence Study

Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, Illinois 60015		
Study Number:	Esomeprazole-1001		
IND Number:	Not applicable	**EudraCT Number:**	Not applicable
Compound:	Esomeprazole		
Date:	07 March 2017	**Version Number:**	2

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 should be provided to the site.

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Takeda Pharmacovigilance PPD
Medical Monitor (medical advice on protocol and study drug)	
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 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 are provided on the last page of this document.

PPD Date

PPD Date

PPD Date

INVESTIGATOR

I confirm that I have read and that I understand this protocol, the Prescribing Information for esomeprazole capsules and tablets, 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 study site agreement.
- Responsibilities of the Investigator (Appendix B).

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/Provence)

Location of Facility (Country)

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Americas, Inc.</td><td colspan="2">Compound:
Esomeprazole</td></tr>
<tr><td>Title of Protocol: A Phase 1, Randomized, Open-label, 2-way Cross-over Study to Evaluate the Bioequivalence between a Single Oral Dose of Esomeprazole 40 mg Capsules and Esomeprazole 40 mg Tablets in Healthy Subjects</td><td>IND No.: not applicable</td><td>EudraCT No.:
not applicable</td></tr>
<tr><td>Study Number: Esomeprazole-1001</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="3">Study Design:
Phase 1, randomized, open-label, 2-way crossover study in healthy adult male and female subjects aged 18 to 55 years, inclusive, to evaluate the bioequivalence between a single oral dose of esomeprazole 40 mg capsules (Nexium) and esomeprazole 40 mg tablets (Nexium).</td></tr>
<tr><td colspan="3">Primary Objective:
To determine the bioequivalence between esomeprazole 40 mg tablets and capsules.</td></tr>
<tr><td colspan="3">Subject Population: Healthy adult male and female subjects aged 18 to 55 years, inclusive.</td></tr>
<tr><td>Number of Subjects: Estimated Total: 52</td><td colspan="2">Number of Sites: 1</td></tr>
<tr><td>Dose Level(s):
Regimen A: A single 40 mg esomeprazole capsule.
Regimen B: A single 40 mg esomeprazole tablet.</td><td colspan="2">Route of Administration:
oral</td></tr>
<tr><td>Duration of Treatment:
Single dose</td><td colspan="2">Period of Evaluation:
36 days</td></tr>
<tr><td colspan="3">Main Criteria for Inclusion:
Healthy adult male or female subjects aged 18 to 55 years, inclusive, and weighing at least 50 kg with a body mass index from 18.5 to 30 kg/m2, inclusive.</td></tr>
<tr><td colspan="3">Main Criteria for Exclusion:
Subject has a known hypersensitivity to any component of the formulation of esomeprazole capsules or tablets or compounds with the same mechanism of action, or related compounds; a history of significant gastrointestinal (GI) disorders manifested with persistent, chronic or intermittent nausea, vomiting, diarrhea, or has a current or recent (within 6 months) GI disease that would influence the absorption of drugs, or any gastrointestinal-related surgical intervention.</td></tr>
</table>

Main Criteria for Evaluation and Analyses:

The concentrations of esomeprazole in plasma following tablet and capsule administration will be measured at 0 (predose), and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours postdose. The primary endpoints for this study are the pharmacokinetic parameters derived from the plasma concentrations of esomeprazole 40 mg administered via capsule and tablet after a single dose including: area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}); area under the concentration-time curve from time 0 to time t (AUC_t) and maximum observed concentration (C_{max}).

Statistical Considerations:

Descriptive statistics (arithmetic mean, SD, percent coefficient of variation (%CV), median, minimum and maximum) will be used to summarize the plasma concentrations and plasma pharmacokinetics parameters for esomeprazole. In addition, geometric mean and %CV will be computed for C_{max}, $AUC_{\infty,}$ and AUC_t.

Natural-logarithmically transformed C_{max} and AUCs will be analyzed using analysis of variance with fixed factors for period, sequence, and regimen, and subject within sequence as a random effect. Bioequivalence will be assessed via point estimates and 90% CI for the ratio of C_{max}, and AUCs central values for esomeprazole tablet (Regimen B – test) versus esomeprazole capsule (Regimen A - reference). Bioequivalence between tablet and capsule will be claimed if the 90% CI for the ratio is within the bioequivalence criteria of 0.80 to 1.25.

Sample Size Justification: The sample size for this study is estimated at 52, which provides an allowance for 4 dropouts. The sample size was estimated based on variability data from a previous study, using a %CV of 28% as the intrasubject variation for the natural logarithm of C_{max} and the assumed true ratio of 0.95 for tablet over capsule. Given the above information, a sample size of 52 subjects provides at least 90% power for concluding bioequivalence for C_{max} and the power for AUCs is greater than 90%.

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 vendors identified for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

PPD

3.3 List of Abbreviations

%CV	percent coefficient of variation
λ_z	terminal disposition rate constant
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_t	area under the concentration-time curve from time 0 to time t
AUC_∞	area under the concentration-time curve from time 0 to infinity
bpm	beats per minute
BMI	body mass index
CHMP	Committee for Medicinal Products for Human Use
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CRO	contract research organization
CS	clinically significant
CYP	cytochrome P-450
ECG	electrocardiogram
eCRF	case report form electronic or paper
EMA	European Medicines Agency
DU	duodenal ulcer
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GU	gastric ulcer
H. pylori	helicobacter pylori
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IEC	independent ethics committee
ICH	International Conference on Harmonisation
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NCS	not clinically significant

PK	pharmacokinetic
PPIs	proton pump inhibitors
PTE	pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
tlag	lag time to first quantifiable concentration
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
Vz/F	apparent volume of distribution during the terminal disposition phase after extravascular administration

3.4 Corporate Identification

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

Acid-related diseases including peptic ulcer and gastroesophageal reflux disease (GERD) are one of the most common gastrointestinal (GI) diseases. The proton pump inhibitors (PPIs), such as esomeprazole magnesium, represent the drugs of first choice for acid-related disorders, and are being widely used all over the world. The PPIs inhibit the H^+, K^+-ATPase enzyme (proton pump) which represents the final step in acid secretion by the parietal cells in the gastric mucosa, and produce potent anti-secretory efficacy for acid-related disorders.

