Title: A Phase 1, Randomized, Open-Label, Single-Center, Single-Dose, Two-Period, Two-Part Crossover Study in Healthy Subjects to Compare the Bioavailability of Dexlansoprazole from Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda GmbH Plant Oranienburg Relative to Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda Pharmaceutical Company Limited Osaka Plant Following a High-Fat Meal

NCT Number: NCT03801148

Protocol Approve Date: 09 January 2019

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

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

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

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 1, Randomized, Open-Label, Single-Center, Single-Dose, Two-Period, Two-Part Crossover Study in Healthy Subjects to Compare the Bioavailability of Dexlansoprazole from Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda GmbH Plant Oranienburg Relative to Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda Pharmaceutical Company Limited Osaka Plant Following a High-Fat Meal

Study Identifier: TAK-390MR-1002

Compound: Dexlansoprazole Delayed-Release Capsules

Date: 09 January 2019

Version/Amendment Number: Amendment 1

Amendment History:

Date	Amendment Number	Amendment Type	Region
17 December 2018	Initial Version		
09 January 2019	01	Not Applicable	United States

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1.0 STUDY SUMMARY

Name of Sponsor: Takeda Pharmaceuticals Takeda Development Center Americas, Inc. One Takeda Parkway, Deerfield, IL 60015	**Compound:** Dexlansoprazole Delayed-Release Capsules (TAK-390)
Study Identifier: TAK-390MR-1002 (CA24021)	**Phase:** 1

Protocol Title: A Phase 1, Randomized, Open-Label, Single-Dose, Two-Period Crossover Study to Compare the Bioavailability of Dexlansoprazole Capsules Manufactured by Takeda GmbH Relative to Dexlansoprazole Capsules Manufactured by Takeda Osaka Following a High-Fat Meal

Trial Design:

This is a phase 1, randomized, open-label, single-center, single-dose, 2-part, 2-way crossover bioavailability (BA) study to compare the BA of 30 or 60 mg dexlansoprazole capsules manufactured at Takeda GmbH Plant Oranienburg (TOB) to the corresponding 30 and or 60 mg dexlansoprazole capsules manufactured at Takeda Pharmaceutical Company Ltd. (TPC) plant in Osaka, Japan under fed conditions. The study will be conducted in 2 parts. In Part 1, 60 healthy subjects will receive dexlansoprazole 30 mg capsules manufactured by TOB and TPC in a crossover fashion. In Part 2, an additional 60 healthy subjects will receive dexlansoprazole 60 mg capsules manufactured by TOB and TPC in a crossover fashion. Due to the difference between the Granules-L used in the 30 mg (Granules-LL) and 60 mg (Granules-LS) capsules, the relative BA of both dosage strengths will be assessed.

Subjects who satisfy the Screening evaluation and selection criteria may be enrolled in the study. For each part, eligible subjects will be randomized on Day 1 of Period 1 in a 1:1 ratio to 1 of 2 sequences, which defines the order in which they will receive dexlansoprazole regimens in Periods 1 and 2. The dosing between periods will be separated by a minimum 5-day washout interval. During Periods 1 and 2, blood samples will be collected predose and over 24 hours postdose to measure dexlansoprazole plasma concentrations. The treatment sequences are outlined in the following tables for Part 1 and for Part 2.

Part 1 Sequences

Sequence	Number of Subjects	Period 1	Period 2
1	30	A	B
2	30	B	A

Regimen A (test): A single dexlansoprazole 30 mg capsule manufactured at TOB administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen B (reference): A single dexlansoprazole 30 mg capsule manufactured at TPC administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.

Part 2 Sequences

Sequence	Number of Subjects	Period 1	Period 2
3	30	C	D
4	30	D	C

Regimen C (test): A single dexlansoprazole 60 mg capsule manufactured at TOB administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen D (reference): A single dexlansoprazole 60 mg capsule manufactured at TPC administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.

In each period of each part, subjects will be confined from Check-in Day -1 until all study procedures have been completed on Day 2. Study drug will be administered in the morning of Day 1 of each period 30 minutes following the beginning of a high-fat/high calorie breakfast. The entire standardized breakfast is to be consumed within 25 minutes. Dosing may be staggered to help facilitate logistics at the site. Subjects will be instructed to swallow the intact capsule with 240 mL of water. During Periods 1 and 2 of each part, blood samples will be collected predose and over 24 hours

postdose to measure dexlansoprazole plasma concentrations.

