Title: A Phase 1, Single-Center, Open-Label, 2-Arm Parallel Group, Single-Dose Study to Evaluate the Pharmacokinetics of Dexlansoprazole 30 mg and 60 mg Delayed-Release Capsules in Healthy Chinese Subjects

NCT Number: NCT03316976

Protocol Approve Date: 28 November 2017

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

PROTOCOL AMENDMENT

A Phase 1, Single-Center, Open-Label, 2-Arm Parallel Group, Single-Dose Study to Evaluate the Pharmacokinetics of Dexlansoprazole 30 mg and 60 mg Delayed-Release Capsules in Healthy Chinese Subjects

Phase 1 Dexlansoprazole PK Study in Healthy Chinese Subjects

Sponsor: Takeda Development Center Asia, Pte. Ltd.
21 Biopolis Road, Nucleos North Tower, Level 4, Singapore 138567

Study Number: TAK-390MR_106

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: TAK-390MR Dexlansoprazole

Date: 28 November 2017 **Amendment Number:** 03

Amendment History:

Date	Amendment Number	Amendment Type	Region
20 June 2011	Initial Protocol	Not applicable	China
22 June 2016	01	Nonsubstantial	China
28 March 2017	02	Nonsubstantial	China
28 November 2017	03	Nonsubstantial	China

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

TDC Asia sponsored Asia Pacific investigators 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	Personally Protected Data
Medical Monitor (medical advice on protocol and compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

1.2 Approval

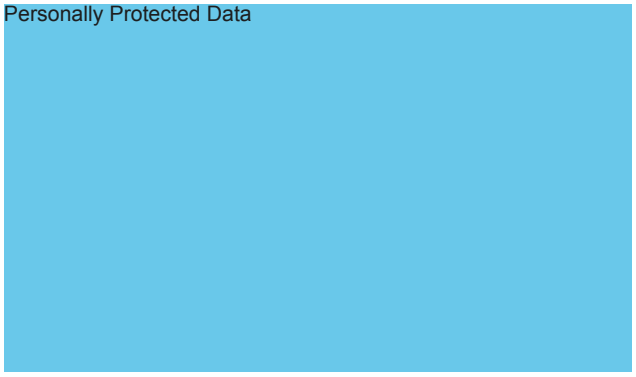
REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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



INVESTIGATOR AGREEMENT

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

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

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

1.3 Protocol Amendment 03 Summary of Changes

Rationale for Amendment 03

This document describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reasons for this amendment are to update blood volume collected for genotype analysis and total volume of blood, and to make minor modifications to specify the relative centrifugal force, remove plasma first to be transferred into 1 aliquot after centrifugation, and to extend the duration for blood collection to freezing plasma sample on processing of plasma samples for pharmacokinetic analysis to allow greater flexibility in Appendix E, and update the reference to lab manual for processing of blood samples for genotype analysis in Appendix E.

For specific descriptions of the changes listed below and where these changes are located, see Appendix F.

Changes in Amendment 03

1. Updated Appendix E Collection, Storage, and Shipment of Bioanalytical Samples.
2. Correct blood volume for genotype analysis and total blood volume.

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2.0 STUDY SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor(s):
Takeda Development Center Asia, Pte. Ltd.</td><td colspan="2">Compound:
TAK-390MR Dexlansoprazole</td></tr>
<tr><td colspan="2">Title of Protocol: A Phase 1, Single-Center, Open-Label, 2-Arm Parallel Group, Single-Dose Study to Evaluate the Pharmacokinetics of Dexlansoprazole 30 mg and 60 mg Delayed-Release Capsules in Healthy Chinese Subjects</td><td>IND No.:
Not Applicable</td><td>EudraCT No.:
Not Applicable</td></tr>
<tr><td colspan="2">Study Number: TAK-390MR_106</td><td colspan="2">Phase: 1</td></tr>
<tr><td colspan="4">Study Design:
This is a phase 1, open-label, single dose, 2-arm parallel study to evaluate the pharmacokinetics (PK) of a single oral dose of dexlansoprazole 30 and 60 mg delayed-release capsules in healthy Chinese subjects. Forty subjects will be enrolled in the study, 20 subjects in Group 1 and 20 subjects in Group 2.</td></tr>
<tr><td colspan="4">Objectives:
Primary:
The primary objective of this study is to assess the PK of single doses of dexlansoprazole 30 and 60 mg delayed-release capsules in healthy Chinese subjects.
Secondary:
The secondary objective of this study is to evaluate the safety and tolerability of dexlansoprazole following oral administration of a single 30 or 60 mg dexlansoprazole delayed-release capsule.</td></tr>
<tr><td colspan="4">Subject Population:
Healthy men and women of Chinese descent aged 18 to 45, inclusive, at the time of informed consent and study medication dose.</td></tr>
<tr><td colspan="2">Number of Subjects:
Estimated Total: 40</td><td colspan="2">Number of Sites:
Estimated total: 1 in China</td></tr>
<tr><td colspan="2">Dose Level(s):
Dexlansoprazole 30 mg
Dexlansoprazole 60 mg</td><td colspan="2">Route of Administration:
Oral</td></tr>
<tr><td colspan="2">Duration of Treatment:
Single dose on Day 1</td><td colspan="2">Period of Evaluation:
Approximately 40 days (including Screening to Follow-up)</td></tr>
<tr><td colspan="4">Main Criteria for Inclusion:
Men and women subjects aged 18 to 45, inclusive, and of Chinese descent who are in good health as determined by a physician.</td></tr>
<tr><td colspan="4">Main Criteria for Exclusion:
Subjects who have hypersensitivity to dexlansoprazole or related compounds, or have a history or clinical manifestations of serious neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine, hematologic, dermatologic, immunologic, psychiatric disorders, or other abnormality which may impact the ability of the subjects to participate or potentially confound the study results. Subject has a positive test result for alcohol or drugs of abuse at Screening or Check-in (Day -1), or a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) antibody at Screening, or an abnormal (clinically significant) ECG or laboratory values at Screening or Check-in (Day -1). In addition, subjects who has taken any excluded medication, supplements, or food products during the time periods listed in the protocol.</td></tr>
</table>

Main Criteria for Evaluation and Analyses:

Primary Endpoints:

The primary endpoints for this study are the PK parameters of dexlansoprazole following a single oral dose of dexlansoprazole 30 and 60 mg delayed-release capsules:

- Maximum observed concentration (C_{max}).
- Area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}).
- Area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}).