However, even with these potent acid-inhibitory effects, the PPIs are not without their limitations and have not necessarily produced adequate improvements in extent and speed of symptom relief [1]. Indeed, the PPIs appear to leave room for improvement, the reasons being that:

1. Being less resistant to acid exposure and provided as enteric-coated drugs, the PPIs vary in time for onset of their action;
2. About 3 to 5 days are required to obtain maximum acid-inhibitory effects with the PPIs;
3. Acid-inhibitory effects with the PPIs appear to be satisfactory during daytime, but not adequate to inhibit acid regurgitations from the stomach to the esophagus occurring during nighttime, leading to nocturnal acid breakthroughs in some individuals;
4. Metabolized by cytochrome P-450 (CYP)2C19 associated with polymorphisms, the PPIs are associated with varying serum concentrations, thus producing disparate acid-inhibitory effects in extensive metabolizers versus poor metabolizers.

The development of new drug treatments for acid-related diseases such as GERD needs to include clinical trials with an active comparator considered an accepted standard of care, ie, PPIs (namely esomeprazole).

TAK-438 (vonoprazan fumarate), a potassium-competitive acid blocker, was developed to overcome some of the limitations of PPIs. It is approved and marketed for the treatment of acid-related diseases in Japan including the indications of: erosive esophagitis healing and maintenance; healing of gastric ulcer (GU) and duodenal ulcer (DU); the prevention of recurrence of GU or DU associated with administration of low-dose aspirin or nonsteroidal anti-inflammatory; and for the eradication of *helicobacter pylori* (H. pylori) infection as a component of triple therapy (co-administered with 2 antibiotics). Vonoprazan is currently undergoing further global development with studies ongoing in Asia and the European Union, and more studies planned globally, where esomeprazole is likely to be used as active comparator.

4.2 Rationale for the Proposed Study

Esomeprazole is available in several pharmaceutical forms including different formulations across regions for the same indications, namely tablets in the European Union and capsules in the United States. To ensure the global applicability of clinical study results utilizing esomeprazole as a comparator, this phase 1, randomized, open-label, 2-way crossover study in healthy adult

male and female subjects is being conducted to evaluate the bioequivalence of a single oral dose of esomeprazole 40 mg capsules and esomeprazole 40 mg tablets. The design is based on previously conducted esomeprazole bioequivalence studies [2-4], and is consistent with regulatory guidance [5,6].

4.3 Benefit/Risk Profile

Given that this study is being conducted in healthy subjects with the aim of establishing bioequivalence of single doses of esomeprazole, this study is not expected to provide benefit to the subjects taking part. In this study it is planned that subjects will receive 2 doses of esomeprazole separated by at least a 6-day washout. Esomeprazole was first approved in 2001 and since this time has been widely used in the treatment of acid-related disorders. Esomeprazole is well characterized in terms of efficacy and safety, and there are no anticipated risks associated with administering esomeprazole in the context of this phase 1 study to this healthy subject population. Finally, although this study requires that blood is withdrawn for the purposes of analyzing clinical laboratory markers, and the bioequivalence of esomeprazole tablets and capsules, the approximate total volume of blood for the study is 356 mL over the course of the study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To determine the bioequivalence of esomeprazole 40 mg tablets and capsules.

5.1.2 Additional Objectives

To determine pharmacokinetic (PK) parameters for each formulation.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints for this study are the PK parameters derived from the plasma concentrations of esomeprazole 40 mg administered via capsule and tablet after a single dose including: area under the concentration-time curve from time 0 to infinity (AUC_∞), area under the concentration-time curve from time 0 to time t (AUC_t), and maximum observed concentration (C_{max}).

5.2.2 Additional Endpoints

Additional endpoints for this study are the PK parameters derived from the plasma concentrations of esomeprazole 40 mg administered via capsule and tablet after a single dose including: time of first occurrence of C_{max} (t_{max}); terminal disposition phase half-life ($t_{1/2z}$); apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration (CL/F); apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration (Vz/F); terminal disposition phase rate constant (λ_z), and lag time to first quantifiable concentration (t_{lag}).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, randomized, open-label, 2-way cross-over study in healthy adult male and female subjects aged 18 to 55 years, inclusive, to evaluate the bioequivalence of a single oral dose of esomeprazole 40 mg capsules (reference [A]) and esomeprazole 40 mg tablets (test [B]).

It is estimated that 52 subjects will be needed to ensure that 48 subjects complete both periods. Screening for potential subjects will occur between 28 and 2 days prior to Day 1. On Day -1, subjects' eligibility will be reconfirmed and eligible subjects will be randomized in a 1:1 ratio to 1 of 2 sequences, which defines the order in which they will receive esomeprazole regimens in Periods 1 and 2. In both periods, subjects will fast for 10 hours prior to study drug administration and refrain from eating until 4 hours after drug administration. Each period will be separated by a minimum 6-day washout period. Blood samples for PK analysis will be drawn up to 10 hours after study drug administration on Day 1 in each period. Subjects will be confined to the phase 1 unit from Day -1 until the end of all assessments on Day 1 of each period.

Given that esomeprazole is a marketed product with a well-characterized safety profile, this study does not include a follow-up evaluation period. In total, the period of evaluation is expected to be a maximum of 36 days (assuming a washout period of 6 days), including the Screening Period.

A schematic of the study design is shown in Figure 6.a. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design

Pretreatment Period		**Period 1 (a)**			**Period 2 (a)**		
Screening (b)	Check-in	Single Dose and PK (c)	Checkout	Washout (d)	Check-in	Single Dose and PK (c)	Checkout
Days -28 to -2	Day -1	Day 1	Day 1	Day 2-6	Day -1	Day 1	Day 1
	Confinement				Confinement		

(a) Subjects will be admitted to the clinic on Day -1 of each period. On Day 1, subjects will be randomized to 1 of 2 sequences of esomeprazole tablet and capsule. Subjects will be discharged from the clinic on Day 1 after dosing and the completion of all scheduled procedures.
(b) For clinical laboratory tests that are required to be taken under fasting conditions, the subject will be asked to return to the unit at a later date under fasting conditions.
(c) PK samples at 0 (predose), and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours postdose.
(d) Minimum 6-day washout between doses. Day -1 of Period 2 could be the sixth day of washout.