Additional Endpoints:

In addition, the following PK variables will be additional endpoints:

- Time of first occurrence of C_{max} (t_{max}).
- Terminal disposition phase rate constant (λ_z).
- Terminal disposition phase half-life ($t_{1/2z}$).
- Volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- Apparent clearance after extravascular administration (CL/F).

Safety Endpoints:

Safety will be assessed by summarizing the incidence of adverse events (AEs), clinical laboratory values, physical examinations, ECGs, and vital signs.

Statistical Considerations:

Pharmacokinetics:

Plasma dexlansoprazole concentrations and the PK parameters will be tabulated and descriptive statistics computed.

Sample Size Justification:

A sample size of 40 subjects, 20 per parallel arm, will be used in this study. This sample size is deemed to be sufficient for the assessment of the PK of dexlansoprazole 30 and 60 mg delayed-release capsules in Chinese population. The study is not statistically powered.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Principal Investigator

Personal Protected Data

3.3 List of Abbreviations

λ_z	terminal disposition phase rate constant
%CV	coefficient of variation
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	area under the plasma concentration-time curve from time 0 to infinity
BMI	body mass index
bpm	beats per minute
CFDA	China Food and Drug Administration
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSR	clinical study report
CYP	cytochrome P450
ECG	electrocardiogram
EE	erosive esophagitis
EM	extensive metabolizer
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GGT	γ-glutamyl transferase
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLT	high level term
HRT	hormone replacement therapy
IBD	international birth date
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine devices

K_2EDTA	potassium ethylenediamine tetraacetic acid.
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MR	modified release
NCS	not clinically significant
PK	pharmacokinetics
PM	poor metabolizer
PPI	proton pump inhibitor
PT	preferred term
PTE	pretreatment event
QD	once daily
OTC	over-the-counter
RBC	red blood cell
RCF	relative centrifugal force
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
ULN	upper limit of normal
V_z/F	volume of distribution during the terminal disposition phase after extravascular administration
WBC	white blood cell
WHO	World Health Organization

3.4 Corporate Identification

Takeda	TDC Asia, TDC Europe, TDC Americas, TCH, and/or TPC, as applicable
TCH	Takeda (China) Holdings Co., Ltd.
TDC	TDC Asia, TDC Europe and/or TDC Americas, as applicable
TDC Americas	Takeda Development Center Americas, Inc.
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TPC	Takeda Pharmaceutical Company Limited

4.0 INTRODUCTION

4.1 Background

Dexlansoprazole is a proton pump inhibitor (PPI) with prolonged elevation of intragastric pH. PPIs inhibit the secretion of H^+ ions in the stomach by inhibiting the (H^+, K^+)-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell [1]. Dexlansoprazole is the *R*-enantiomer of the racemate lansoprazole. Lansoprazole, initially approved in France in 1990 and in China in 1994, is currently marketed in over 90 countries and has a well-established safety profile.

Takeda Development Center Americas, Inc. developed dexlansoprazole delayed-release capsules (also referred to as dexlansoprazole modified-release capsules) as a new therapy for treating acid-related disorders including symptomatic non-erosive gastroesophageal reflux disease (GERD), erosive esophagitis (EE), and maintenance of healed EE and relief of heartburn. Dexlansoprazole capsules are approved for use in adults (≥18 years of age) in over 35 countries in North and South America, Europe, Asia, and the Middle East. Dexlansoprazole capsules were first approved for use in adults in the United States in January 2009. The international birth date (IBD) is 30 January 2009.

The clinical pharmacology program for dexlansoprazole capsules was extensive and evaluated the pharmacokinetics (PK), pharmacodynamics, extrinsic factors (eg, drug-drug interactions and food effect), and intrinsic factors (eg, age, gender, race, hepatic impairment) [1]. Dexlansoprazole mean maximum observed plasma concentration (C_{max}) and mean area under the plasma concentration-time curve (AUC) values appeared to increase proportionally to the dose following oral administration of dexlansoprazole delayed-release capsule single-doses or multiple-doses ranging from 30 to 120 mg. The apparent terminal disposition phase half-life ($t_{1/2z}$) of dexlansoprazole typically ranged from 1 to 2 hours, regardless of the dose, and no appreciable accumulation of dexlansoprazole was observed following once daily (QD) dosing. In addition, the PK of dexlansoprazole were shown to be time independent based on the similar systemic exposure after oral administration of a single dose of dexlansoprazole capsules and that which was observed following QD oral dosing [2].

Dexlansoprazole is primarily metabolized by the cytochrome P450 (CYP) enzymes CYP3A4 and polymorphic CYP2C19 [1]. The CYP2C19 poor metabolizer (PM) phenotype is present in 12% to 23% of the Asian population, and the prevalence of CYP2C19 PMs in Chinese subjects is similar to that of other Asian populations [3]. Study TAK-390MR/CPH-002 assessed the PK of multiple doses of dexlansoprazole 30 and 60 mg capsule doses in male Japanese PM and extensive metabolizer (EM) subjects. In the Japanese PMs, dexlansoprazole $t_{1/2z}$ was approximately 3 times longer than in EMs, and apparent clearance after extravascular administration (CL/F) in the EMs was approximately 4-times greater than PMs. Although the availability of PK data in PMs in the Caucasian and African American population is limited, it is expected that dexlansoprazole exposure in these races will be affected by CYP2C19 phenotypes as well.

The majority of the dexlansoprazole capsule phase 1 studies were conducted in the United States. As development of dexlansoprazole expands to other countries, additional studies are needed to bridge between the data acquired previously in North American and Asian populations.

4.2 Rationale for the Proposed Study

The rationale for the current study is to add to the current knowledge of dexlansoprazole by assessing the PK and safety of dexlansoprazole 30 and 60 mg capsules in healthy Chinese subjects.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to assess the PK after a single dose of dexlansoprazole 30 and 60 mg delayed-release capsules in healthy Chinese subjects.

5.1.2 Secondary Objective

The secondary objective of this study is to evaluate the safety and tolerability of dexlansoprazole following oral administration of a single 30 or 60 mg dexlansoprazole delayed-release capsule.

5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints for this study are the PK parameters of dexlansoprazole following a single oral dose of dexlansoprazole 30 and 60 mg delayed-release capsules:

- C_{max}.
- Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}).
- Area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}).

5.2.2 Additional Endpoints

- Time of first occurrence of C_{max} (t_{max}).
- Terminal disposition phase rate constant (λ_z).
- $t_{1/2z}$.
- Volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).
- CL/F.

5.2.3 Safety Endpoints

Safety will be assessed by summarizing the incidence of treatment-related AEs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, electrocardiograms (ECGs), and physical examinations.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 1, open-label, single dose, 2-arm parallel study to assess the PK of a single oral dose of dexlansoprazole 30 and 60 mg delayed-release capsules. Forty subjects will be enrolled in the study, 20 subjects in Group 1 and 20 subjects in Group 2 (Table 6.a).

Table 6.a Parallel Groups

Group	Regimen
1	A single oral dose of dexlansoprazole 30 mg delayed-release capsule
2	A single oral dose of dexlansoprazole 60 mg delayed-release capsule

A schematic of the study design is included as Figure 6.a. A schedule of study procedures is listed in Appendix A.

Figure 6.a Schematic of Study Design

Pretreatment Period		Treatment Period		Follow-Up
Screening	Check-in	Dexlansoprazole Delayed-Release Capsule Single Dose (30 or 60 mg)	Discharge/Study Exit/Premature Termination	Follow-up Site/ Telephone Visit
Days -28 to -2	Day -1	Day 1	Day 2	5 to 10 days postdose
	←——Confinement to Clinic——→			

Note: A follow-up site/telephone visit will be made for collection of adverse events, serious adverse events, and concomitant medications taken since final dose.

6.2 Justification for Study Design, Dose, and Endpoints

This study was designed based on the requirements of the China Food and Drug Administration (CFDA) for successful registration of dexlansoprazole in China. Phase 3 safety and efficacy trials with dexlansoprazole will be performed concurrently in China. A single-dose study will provide adequate information on the PK of dexlansoprazole in Chinese subjects to allow the data to be bridged to data previously acquired in North American and Japanese populations at both the 30 and 60 mg doses.

This is a single-center, open-label, single-dose, 2-arm parallel study using dexlansoprazole delayed-release capsules (30 and 60 mg). Healthy adult Chinese subjects will be enrolled. Since PPIs are intended to be used by both genders, effort will be made to enroll an equal number of men and women. The study will assess the PK of dexlansoprazole 30 and 60 mg delayed-release capsules.

The CYP2C19 PM phenotype is present in 12% to 23% of the Asian population, and the prevalence of CYP2C19 PMs in Chinese subjects is similar to that of other Asian populations [3].

The CYP2C19 isozyme is a polymorphic enzyme that is involved in the metabolism of dexlansoprazole, and administration of dexlansoprazole may result in higher plasma levels in subjects who are CYP2C19 PMs [1]. Therefore, the CYP2C19 metabolizer status of the subjects will be determined and, if appropriate, the effect of metabolizer status on the PK of dexlansoprazole will be assessed.

The objective of the study is to evaluate the PK of dexlansoprazole at both doses that will be included in the phase 3 studies. Standard PK parameters will be calculated. The design of the study will provide information on the PK of a single dose of dexlansoprazole 30 and 60 mg in healthy Chinese subjects. The safety of dexlansoprazole delayed-release capsules has been evaluated following oral administration in phases 1 and 3 studies. In the previous phase 3 studies, dexlansoprazole 30 and 60 mg had a comparable safety profile to lansoprazole 30 mg. Dexlansoprazole delayed-release capsule doses of 30 and 60 mg were well tolerated.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

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

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to first dose of study medication on Day 1.

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.
3. The subject is a healthy adult man or woman of Chinese descent.
4. The subject is aged 18 to 45 years, inclusive, at the time of informed consent and study medication dose.
5. The subject weighs at least 50 kg and has a body mass index (BMI) from 19.0 to 26.0 kg/m^2, inclusive at Screening Visit.
6. A man who is nonsterilized* and sexually active with a woman of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 30 days after last dose of study drug.
7. If a woman of childbearing potential* is sexually active with a nonsterilized* man, she agrees to routinely use adequate contraception* from signing of informed consent throughout the duration of the study and for 30 days following the last dose of study drug. Women of childbearing potential* must have a negative pregnancy test at Screening and Check-in (Day -1 of Period 1) and they must not be nursing.

   *Definitions and acceptable methods of contraception are defined in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.10 Pregnancy.

8. Subject has clinical chemistry, hematology, and complete urinalysis (fasted for at least 8 hours) at the Screening Visit and Check-in (Day -1) results within the reference range for the testing laboratory unless the out of range results are deemed not clinically significant by both the investigator and Medical Monitor.

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 3 months prior to Check-in (Day -1).