6.2 Justification for Study Design, Dose, and Endpoints

Study design

This phase 1, randomized, open-label, single-dose, 2-way crossover relative bioequivalence study is designed in accordance with the draft Food and Drug Administration (FDA) guidance [6], and European Medicines Agency (EMA) guidance [5].

A single-dose study under fasting conditions for assessing the relative bioequivalence between formulations is recommended in FDA and Committee for Medicinal Products for Human Use (CHMP) guidance and will be used for comparison of the 2 different formulations. The crossover design is appropriate for the objectives of this study because each subject receives both regimens and serves as his or her own control.

The sample size for this study is estimated as 52 which allows for 4 dropouts (see Section 13.3 for further details of sample size calculation).

In humans, esomeprazole has a mean PK $t_{1/2z}$ of approximately 1 hour, and a mean pharmacodynamic $t_{1/2z}$ of approximately 50 hours for sulphenamide complex. The pH levels have been shown to return to Baseline ~48 hours after the previous dose. Therefore, a minimum 6-day washout interval between the doses is sufficient to ensure that there is no drug carryover effect, and collection of PK blood samples for 10 hours postdose is appropriate to characterize the PK of esomeprazole. The primary PK endpoints, AUC_{∞}, C_{max} and AUC_t are standard parameters to assess bioequivalence.

Dose selection

This study is testing the bioequivalence between esomeprazole capsules and tablets at the highest dose strength, 40 mg, consistent with the published data [2]. Administered as a single-dose with a minimum 6-day washout between doses, this dose is expected to be generally well tolerated in healthy subjects.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the esomeprazole, such that the risk 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.
  - Two or more subjects experience any of the Takeda Medically Significant List events (as outlined in Table 10.a).*

- Two or more subjects experience alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevations >5 × upper limit of normal (ULN) in the absence of a concomitant bilirubin increase [see below].*
- One or more subjects experience ALT and/or AST elevations >3 ×ULN in the presence of a total bilirubin increase >2 ×ULN or an international normalized ratio (INR) >1.5 without findings of cholestasis or other alternate etiology to explain the elevations (ie, "Hy's Law cases").
- Two or more subjects experience ALT and/or AST elevations >3 ×ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).*

  * Please note that the study may be terminated early prior to full attainment of these criteria (eg, if just 1 subject experiences 1 of these events) if warranted by safety data from the other subjects dosed in the study to date.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

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

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study 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 a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

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 including requesting that a subject fast for any laboratory evaluations. [Note: this is not a contradiction of Criterion 1. A subject may understand and be able to comply with the protocol but physically unable to sign (eg, blind / broken hand).]
3. The subject is a healthy adult male or female subject.
4. The subject is aged 18 to 55 years, inclusive, at the time of informed consent and first study medication dose.
5. The subject weighs at least 50 kg and has a body mass index (BMI) from 18.5 to 30 kg/m^2, inclusive at Screening and Day -1.
6. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception* from signing of informed consent throughout the duration of the study and for 31 days after the last dose of the study drug.

   * Definitions and highly effective methods of contraception are defined in Section 9.1.9 and reporting responsibilities are defined in Section 9.1.10.

7. The subject is willing to abstain from caffeine from 72 hours before Day -1 and alcohol from 7 days before Day -1 and throughout the duration of the study.
8. The subject is willing to abstain from strenuous exercise from 72 hours before first dose (Day 1) in Period 1 and throughout the duration of the study.
9. Subject has clinical chemistry, hematology, and complete urinalysis at Screening and Check-in (Day -1 of Period 1) results within the reference range for the testing laboratory unless the out-of-range results are deemed not clinically significant by the investigator.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 30 days prior to first dose
2. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

3. The subject has uncontrolled, clinically significant neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, or endocrine disease or other abnormality, which may impact the ability of the subject to participate or potentially confound the study results. It is the responsibility of the investigator to assess the clinical significance; however, consultation with the Takeda Medical Monitor may be warranted.
4. The subject has a history of significant GI disorders manifested with persistent, chronic or intermittent nausea, vomiting, diarrhea, or has a current or recent (within 6 months) GI disease that would influence the absorption of drugs (eg, a history of malabsorption, severe esophageal reflux, peptic ulcer disease or erosive esophagitis), or any gastrointestinal-related surgical intervention.
5. Subject has a known hypersensitivity to any component of the formulation of esomeprazole capsules or tablets or compounds with the same mechanism of action (dexlansoprazole, lansoprazole, omeprazole, rabeprazole, pantoprazole), or related compounds.
6. The subject has a positive urine/blood drug result for drugs of abuse, (defined as any illicit drug use) or alcohol at Screening or Check-in (Day -1***).***
7. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse (defined as regular consumption of 4 or more units per day) within 1 year prior to the Screening visit or is unwilling to agree to abstain from alcohol and drugs throughout the study. One unit is equivalent to a half-pint of beer or 1 measure of spirits or 1 glass of wine.
8. Subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications and Dietary Products table (listed in Section 7.3).
9. If female, the subject is pregnant or lactating or intending to become pregnant before participating in this study, and during the study and within 31 days after last dose of the study drug; or intending to donate ova during such time period.
10. Subject has evidence of current cardiovascular, central nervous system, hepatic, hematopoietic disease, renal dysfunction, metabolic or endocrine dysfunction, serious allergy, asthma, hypoxemia, hypertension, seizures, or allergic skin rash. There is any finding in the subject's medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking esomeprazole, or a similar drug in the same class, or that might interfere with the conduct of the study. This includes, but is not limited to, peptic ulcer disease, seizure disorders, and cardiac arrhythmias.
11. Subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1 of Period 1.
12. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) antibody at Screening.
13. Subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 28 days prior to Check-in on Day -1 of Period 1 and throughout the study. Cotinine test is positive at Screening and Check-in (Day -1).