2. The subject has received dexlansoprazole in a previous clinical study or has received dexlansoprazole or lansoprazole as a therapeutic agent within 30 days prior to Check-in (Day -1 of Period 1).
3. Subject has a known hypersensitivity to any component of the formulation of dexlansoprazole or other drug with the same mechanism of action (including lansoprazole, omeprazole, esomeprazole, rabeprazole, ilaprazole, or pantoprazole), or related compounds.
4. The subject is an immediate family member, study site employee, or is in a dependant relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
5. The subject has 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 (eg, a history of malabsorption, severe esophageal reflux, peptic ulcer disease or erosive esophagitis with frequent [more than once per week] occurrence of heartburn).
6. The subject has a history or clinical manifestations of serious neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine, hematologic, dermatologic, immunologic, psychiatric disorders, or other abnormality which may impact the ability of the subjects to participate or potentially confound the study results.
7. Subject has received any known hepatic or renal clearance altering agents (eg, erythromycin, cimetidine, barbiturates, phenothiazines, fluvoxamine, etc.) within 28 days prior to the Check-in (Day -1) Visit.
8. Subject has had an acute, clinically significant illness within 30 days prior to Day 1.
9. The subject has a positive test result for alcohol or drugs of abuse at the Screening Visit or Check-in (Day -1) Visit.
10. The subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening visit or is unwilling to agree to abstain from alcohol for 48 hours prior to Check-in (Day -1) throughout the confinement and for 48 hours prior to each clinic visit and drugs throughout the study.
11. Subject has taken any excluded medication, supplements, or food products during the time periods listed in the Excluded Medications, Supplements, and Dietary Products Table 7.a listed in Section 7.3.
12. If a woman is pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study; or is intending to donate ova during such time period.
13. If a man intends to donate sperm during the course of this study or for 30 days thereafter.
14. Subject has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Day 1.

15. 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.
16. 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 (Day -1) or is unwilling to abstain from these products for the duration of the study.
17. The subject has poor peripheral venous access.
18. Subject has donated blood products (such as plasma), whole blood or had a significant blood loss (450 mL) within 56 days of Day 1.
19. Subject has a Screening or Check-in (Day -1) abnormal (clinically significant) ECG. Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by signature by both the principal investigator and the medical monitor.
20. Subject has abnormal Screening or Check-in (Day -1) laboratory values that suggest a clinically significant underlying disease or subject with the following lab abnormalities: creatinine >1.5 mg/dL, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2.5x the upper limits of normal (ULN), or total bilirubin >2.0 mg/dL.

7.3 Excluded Medications and Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified until completion of all study activities.

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 (a)	Over-the-counter (OTC) medications (b)	Products containing caffeine and/or xanthine
Nicotine-containing products	Vitamin supplements	Poppy seeds
Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)	Foods or beverages containing grapefruit or grapefruit juice, star fruit or star fruit juice, Seville-type (sour) oranges and marmalade, apple, orange, or pineapple juice, vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, mustard), and charbroiled meats	
Hepatic or renal clearance altering agents	Alcohol-containing products	
Immunization/Vaccines (c)		
Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 (d)		

(a) Hormonal contraception and HRT are allowed, as long as the subject has been on a stable dose for a minimum of 90 days prior to Day 1.
(b) Occasional use of acetaminophen (≤2 g/day) is allowed or other medication as approved by Takeda on a case-by-case basis. Acetaminophen is not allowed on Day 1.
(c) Inclusive of but not limited to H1N1 and flu vaccinations.
(d) Examples include: omeprazole, cimetidine, ranitidine, and chlorpheniramine.

Subjects must be instructed not to take any medications including OTC products without first consulting with the investigator.

7.4 Diet, Fluid, and Activity Control

Diet and Fluid

During each day of the confinement period, subjects will receive standardized meals and an evening snack. The menu of the standardized meals from the clinical research site needs to be approved by Takeda before the implementation. The clinical research site will ensure the same meals are served to all subjects on Day 1. All subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration.

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 8 hours prior to dosing. On Day 1, breakfast will be served 1 hour postdose. Lunch will be served approximately 4 hours postdose. Dinner will be served approximately 9 hours postdose. A snack will be served approximately 12 hours postdose. No

additional meals will be served on Day 1. The start and stop times of meals on Day 1 will be recorded in the source documentation and on the case report form (eCRF). Subjects will be fasting for a minimum of 8 hours prior to collection of safety labs on Day 2.

Activity Control

Subjects will refrain from strenuous exercise beginning upon confinement 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 should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.15.

1. Pretreatment event (PTE) or adverse event (AE). The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.
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.
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. In addition, efforts should be made to perform all procedures scheduled for Early Termination as noted in Appendix A. Discontinued or withdrawn subjects will not be replaced after enrollment.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

The following study medications manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan will be provided for this study:

- Dexlansoprazole 30 mg delayed-release capsules.
- Dexlansoprazole 60 mg delayed-release capsules.

The study drug will be foil/foil blistered and packaged in 1-day child resistant blister cards containing 1 capsule. The card label will be compliant with requirement of CFDA.

8.1.2 Storage

All clinical drug supplies used to conduct this study should be stored at: 20°C to 25°C; excursions allowed between 15°C and 30°C.

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

8.1.3 Dose and Regimen

Subjects will fast for a minimum of 8 hours prior to dosing. On Day 1, breakfast will be served 1 hour postdose. Subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration. Dosing will commence at approximately 0800 hours on Day 1. Study drug will be administered with 240 mL of water. Subjects must drink all of the water provided with the dose.

Following administration of the study drug, hand and mouth checks will be performed to ensure that the study drug was swallowed. Although the timing of events requires that each subject will be consistently administered the appropriate study drug 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.