14. The subject has poor peripheral venous access.
15. The subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 30 days prior to Day 1 of Period 1.
16. Subject has a Screening or Check-in (Day -1) abnormal (clinically significant) electrocardiogram (ECG).

7.3 Excluded Medications, Supplements, Dietary Products

Use of the agents in Table 7.a is prohibited from the time points specified until completion of all study activities on Period 2, Day 1 Checkout.

Table 7.a Prohibited Medications, Supplements, and Dietary Products

28 Days Prior to Check-in (Day -1)	7 Days Prior to Check-in (Day -1)	72 Hours Prior to Check-in (Day -1)
Prescription medications Any other investigational drugs(a)	OTC medications (b)	Products containing caffeine or xanthine
Neutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Vitamin supplements	poppy seeds
Immunization/Vaccines	Foods or beverages containing grapefruit or Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juices, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	
Nicotine-containing products	Alcohol (including alcohol-based mouthwash)	
Intake of inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6		

OTC=over-the-counter.
(a) Subjects are excluded from receiving any other investigational compound within 30 days prior to first dose.
(b) Occasional use of acetaminophen/paracetamol (≤1 g/day) or other medication as approved by Takeda on a case-by-case basis is allowed.

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

7.4 Diet, Fluid, and Activity Control

7.4.1 Confinement

Subjects enrolled in this study will be confined in the clinical research unit for 1 night in each period, beginning at Check-in (Day -1) to the completion of all assessments on Day 1. There will be a minimum 6-day washout interval between the dose in the first period and the dose in the second period. Subjects will be released from the clinic during the washout interval.

7.4.2 Diet and Fluid

During each day of the confinement period, subjects will receive standardized meals and an evening snack, each of which contains approximately 30% fat (caloric value). The clinical research site will ensure the same meals are served to all subjects on Day 1 of both study periods. All subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration. The study menu should be recorded and submitted to the study file with a copy provided to the sponsor prior to the start of the study.

During confinement, foods and beverages listed in Table 7.a will be prohibited, and all subjects will be limited to only standardized meals and snacks provided by the site.

Subjects will fast for a minimum of 10 hours prior to dosing on Day 1 of each period and will continue to fast for a further 4 hours after dosing. On Day 1 of each period, breakfast will not be served. Lunch will be served approximately 4 hours postdose. Dinner/snack will be served approximately 10 hours postdose. No additional meals will be served on Day 1 of each period. The start and stop times of meals on Day 1 of each period, along with whether the meal was completely consumed, will be recorded in the source documentation and on the electronic case report form (eCRF).

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

7.4.3 Activity Control

Subjects will remain upright (seated, standing, semirecumbent, or ambulatory) for 2 hours following the dose administration, except as necessitated by the occurrence of an adverse event (AE) /or study procedures (eg, obtaining 12-lead ECG). Subjects will refrain from strenuous exercise 72 hours before first dose in Period 1 and for the duration of their participation in the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.14.

1. Pretreatment event (PTE) or 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

     In multidose studies study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.1.8), if the following circumstances occur at any time during study drug treatment:

     – ALT or AST >8 × ULN, or

     – ALT or AST >5 × ULN and persists for more than 2 weeks, or

     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or INR >1.5, or

     – ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. Significant protocol deviation. The discovery after the first dose of study drug 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 in the subject's source documentation.

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 should not be recorded in the "voluntary withdrawal" category.

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 9.1.10.

7. 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 STUDY MATERIAL MANAGEMENT

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

8.1 Study Drug

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study medication refers to esomeprazole 40 mg capsules manufactured for the US market and esomeprazole 40 mg tablets manufactured for the EU market, both sourced by the Sponsor as defined below.

Commercially available esomeprazole magnesium (Nexium), 40 mg hard capsules, delayed release (bottle of 30 capsules)

Commercially available esomeprazole magnesium (Nexium), 40 mg gastro-resistant tablets (2 blisters of 14 tablets in a carton)

Each bottle and each carton will bear a single panel open computer- generated label containing the required information, including the Federal caution statement: "CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use.

The sponsor will supply a site with study drug as shown in Table 8.a.

Table 8.a Study Medication – Sponsor Supplied

Formulation	Investigational Product	Dosage	Manufacturer and Location
A (test)	Esomeprazole capsule	40 mg	AstraZeneca, France
B (reference)	Esomeprazole tablet	40 mg	AstraZeneca, UK

UK=United Kingdom.

8.1.1.1 Investigational Drug

Esomeprazole capsules, 40 mg are manufactured and packaged in bottles by AstraZeneca with single-panel Takeda clinical study label applied on the bottle. The label includes study information along with the caution statement. Each bottle contains 30 tablets.

Esomeprazole tablets, 40 mg are manufactured and packaged in a carton by AstraZeneca with single-panel Takeda clinical study label on the carton. The label includes study information along with the caution statement. Each carton contains 28 tablets.

8.1.1.2 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the following: esomeprazole capsule, 40 mg and esomeprazole tablet, 40 mg.

8.1.2 Storage

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.

Drug supplies must be stored at 25°C (77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) in a secure location until dispensed to study subjects or returned to Takeda. Temperature excursions must be reported to the sponsor. In order to protect drug supply from moisture, the container should be kept tightly closed (bottle) or stored in the original package (blister). Do not take a tablet out of the blister foil until the subject is ready to take it.

8.1.3 Dose and Regimen

Subjects will fast for a minimum of 10 hours prior to dosing in Periods 1 and 2. On Day 1 at approximately 0800 hours, subjects will be instructed to swallow the intact capsule/tablet with 240 mL of water. All subjects may consume water ad libitum, except for 1 hour prior to and 1 hour post drug administration. Subjects must drink all of the water provided with the dose. Subjects will continue to fast for 4 hours after dose administration in both periods.

Following the administration of the study drug, hand and mouth checks will be performed to ensure the dose was swallowed. Although the timing of events requires that each subject will be consistently administered the appropriate dose at specific times, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule.