Table 8.a Study Medication Supplies

Parallel Group	Dose
1	Single oral dose of dexlansoprazole 30 mg delayed-release capsule
2	Single oral dose of dexlansoprazole 60 mg delayed-release capsule

8.1.4 Overdose

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

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

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

The site will assign a 4-digit enrollment number in the order subjects become eligible for enrollment starting from 1001. This enrollment sequence number will be entered onto the eCRF. This 4-digit number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all 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 screening number which is assigned at the time the informed consent is obtained (Section 9.1.1) and which is used for all other procedures to identify the subjects throughout the study.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to a designated facility for destruction.

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study medication, the investigator must maintain records of all study medication 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 must maintain 100% accountability for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

The investigator must record the current inventory of all study medication 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 study medication, expiry date and amount dispensed, including the initials of the person dispensing the drug. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical trial material accountability and reconciliation before clinical trial materials are returned to the sponsor or its designee for destruction. The investigator will retain the original documentation regarding clinical trial material accountability, return, and destruction, and copies will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of clinical trial material 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 clinical trial material for return to the sponsor or its designee for destruction.

In the event of expiry date extension of supplies already at the study site, clinical trial material may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

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

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed, including requesting that a subject fast for laboratory evaluations.

A unique subject identification number (site number + subject number) will be assigned to each subject at the time 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, gender, race as described by the subject, height, weight, and smoking status of the subject at Screening. Caffeine consumption and alcohol history will also be collected at Screening. Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped 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 baseline physical examination (defined as the pretreatment assessment immediately prior to the start of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other.

Any abnormal findings from the baseline physical examination 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 investigational drug (Day1) 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:

Metric: $BMI = weight\ (kg)/[height\ (m)]^2$

Height will be collected in centimeters to 1 decimal place and weight will be collected in kilograms (kg) to 1 decimal place. BMI will only be calculated at the Screening Visit and results for BMI will be expressed with 1 decimal place.

Example: Height=176.2 cm (or 1.762 m), weight=79.2 kg; $BMI=79.2/1.762^2=25.5\ kg/m^2$.

9.1.5 Vital Sign Procedure

Vital signs will include oral or axillary body temperature measurement, sitting blood pressure (after 5 minutes resting), respiration rate and pulse beats per minute (bpm). Only blood pressure and pulse will be taken on Check-in (Day -1) through Day 2.

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

9.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Takeda. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. 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 Screening. 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. The maximum volume of blood at any single visit is approximately 84 mL, and the total volume of blood for the study is approximately 152 mL. 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**
Red blood cells (RBC) White blood cells (WBC) with differential Hemoglobin Hematocrit Platelets	ALT Albumin Alkaline phosphatase AST Glucose Total bilirubin Total protein Total cholesterol Triglycerides Serum creatinine Blood urea nitrogen or urea Uric acid γ-Glutamyl transferase (GGT) Calcium Phosphorus Potassium Sodium Chloride Bicarbonate or carbon dioxide	pH Specific gravity Protein Glucose Ketones Bilirubin Microscopic Analysis (RBCs, WBCs, epithelial cells, casts) if significant findings on dipstick urinalysis
Diagnostic Screening:		
Serum	**Urine**	**Breath**
HIV test – *Screening Visit only* Hepatitis panel, including HBsAg and anti-HCV – *Screening Visit only* *Women only* FSH (if menopause is suspected) *Women of childbearing potential only* serum hCG (for pregnancy) – Screening, Day -1, Day 2, or if a subject prematurely terminates from the study.	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates.	Alcohol test

hCG=human chorionic gonadotropin, FSH=follicle stimulating hormone.

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. 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.

If subjects experience ALT or AST >3×ULN, follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48-72 hours after the abnormality was found.

(Please refer to Section 10.2.3 for the appropriate guidance on Reporting of Abnormal Liver Function Tests in relation to ALT or AST >3×ULN in conjunction with total bilirubin >2×ULN.)

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 medication, 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 Reporting of Abnormal Liver Function Tests for reporting requirements).

Laboratory reports must be signed and dated by the principal investigator or the study doctor delegated by the principal investigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance.

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

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study medication, nonsterilized** men who are sexually active with a woman of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (defined as continuous amenorrhea of at least 1 year and FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented, confirmed before any study medication is administered). Subject without bilateral tubal ligation documentation must follow one of the other methods of contraception as described below.

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

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, where medications and devices containing hormones are included (provided the subject has been on a stable dose for a minimum of 90 days prior to Day 1), the only acceptable methods of contraception are:

Barrier methods (each time the subject has intercourse):

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

Intrauterine devices (IUDs):

- Copper T PLUS condom or spermicide.
- Progesterone T PLUS condom or spermicide.

Hormonal contraceptives:

- Implants.
- Hormone shot/injection.
- Combined pill.
- Minipill.
- Patch.
- Vaginal ring PLUS male condom and spermicide.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

During the course of the study, regular serum hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative serum hCG pregnancy test Check-in (Day-1) prior to receiving any dose of study medication. Women will also be given a serum hCG pregnancy test upon Study Exit (Day 2) or Early Termination.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a man during the study or for up to 30 days after the last dose should also be recorded following authorization from the subject's partner.

If the pregnancy occurs during administration of active study medication, eg, after Day 1 or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

If the woman or female partner of a man subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of treatment 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 at the time points stipulated in Appendix A. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The results of the ECG will be captured on the source documents and appropriate eCRF and the original hard copies should be kept as source documentation. ECGs on thermal paper must be photocopied and the copy should be kept in the subjects' source documents.

All stationary 12-lead ECG machines will be supplied by the site. The ECGs should be collected following an approximate 5-minute rest period. Should technical difficulties occur during collection of the ECG, a reasonable attempt should be made to repeat the ECG shortly after the failed attempt.

9.1.12 Sample Collection for Genotype Analysis

Genotyping and phenotyping analysis for CYP2C19 will be required for all subjects because dexlansoprazole is metabolized by the polymorphic isozyme CYP2C19. On Day 1, one blood sample (approximately 2 mL) for genotype analysis will be collected into vacutainers containing anticoagulant K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in Appendix E.