On each dosing day (Day 1 of Periods 1 and 2) subjects will be administered dosing regimens according to the sequence group to which they are assigned (Table 8.b).

The 2 dosing regimens are:

Regimen A: A single 40 mg esomeprazole capsule.

Regimen B: A single 40 mg esomeprazole tablet.

Following the completion of all assessments on Day 1 of Period 1, subjects will be discharged from the study site for a minimum washout interval of 6 days between the dose in the first period and the dose in the second period.

Table 8.b Dose and Regimen

Treatment Sequence	Number of Subjects	Period 1 Regimen	Period 2 Regimen
1	26	A	B
2	26	B	A

Regimen A: A single 40 mg esomeprazole capsule administered orally on Day 1 following a 10-hour fast.
Regimen B: A single 40 mg esomeprazole tablet administered orally on Day 1 following a 10-hour fast.

No additional preparation is necessary.

8.1.4 Overdose

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

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

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

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

8.2 Study Drug Assignment and Dispensing Procedures

Qualified subjects will be assigned, in the order in which they are randomized into the study, to receive study drug according to the randomization schedule allocated to the site. Subjects who qualify for this study will be assigned to receive a 4-digit randomization number. The number will be assigned by the clinic site personnel in sequential order beginning with 1001 and ending with 1052. This 4-digit number will be entered into the eCRF and used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.

8.3 Randomization Code Creation and Storage

The randomization schedule will be generated by the Quantitative Science Department at Takeda Development Center, Inc. (TDC Americas) unless delegated to the CRO prior to the start of the study. The randomization schedule will be provided to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 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 destroyed.

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, 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 signing bottom half of the packing list and faxing per instructions provided on the form. 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 drug lot 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. Note that expiry date monitoring will not be required as the drug provided will have more than 2 years before expiry.

The investigator or designee must record the current inventory of all sponsor-supplied esomeprazole 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 date and amount dispensed, including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, 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 drug 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.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

8.5 Reserve Study Medication Samples for Retention

The investigator will retain a reserve sample (5 times the amount required for full analytical release testing) of esomeprazole in accordance with FDA regulations. The investigator or the investigator's designee will select the appropriate number of containers of study drug for retention, as specified in the bioretention letter to be provided by Takeda Clinical Supplies. Reserve samples will be stored under conditions consistent with the product's labeling and in a segregated area with access limited to authorized personnel. Each reserve sample will be retained for a period of at least 5 years following the date the application or supplemental application is approved by the FDA. If the application is not approved, regulations specify that these samples must be stored for at least 5 years following the date of completion of this bioequivalence study. The clinical site should not dispose of the reserve samples without written authorization from Takeda. If at any time the investigator is unable to comply with these requirements, the investigator should immediately notify Takeda regarding arrangements for storing reserve samples and associated study records on the investigator's behalf.

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, including requesting that a subject fast for laboratory evaluations.

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.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, Hispanic ethnicity, race as described by the subject, height, weight, caffeine consumption, xanthine consumption, alcohol use, reproductive status (including last menstrual period) and smoking status of the subject at Screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.7).

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 28 days prior to signing of informed consent.

9.1.3 Physical Examination Procedure

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

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the source document and eCRF. All CS findings/changes will be recorded as a PTE or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the study drug (Day 1) must be assessed as

NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

9.1.4 Weight, Height and BMI

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The BMI is calculated, using metric units with the formula provided below. The Takeda standard for collecting height is centimeters without decimal places and for weight it is kilograms (kg) with 1 decimal place. BMI should be derived as:

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

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

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2. However, if the BMI is used as entry criteria based on the range 18.5-30 kg/m^2 cut-off point, then this determination must be made after rounding.

9.1.5 Vital Sign Procedure

Vital signs will include oral body temperature, respiratory rate, sitting blood pressure (resting in a sitting or supine position for at least 5 minutes), and pulse (beats per minute [bpm]).

Vital signs may be repeated once. All measurements will be recorded on the source documents and in the eCRF.

9.1.6 Documentation of Concomitant Medications

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

9.1.7 Documentation of Concurrent Medical Conditions

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

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following a minimum 8 hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	Alanine aminotransferase	pH
WBC (with differential)	Albumin	Specific gravity
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	Aspartate aminotransferase	Ketones
Platelets	Glucose (a)	Glucose
MCHC	Gamma-glutamyl transferase	Bilirubin
MCV	Total bilirubin	Blood
RDW	Total protein	Nitrites
Reticulocyte count	Serum creatinine	Leukocyte esterase
PT/INR	Blood urea nitrogen	Microscopic Analysis (only of positive dipstick result):
aPTT	Phosphorous	RBC/high power field
	Potassium	WBC/high power field
	Chloride	Epithelial cells, casts
	Bicarbonate or carbon dioxide	
	Sodium	

Diagnostic Screening:	
Serum	**Urine**
HIV test Hepatitis panel, including HBsAg and anti-HCV Ab *Female subjects:* Human chorionic gonadotropin (for pregnancy) *Female subjects of child-bearing potential only when menopause is suspected:* Follicle-stimulating hormone	Drug screen, including alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine

anti-HCV Ab=anti-hepatitis C virus antibody, aPTT=activated partial thromboplastin time, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, PT=prothrombin time, RBC=red blood cell, RDW=red cell distribution width, WBC=white blood cell.
(a) Conducted under fasting conditions.

The local 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 ALT or AST >3 ×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, γ-glutamyl transferase [GGT], and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the

abnormality was noted. (Refer to Section 7.5 and Section 10.2.3 for the appropriate guidance on reporting abnormal liver function tests.)

If the ALT or AST remains elevated >3 ×ULN on these 2 consecutive occasions, the investigator must contact the Medical Monitor for consideration of additional testing, close monitoring, possible discontinuation of study drug, discussion of the relevant subject details and possible alternative etiologies. The abnormality should be recorded as an AE (please refer to Section 10.2.3 for reporting requirements).

All laboratory safety data will be transferred electronically to Takeda or designee in the format requested by Takeda. If the laboratory is unable to electronically transfer data, the study site coordinator or designee is responsible for transcribing laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

Laboratory reports must be signed and dated by the principal investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will require clear and complete documentation in the source documents as to the investigator's assessment of not clinically significant before proceeding with enrollment/randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the subject's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained.

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Male Subjects and Their Female Partners

Male subjects are not required to use barrier contraception.

9.1.9.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 31 days after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective method of contraception (from the list below).

In addition they must be advised not to donate ova during this period.

9.1.9.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential (WOCBP), that is, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, or bilateral oophorectomy. A postmenopausal state is defined as

no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 years old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized males should be at least 1 year post-bilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
    - Non-hormonal Methods:
        - Intrauterine device (IUD).
    - Hormonal Methods:
        - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
            - Oral.
            - Intravaginal (eg, ring).
            - Transdermal.
        - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 3 months;
            - Oral.
            - Injectable.
            - Implantable.
2. Subjects will be provided with information on highly effective 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.

3. During the course of the study, serum human chorionic gonadotropin (hCG) pregnancy tests will be performed in all women and all female subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")?
      iv. Is there a chance you could be pregnant?
4. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative serum hCG pregnancy test at Day -1 of either period.

9.1.10 Pregnancy

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

If the pregnancy occurs during administration of active study drug, eg, after Day -1 of Period 1 until check out in Period 2 the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

If the female subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the female subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

All reported pregnancies, will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. A copy of the ECG trace should be kept with the subject's notes.

9.1.12 PK Sample Collection

9.1.12.1 Collection of Blood for PK Sampling

Blood samples (one 6 mL sample per scheduled time) for PK analysis of esomeprazole will be collected into chilled vacutainers containing anticoagulant potassium EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in Appendix E.

Serial blood samples for determination of esomeprazole will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for PK Analysis

Analyte	Matrix	Dosing Day	Scheduled Time (hours)
Esomeprazole	Plasma	1	Predose, 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours

The actual time of sample collection will be recorded on the source document and eCRF. The PK sample should not be collected on early termination if a PK collection is not scheduled.

9.1.12.2 Bioanalytical Methods

Plasma concentrations of esomeprazole will be measured by high-performance liquid chromatography with tandem mass spectrometry.

9.1.13 Pharmacokinetic Parameters

The PK parameters of esomeprazole will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. The following PK parameters will be calculated for plasma concentration values of esomeprazole.

Symbol/Term	Definition
Plasma	
AUC_t	Area under the concentration-time curve from time 0 to time t
AUC_∞	Area under the concentration-time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration.
C_{max}	Maximum observed concentration.
CL/F	Apparent clearance after extravascular administration, calculated using the observed value of the last quantifiable concentration.
λ_z	Terminal disposition phase rate constant.
$t_{1/2z}$	Terminal disposition phase half-life.
t_{lag}	Lag time to first quantifiable concentration.
t_{max}	Time of first occurrence of C_{max}.
V_z/F	Apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.

Subjects who have experienced vomiting, diarrhea, or have predose concentrations >5% C_{max} or a mean exposure <5% of the population mean may be excluded from the analysis of PK parameters. Samples may also be excluded prior to bioanalysis if their validity is of concern.

9.1.14 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If a subject is withdrawn at the Screening Visit, the investigator should complete the eCRF screen failure form. 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 <specify reason>.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.

Subject identification numbers assigned to subjects who fail screening should not be reused. If a subject fails screening, a subject may be rescreened at the investigator's discretion. If a subject is later successfully rescreened, the data for the subject will be entered as if these were 2 separate subjects. Therefore the data should be entered as follows:

1. The screen failure data should be entered as a screen failure subject.
2. Rescreened subjects should be assigned a new subject number and treated as a stand-alone subject.

9.1.15 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.

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

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study drug, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study drug supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

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).

9.3.1 Screening (Day -28 to Day -2)

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.14 for procedures for documenting screening failures. Procedures to be carried out at Screening are described in Appendix A.

9.3.2 Check-in (Day -1 of Periods 1 and 2)

On Day -1 of Period 1, eligibility will be confirmed. If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be admitted to the Unit overnight. The procedure for documenting screening failures is provided in Section 9.1.14. Procedures to be carried out on Day -1 of each period are described in Appendix A.

9.3.3 Treatment (Day 1 of Periods 1 and 2)

On Day 1 of Period 1, subjects will be randomized as described in Section 8.2. On Day 1 of each period, subjects will be administered study drug in the unit under the supervision of the investigator or designee, as described in Section 8.2. Procedures to be carried out on Day 1 of each period are described in Appendix A. Subjects will be discharged from the unit following the completion of all scheduled procedures on Day 1 of Periods 1 and 2.

9.3.4 Washout

Subjects will undergo a minimum 6-day washout period between doses in Period 1 and Period 2. Day -1 of Period 2 could be the sixth day of washout.

9.3.5 Early Termination

The reason for discontinuation must be documented in the source document and eCRF. The PK sample should not be collected on early termination if a PK collection is not scheduled. Procedures to be carried out on early termination in either period are described in Appendix A.

For all subjects receiving study drug, the investigator must complete the End of Study eCRF page.

9.4 Blood Volume

Total blood sampling volume for an individual subject is shown in Table 9.c

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Screening	Number of Samples				Total Volume (mL)
			Period 1		Period 2		
			Day -1	Day 1	Day -1	Day 1	
Biochemistry, FSH and hCG for pregnancy tests (a)	8.5	1	1	1	1	1	**42.5**
Hematology	4.0	1	1	1	1	1	**20.0**
Hepatitis Panel	8.5	1	0	0	0	0	**8.5**
PK blood collection	6.0	NA	0	19	0	19	**228**
			Total Approximate Blood Sampling Volume				**299**

NA=not applicable.
(a) FSH test will be conducted at the Screening visit only.

The maximum volume of blood at any single day is approximately 126.5 mL, and the approximate total volume of blood for the study is 299 mL.