9.1.13 Pharmacokinetic Sample Collection

9.1.13.1 Collection of Blood for Pharmacokinetic Sampling

On Day 1, blood samples (one 6-mL sample per scheduled time) for the determination of dexlansoprazole plasma concentrations will be collected into chilled vacutainers containing anticoagulant K_2EDTA according to the schedule in Appendix A.

Instructions for sample processing and shipment are provided in Appendix E.

Blood samples will be collected according to Table 9.b.

Table 9.b Collection of Blood Samples for Pharmacokinetic Analysis

Day	Blood Sample Collection Time (hours)
Day 1	One 6 mL sample at predose (no earlier than 30 min predose) (0 hour) and, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours postdose

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

9.1.14 Pharmacokinetic Parameters

The PK parameters of dexlansoprazole 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 from plasma concentration values:

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

Other parameters may be calculated, if appropriate.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent. If the subject is found to be not eligible at this visit, the investigator should complete the relevant eCRF.

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

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

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

9.1.16 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the study.

If the subject is found to be not eligible for entrance, 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 medication, 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 medication 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).

9.4 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)	Estimated Blood Collection		Total Volume (mL)
		Number of Samples	Treatment Days	
Clinical laboratory tests	20 mL	3	Screening, Check-in (Day -1), Study Exit	**60**
Genotyping	2 mL	1	Day 1	**2**
PK blood collection	6 mL	15	Day 1 to 2	**90**
			Total Approximate Blood Sampling Volume	**152**

The maximum volume of blood at any single day is approximately 84 mL, and the approximate total volume of blood for the study is 152 mL.

Direct venipuncture is the preferred method of blood collection.

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 finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

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

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

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is

performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Overdose:

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

10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is 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 Acute liver failure
Torsade de pointes / ventricular fibrillation / ventricular tachycardia	Anaphylactic shock Acute renal failure
Malignant hypertension	Pulmonary hypertension
Convulsive seizure	Pulmonary fibrosis
Agranulocytosis	Confirmed or suspected endotoxin shock
Aplastic anemia	Confirmed or suspected transmission of infectious agent by a medicinal product
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Neuroleptic malignant syndrome / malignant hyperthermia Spontaneous abortion / stillbirth and fetal death

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

10.1.5 Severity of PTEs and AEs

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

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

10.1.6 Causality of AEs

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

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

10.1.7 Relationship to Study Procedures

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

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

10.1.8 Start Date

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

10.1.9 Stop Date

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

10.1.10 Frequency

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

10.1.11 Action Concerning Study Drug

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

10.1.12 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining “Not recovered/not resolved”.
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs/PTEs which are considered as the cause of death.

- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication (Day 1) or until screen failure. For subjects who discontinue prior to study medication administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until Final Visit or Early Termination. A follow-up site/telephone visit will be made by each subject 5 to 10 days following the last dose of study drug to collect any AEs that may have occurred.

10.2.1.2 PTE and AE Reporting

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

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

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Severity.
5. Investigator's opinion of the causal relationship between the event and administration of study medication(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 medication (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 medication(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 immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

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

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

11.0 STUDY-SPECIFIC COMMITTEES

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

12.0 DATA HANDLING AND RECORDKEEPING

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

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

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.

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 clinical study database, any change of, modification of or addition to the data on the eCRF 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.

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper should be copied and certified, 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 audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5

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

Refer to the phase 1 Site Specifications document 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.

The targeted review plan will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

All subjects who are enrolled in the study and take at least 1 dose of study drug will be included in the safety set.

All subjects who receive at least 1 dose of study drug and have at least 1 measureable plasma concentration of dexlansoprazole will be included in the PK set.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by dose group. Summary statistics (number of subjects, mean, median, SD and range) will be generated for continuous variables (eg, age, weight, and body mass index) and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, race and ethnicity).

13.1.3 Pharmacokinetic Analysis

The concentration of dexlansoprazole in plasma will be summarized by scheduled sampling time points and dose group using descriptive statistics. Individual plasma concentration data will be presented in a data listing.

Descriptive statistics (number of subjects, arithmetic mean, SD, %CV, median, minimum and maximum) will be used to summarize the plasma PK parameters for dexlansoprazole from each dose group.

A more detailed analysis will be presented in the SAP.

13.1.4 Safety Analysis

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the MedDRA. Treatment-emergent adverse events (TEAEs) with onset occurring within 30 days (onset date – last date of dose +1≤30) after study drug administration will be included in the summary tables. All AEs will be in the listings. TEAEs will be summarized by SOC and PT. The following summary tables will be included in the report: summary of TEAEs and drug-related AEs, relationship of AEs to study drug (related vs not related), severity of AEs, and related AEs. Data listings will be provided for all AEs including PTEs, TEAEs, AEs leading to study drug discontinuation, and SAEs.

Baseline, postdose, and change from baseline to postdose laboratory values will be summarized using descriptive statistics for each dose group. A table with predefined criteria for markedly abnormal values for laboratory variables will be presented. All clinical laboratory data will be listed.

Vital signs will be summarized for each dose group by presenting descriptive statistics for baseline, postdose, and change from baseline to postdose values. Vital signs that meet predefined markedly abnormal criteria will be presented. All vital sign data will be provided in the data listings.

Shift tables for ECG evaluation will be provided overall. All ECG data will be listed in the data listings.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

No formal sample size calculations were conducted. A sample size of 40 subjects, 20 subjects per parallel group, will be used in this study. This sample size is deemed to be sufficient for the assessment of the PK of dexlansoprazole 30 and 60 mg delayed-release capsules in the Chinese population.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

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. However, blood samples not collected within the interval specified for the scheduled sample time should be reported to Takeda using the Protocol Deviation Form.