Direct venipuncture is the preferred method of blood collection. A catheter with a normal saline flush may be used; however, the 299 mL total blood volume does not include discarded blood from predraws (assuming minimally the catheter dead volume plus 1.5 mL of blood is discarded each time a sample is collected from a catheter). Should a catheter be used, the total blood volume taken during the study is not expected to exceed 356 mL.

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 drug; 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 value), 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 or 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 drug 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 findings 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 or ECG retest and/or continued monitoring of an abnormal value or finding is 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 medical condition, the worsening or complication should be recorded appropriately as a PTE(worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). 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 concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a pre-existing degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. 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 the start of study drug, the worsening or complication should be recorded 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 drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs /Serious PTEs:

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

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. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Acute liver failure
	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

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

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 Intensity 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 Relationship of AEs to Study Drug(s)

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

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

10.1.7 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 investigator.

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.

10.1.10Frequency

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

10.1.11Action Concerning Study Drug

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

10.1.12Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 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 drug (Day 1, Period 1) or until screen failure. For subjects who discontinue prior to study drug 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 drug (Day 1, Period 1). Routine collection of AEs will continue until check-out following the completion of all assessments on Day 1 of Period 2.

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 drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All 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. Frequency.

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

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 drug(s).
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact listed in Section 1.0.

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

If a subject is noted to have ALT or AST elevated >3 ×ULN on 2 consecutive occasions, the abnormality should be recorded as an AE. In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

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 9.1.8 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 is 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 fax it 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 and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs, 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 the study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB in accordance with local 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 medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 CRFs (Electronic and Paper)

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

The sponsor or its designee will supply study sites with 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 e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign, and date.

The eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. 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 study site agreement between the investigator and sponsor.

Refer to the 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 database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

PK Set

The PK set will consist of all subjects who are in Safety Set and have at least 1 measurable plasma concentration for esomeprazole. If any subjects are found to be with incomplete data, a decision will be made on a case-by-case basis as to their inclusion in the analysis, but will be presented in the subject listings.

Safety Set

The Safety Analysis Set will consist of all subjects who are enrolled and receive study drug. Subjects in this analysis set will be used for demographic, baseline characteristics, and safety summaries.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for all enrolled subjects by sequence, and overall. Summary statistics (eg, number of subjects, mean, median, standard deviation and range) 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, gender, ethnicity, race, smoking status).

13.1.3 PK Analysis

The concentration of esomeprazole in plasma will be summarized by formulation over each scheduled sampling time point using descriptive statistics (arithmetic mean, SD, percent coefficient of variation [%CV], median, minimum and maximum). Individual plasma/ concentration data versus time will be presented in a data listing.

Descriptive statistics will also be used to summarize the plasma pharmacokinetics parameters for esomeprazole. In addition, geometric mean and coefficient of variation will be computed for C_{max} and AUCs (AUC_{∞} and AUC_t).

Natural-logarithmically transformed C_{max} and AUCs will be analyzed using analysis of variance with fixed factors for period, sequence, and regimen, and subject within sequence as a random effect. The bioequivalence will be assessed via point estimates and 90% CI for the ratio of C_{max} and AUCs central values for esomeprazole tablet (Regimen B – test) versus esomeprazole capsule (Regimen A - reference). Bioequivalence between tablet and capsule will be claimed if the 90% CI for the ratio is within the bioequivalence criteria of 0.80 to 1.25 [5,6].

A more detailed analysis will be presented in the SAP.

13.1.4 Safety Analysis

AEs will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated. All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

For safety laboratory tests, vital signs, and ECG, data will be listed and summarized, as appropriate.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

The sample size for this study is estimated at 52, which provides an allowance for 4 dropouts. The sample size was estimated based on variability data from a previous study[2], using a %CV of 28% as the intrasubject variation for the natural logarithm of C_{max} and the assumed true ratio of 0.95 for tablet over capsule. Given the above information, a sample size of 52 subjects provides at least 90% power for concluding bioequivalence for C_{max} and the power for AUCs is greater than 90%.

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

14.2 Protocol Deviations

The investigator 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.

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. Table 14.a defines the windows allowed for sample collections.

However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda/ CRO using the Protocol Deviation Form. Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals:

Table 14.a Windows for PK Blood Sample Collection

Minutes	Nominal Sampling Time
no more than 30 minutes predose	0 hour
±5	immediately postdose to ≤6 hours
±10	>6 hours to ≤10 hours postdose

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 study site 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, Prescribing Information, 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 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 study. Until the site receives drug no protocol activities, including screening may occur.

Study 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, and submission of the investigator's final status report to IRB or IEC. All IRB or 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 trial database or documentation via a subject 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 the monitor or the sponsor's designee, 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/or 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 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 study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the 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 all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/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 Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study 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 the sponsor providing this information to callers must provide the sponsor 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 study subjects. Refer to the 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.

16.0 REFERENCES

1. Fass R, Shapiro M, Dekel R, Sewell J. Systematic review: proton-pump inhibitor failure in gastro-oesophageal reflux disease--where next? Aliment Pharmacol Ther 2005;22(2):79-94.
2. Bladh N, Blychert E, Johansson K, Backlund A, Lundin C, Niazi M, et al. A new esomeprazole packet (sachet) formulation for suspension: in vitro characteristics and comparative pharmacokinetics versus intact capsules/tablets in healthy volunteers. Clin Ther 2007;29(4):640-9.
3. Food and Drug Administration, Center for Drug Evaluation and Research. Approval Package for Nexium (esomeprazole magnesium) delayed-release oral suspension. Application 21-957 S005: Clinical Review for Short-term GERD Symptoms in 0-11 Month Olds, Inclusive. AstraZeneca: 18 June 2009.
4. Food and Drug Administration, Center for Drug Evaluation and Research. Approval Package for Nexium (esomeprazole magnesium) delayed-release capsules. Application NDA 21153/S-008. AstraZeneca LP: 01 September 2004.
5. Guideline on the Investigation of Bioequivalence. European Medicines Agency, Committee for Medicinal Products for Human Use. 20 January 2010. Publication No. CPMP/EWP/QWP/1401/98 Rev. 1.
6. Guidance for Industry: Bioavailability and Bioequivalance Studies Submitted in NDAs or INDs - General Considerations. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). March 2014.