Protocol Deviation Forms are to be completed for PK samples collected outside of the following intervals shown in Table 14.a:

Table 14.a Windows for Pharmacokinetic Sample Collection

Minutes	Nominal Sampling Time
no more than 30 minutes predose	0 hour
±5	immediately postdose to ≤6 hours
±10	>6 hours to ≤12 hours postdose
±15	>12 hours to ≤24 hours

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 CFDA, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure or package insert, 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 and notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing. For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor. Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

1. Dexilant (dexlansoprazole) Delayed Release Capsules. Full Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc., Revised 16 January 2016.
2. Vakily M, Zhang W, Wu J, Atkinson SN, Mulford D. Pharmacokinetics and pharmacodynamics of a known active PPI with a novel dual delayed release technology, dexlansoprazole MR: a combined analysis of randomized controlled clinical trials. Curr Med Res Opin 2009;25(3):627-38.
3. Yin OQ, Tomlinson B, Chow AH, Waye MM, Chow MS. Omeprazole as a CYP2C19 marker in Chinese subjects: assessment of its gene-dose effect and intrasubject variability. J Clin Pharmacol 2004;44(6):582-9.

Appendix A Schedule of Study Procedures

Procedure	Pretreatment Period		Treatment Period		Early Termination	Follow-up Site/Telephone Visit Postdose 5-10 days (b)
	Screening Days -28 to -2 (a)	Check-in Day -1	Day 1	Day 2/ Study Exit		
Confinement		X	X	X (c)		
Informed consent (d)	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X					
Medication history	X					
Concurrent medical conditions	X					
Complete physical exam	X	X		X	X	
Body weight and height	X	X (e)		X (e)	X (e)	
12-Lead ECG	X	X		X	X	
Vital signs (f)	X	X (f)	X (f)	X (f)	X	
Fasting safety laboratory evaluations (g)	X	X		X	X	
Serum pregnancy test (h)	X	X		X	X	
FSH (i)	X					
HIV, HBsAg, and anti-HCV screening	X					
Urine drug screen	X	X				
Alcohol breath test	X	X				
Blood sampling for PK analysis			X (j)	X (j)		
Blood sample for CYP2C19 genotype testing			X			
Administration of study drug (k)			X			
Pretreatment event/Adverse event (l) assessment (l)	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X

Footnotes are on the following page.

(a) Screening procedures must be performed within 28 days prior to administration of investigational product.
(b) The routine collection of AEs will continue after dosing through the Follow-up site/telephone visit which will be made 5-10 days postdose.
(c) Following study procedure completion on Day 2 subjects will be discharged from the study.
(d) HIPAA=Health Insurance Portability and Accountability Act, must be signed before any study-specific procedures are performed.
(e) Excluding height. BMI will be calculated at Screening only.
(f) Blood pressure, pulse, respiratory rate and oral or axillary temperature will be collected at Screening. Only blood pressure and pulse will be collected on Day -1 through Day 2. Vital signs will be obtained upon admission, morning rising and 8 hours postdose.
(g) Obtained after minimum 8-hour fast.
(h) A serum pregnancy test for all women of childbearing potential will be done at Screening, Day -1, Day 2, or if a subject prematurely terminates from the study.
(i) For women where menopause is suspected.
(j) Blood samples obtained predose (no more than 30 minutes prior to study drug administration) (0 hr) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours postdose.
(k) Study drug administered beginning at approximately 0800 hours.
(l) Pretreatment AEs will be captured immediately following the signing of the informed consent at Screening and prior to study drug administration. Follow-up site or telephone visit will be made 5-10 days after last dose of study drug to inquire about any TEAE or SAEs, and concomitant medications taken since final dose. Any TEAE/SAE spontaneously reported within 30 days postdose will be included within the database as a TEAE.

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (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 may discontinue

participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) that the subject's identity will remain confidential in the event that study results are published.

25. Women of childbearing potential (eg, nonsterilized, premenopausal women) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study, and for 30days weeks after last dose of study medication. Regular pregnancy tests will be performed throughout the study for all women of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Men must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

Instructions for Processing of Plasma Samples for Pharmacokinetic Analysis

1. Collect 6 mL of venous blood into a chilled Becton-Dickinson Vacutainer. For all TAK-390MR samples, blood samples should be collected into vacutainers containing anticoagulant 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 or keep at ambient temperature.
3. Centrifuge the vacutainers for 10 minutes at approximately 1200 relative centrifugal force (RCF) at approximately 4°C in a refrigerated centrifuge or at ambient temperature. 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. Split the plasma evenly between the 2 aliquots. A minimum of approximately 1.2 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-390MR_106), matrix (ie, plasma), analyte (TAK-390MR), enrollment number, nominal day and 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. No more than 120 minutes will elapse between blood collection and freezing the plasma sample.
6. Keep samples frozen at approximately -20°C or lower until shipment site. 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.

Shipping of Plasma Samples

Site may adhere to the site's SOPs on shipping samples if the SOP differs from the sample instructions provided.

Biological samples should be shipped on sufficient dry ice to prevent thawing during transit. Samples should be shipped to arrive at their destination during normal business hours (local time). It is recommended that samples be shipped on Monday, Tuesday or Wednesday and 2 days before a national holiday, in order to minimize the possibility of samples arriving at their destination on a weekend or holiday. For shipments outside these periods, it is recommended that a premium carrier who will replenish dry ice during shipment as necessary be used. Other shipping arrangements may be allowed with the agreement of the Sponsor. If duplicate samples are to be shipped, send SET 1 samples and await confirmation of arrival before shipping the duplicate SET 2 samples.

Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:

1. Separate the duplicate SET 2 samples from the SET 1 samples.

2. Place SET 1 samples for each subject into zipper lock bag containing additional absorbent material.
3. Using a permanent marker, write the enrollment number, sample matrix (ie, plasma or urine), analyte (TAK-390MR), number of samples, and "SET 1" on each zipper lock bag.
4. 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.
5. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study drug (TAK-390MR), protocol number (TAK-390MR_106), investigator's name, sample type (ie, plasma), subject's enrollment number, 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 zipper lock 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.
6. For sample packing, use 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.
7. 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.
8. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
9. Affix an address label to each shipping carton. Complete the address label with the following information:
   Plasma Samples for TAK-390MR 106
   Personally Protected Data
10. 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)

11. 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.
12. Obtain the airway bill number and a receipt of shipment from the carrier.
13. After shipping of the samples, **contact the analytical site and CRO representative** to notify them of next day delivery. When calling, provide the following information:

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

Instructions for processing and shipping of blood samples for genotyping analysis

Detailed instructions for the handling and shipping of samples will be provided in the Lab Manual.

Appendix F Detailed Description of Amendments to Text

The primary sections of the protocol affected by the changes in Amendment No. 03 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Updated Appendix E Collection, Storage, and Shipment of Bioanalytical Samples.

The change occurs in Appendix E Collection, Storage, and Shipment of Bioanalytical Samples:

Initial wording:	Appendix E Collection, Storage, and Shipment of Bioanalytical Samples 3. Centrifuge the vacutainers for 10 minutes at approximately 1100-1300 relative centrifugal force (RCF) at approximately 4°C in a refrigerated centrifuge or at ambient temperature. 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 1.2 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-390MR_106), matrix (ie, plasma), analyte (TAK-390MR), enrollment number, nominal day and 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. No more than 45 minutes will elapse between blood collection and freezing the plasma sample. **Instructions for processing and shipping of plasma samples for genotyping analysis** To be determined when laboratory is selected.

Amended or new wording:

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

3. Centrifuge the vacutainers for 10 minutes at approximately ~~1100-1300~~ **1200** relative centrifugal force (RCF) at approximately 4°C in a refrigerated centrifuge or at ambient temperature. 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, s~~**S**plit the plasma evenly between the 2 aliquots. A minimum of approximately 1.2 mL needs to be obtained for each sample. Labeling may include protocol number (TAK-390MR_106), matrix (ie, plasma), analyte (TAK-390MR), enrollment number, nominal day and 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. No more than ~~45~~**120** minutes will elapse between blood collection and freezing the plasma sample.

Instructions for processing and shipping of ~~plasma~~ blood samples for genotyping analysis

~~To be determined when laboratory is selected.~~ **Detailed instructions for the handling and shipping of samples will be provided in the Lab Manual**

Rationale for Change:

Updated to reflect the current procedures for plasma samples for pharmacokinetic analysis and to provide the reference to the lab manual for information regarding processing and shipment of blood samples for genotyping analysis.

Change 2: Correct blood volume for genotype analysis and total blood volume.

The change occurs in Section 9.1.8 Procedures for Clinical Laboratory Samples, Section 9.1.12 Sample Collection for Genotype Analysis, and Section 9.4 Blood Volume:

Initial wording:

Section 9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 84 mL, and the total volume of blood for the study is approximately 156 mL. Laboratory samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Section 9.1.12 Sample Collection for Genotype Analysis

Genotyping and phenotyping analysis for CYP2C19 will be required for all subjects because dexlansoprazole is metabolized by the polymorphic isozyme CYP2C19. On Day 1, one blood sample (approximately 6 mL) will be collected for genotype analysis. Detailed instructions for the handling and shipping of samples will be provided in the Lab Manual.

Section 9.4 Blood Volume

		Estimated Blood Collection		
Sample Type	**Sample Volume (mL)**	**Number of Samples**	**Treatment Days**	**Total Volume (mL)**
Clinical laboratory tests	20 mL	3	Screening, Check-in (Day -1), Study Exit	**60**
Genotyping	6 mL	1	Day 1	**6**
PK blood collection	6 mL	15	Day 1 to 2	**90**
		Total Approximate Blood Sampling Volume		**156**

The maximum volume of blood at any single day is approximately 84 mL, and the approximate total volume of blood for the study is 156 mL.

Amended or new wording:

Section 9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 84 mL, and the total volume of blood for the study is approximately 15~~6~~**2** mL. Laboratory samples will be taken following a minimum 8-hour overnight fast on the days stipulated in the Schedule of Study Procedures (Appendix A).

Section 9.1.12 Sample Collection for Genotype Analysis

Genotyping and phenotyping analysis for CYP2C19 will be required for all subjects because dexlansoprazole is metabolized by the polymorphic isozyme CYP2C19. On Day 1, one blood sample (approximately ~~6~~**2** mL) ~~will be collected~~ for genotype analysis **will be collected into vacutainers containing anticoagulant K_2EDTA according to the schedule in Appendix A. Instructions for sample processing and shipment are provided in Appendix E**.

Section 9.4 Blood Volume

		Estimated Blood Collection		
Sample Type	**Sample Volume (mL)**	**Number of Samples**	**Treatment Days**	**Total Volume (mL)**
Clinical laboratory tests	20 mL	3	Screening, Check-in (Day -1), Study Exit	**60**
Genotyping	~~6~~**2** mL	1	Day 1	~~6~~**2**
PK blood collection	6 mL	15	Day 1 to 2	**90**
		Total Approximate Blood Sampling Volume		**15~~6~~2**

The maximum volume of blood at any single day is approximately 84 mL, and the approximate total volume of blood for the study is 15~~6~~**2** mL.

Rationale for Change:

Updated current blood volume for genotype analysis and overall blood volume.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personally Protected Data	Statistical Approval	29-Nov-2017 15:37 UTC
	Clinical Pharmacology Approval	29-Nov-2017 15:51 UTC
	Clinical Science Approval	29-Nov-2017 16:49 UTC
	Clinical Science Approval	29-Nov-2017 18:21 UTC