Appendix A Schedule of Study Procedures

	Pretreatment Period		Treatment Periods 1 and 2	Washout (a)	Study Exit / Early Termination
Study Day:	**Days -28 to -2**	**Day -1 (Check-in)**	**Day 1**	**Days 2-6**	**Day 1 of Periods 1 and 2 (prior to Checkout)**
Confinement		X	X		X
Informed consent	X				
Inclusion/exclusion criteria	X	X			
Demographics and medical history	X				
Medication history	X	X			
Physical examination	X	X (b)			X
Vital signs (c)	X	X	X		X
Height, weight and BMI (d)	X	X			
Concomitant medications		X	X	X	X
12-lead ECG	X	X			X
Clinical laboratory tests (e)	X	X			X
Urine drug, alcohol, and cotinine screen	X	X			
Pregnancy test (hCG)	X	X			X
Serum FSH (f)	X				
HIV test	X				
Hepatitis panel	X				
Randomization			X		
Administration of study drug (g)			X		
PK blood collection (h)			X		
Adverse Event assessment (i)	X	X	X	X	X

(a) There will be a minimum 6-day washout period between doses. Day -1 of Period 2 could be the sixth day of washout.
(b) Can be conducted up to 24 hours prior to dosing.
(c) Vital signs: oral body temperature, sitting blood pressure (after resting 5 minutes), respiratory rate, and pulse (beats per minute) at Screening. Only blood pressure and pulse will be collected on Check-in (Day -1) through Day 1 of each period, or if the subject early terminated from study. On Day 1 of each period, vital signs will be taken at predose.
(d) Height only measured at Screening.
(e) Hematology, serum chemistries, and urinalysis tests.
(f) For women where menopause is suspected.
(g) Study drug administered beginning at approximately 0800 hours.
(h) Blood samples for PK obtained predose (within 15 minutes prior to dose), and at 0.33, 0.66, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, and 10 hours postdose on Day 1 of each period. The PK sample should not be collected on Early Termination if a PK collection is not scheduled.
(i) Pretreatment adverse events will be captured immediately following the signing of the informed consent at Screening until dosing on Day 1 of Period 1. The routine collection of AEs will continue after dosing through to check out on Period 2, Day 1.

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 responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

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 (nonroutine/nonstandard 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 eCRFs, 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 are 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 or the

subject's legally acceptable representative 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. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
23. 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 drug(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.
24. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening and throughout the duration of the study, and for 31 days after last

dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

25. 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 drug.
- 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, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Plasma Samples for Pharmacokinetic Analysis of Esomeprazole

1. Collect 6 mL of venous blood for the plasma into a chilled Becton-Dickinson Vacutainer. All esomeprazole blood samples should be collected into vacutainers containing K_2EDTA.
2. Gently invert the vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the vacutainers for 10 minutes at approximately 1100 to 1300 (relative centrifugal force [RCF]) at 4°C. Note: 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 approximately 1 mL needs to be obtained for each sample. Labeling or manifest to the bioanalytical laboratory should include protocol number (Esomeprazole_1001), sample matrix (ie, plasma) enrollment number, period, profile day (optional) and nominal time, and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower until shipment to (vendor name, city, state/country). No more than 45 to 60 minutes will elapse between blood collection and freezing the plasma sample.

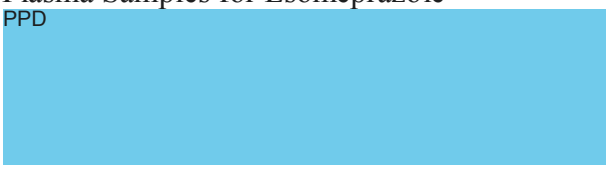
Shipping of Plasma Samples

The following instructions are recommended unless they differ from the site's SOPs for labeling, packaging, or shipping of pharmacokinetic samples.

1. Biological samples (ie, plasma) should be shipped on dry ice to prevent thawing during transit. Samples should be shipped only on Monday, Tuesday, or Wednesday, and at least 2 days prior to a national holiday, in order 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.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
4. Place SET 1 samples for each subject into self-sealing bag (eg, Ziploc) containing additional absorbent material.
5. Using a permanent marker, write the 4-digit {randomization sequence/enrollment} number, sample matrix (ie, plasma), number of samples, and "SET 1" on each self-sealing bag.
6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage.

Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2."

7. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study drug (esomeprazole), protocol number (Esomeprazole-1001), investigator's name, sample type (ie, plasma), subject randomization/enrollment number, period, nominal collection day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. 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 analytical laboratory.
8. For sample packing, utilize dry ice generously (eg, 20-25 pounds per day of transit) to safeguard against longer than expected shipping times and delays. Use newspaper or other material to insulate the double-bagged samples from direct contact with the dry ice. Place the sample bundles into a Styrofoam container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
9. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the Styrofoam container. Place the lid on the Styrofoam container and seal completely with strapping tape. Place the Styrofoam container in a cardboard shipping carton and seal securely with strapping tape.
10. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
11. Affix an address label to each shipping carton. Complete the address label with the following information:

    Plasma Samples for Esomeprazole
    PPD
    
12. Affix a carbon dioxide label on each carton, specifically:

    Carbon Dioxide Solid UN-1845
    Class 9 PKG GR III
    Quantity _____
    (fill in weight to nearest lb/kg and specify unit of measure used)
13. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark **KEEP FROZEN** on each carton. Specify a return address and contact person on the carton.
14. Obtain the airway bill number and a receipt of shipment from the carrier.

15. After shipping of the esomeprazole samples, **please contact** PPD **via e-mail:** PPD to notify of next day delivery. Please provide the following information:

    Name of courier or transport company
    Time and date the shipment left the clinical site
    Airway bill number

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Science Approval	08-Mar-2017 00:20 UTC
	Clinical Pharmacology Approval	08-Mar-2017 10:46 UTC
	Statistical Approval	08-Mar-2017 13:34 UTC