Subjects will be discharged from the study site on Day 2 of each period (subjects will exit the study on Day 2 of Period 2 within each part), and the dosing between periods within each part will be separated by a minimum 5-day washout interval.

A follow-up phone call will be made 10 (±2) days post last dose of study drug to inquire for any ongoing adverse events (AEs) or serious adverse events (SAEs), as well as new AEs or SAEs, and concomitant medications taken since final dose. Subjects who received at least one dose of study drug and terminate from the study early will still be contacted for a safety follow-up call. The contact will only be recorded in their source documents and the case report forms (CRFs), according to data protection regulations.

Primary completion date will be based on the final data collection for the primary endpoint, Day 2 of Period 2. End of trial (study completion date) will be based on the final data collection date for the entire study, which is the follow-up phone call.

A schematic of the study design is shown below.

Schematic of Study Design

Screening Period	Check-in (Periods 1 and 2)	Treatment Periods 1 and 2		Study Exit (Period 2)	Follow-up Phone Call
		Dexlansoprazole 30 and 60 mg capsule Single Dose PK	Discharge (Period 1)		
Days -28 to -2	Day -1	Day 1	Day 2 Period 1	Day 2	Day 10 (±2 days)
		←——Confinement——→			

PK=Pharmacokinetic.
Note: There is a minimum 5-day washout period between the dose in Period 1 and the dose in Period 2. A follow-up phone call will be made for collection of AEs, SAEs, and concomitant medications taken since the final dose.

Trial Primary Objective:

- To assess the BA of dexlansoprazole from a 30 mg capsule manufactured at TOB relative to that of dexlansoprazole from a 30 mg capsule manufactured at TPC.
- To assess the BA of dexlansoprazole from a 60 mg capsule manufactured at TOB relative to that of dexlansoprazole from a 60 mg capsule manufactured at TPC.

Secondary Objectives:

To evaluate the safety and tolerability of dexlansoprazole following oral administration of a single dexlansoprazole 30 or 60 mg capsule.

Trial Subject Population: Healthy subjects aged 18 to 55 years, inclusive, who have a body mass index between 18 and 30 kg/m^2.

Planned Number of Subjects:	**Planned Number of Sites:**
Per dose level: 60 Estimated Total: 120	Estimated total: 1 in the United States
Dose Levels:	**Route of Administration:**
Part 1: 30 mg dexlansoprazole Part 2: 60 mg dexlansoprazole	Oral

Duration of Treatment:	**Planned Trial Duration:**
Part 1: Dexlansoprazole 30 mg capsule (manufactured at TOB or TPC) administered on Day 1 of Periods 1 and 2. Part 2: Dexlansoprazole 60 mg capsule (manufactured at TOB or TPC) administered on Day 1 of Periods 1 and 2. Total number of dosing days: 2 per part.	Screening: 27 days. Check-in (Day -1) for each Period: 2 days total. Treatment Period (Days 1 to 2) for each Period: 4 days total. Washout between dosing: at least 5 days. Follow-up phone call: 10 days (±2) after last dose. Total Study Duration including Screening: Approximately 43 days per part.

Main Criteria for Inclusion:

Healthy men and women aged 18 to 55 years old, inclusive, with a body mass index between 18 and 30 kg/m^2, inclusive, who are capable of understanding and complying with protocol requirements. Subjects must be in good health as determined by a physician based upon medical history, vital signs, electrocardiogram (ECG), and physical examination. Subjects must have clinical chemistry, hematology, and complete urinalysis (after fasting for at least 12 hours) at Screening and Check-in (Day -1 of Period 1) results within the reference range for the testing laboratory unless the out-of-range results are deemed not clinically significant by the investigator. Subjects must sign a written informed consent form (ICF) prior to initiation of study procedures.

Main Criteria for Exclusion:

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 (EE) with frequent [more than once per week] occurrence of heartburn); or has consumed medications, certain foods, and supplements, including prescription and over-the-counter medications, within the protocol-specified time periods prior to Check-in (Day -1 of Period 1), or is unwilling to agree to abstain from these products. The subject must not have received dexlansoprazole in a previous clinical study or as a therapeutic agent within 6 months of Screening, or have a known hypersensitivity to any component of the formulation of dexlansoprazole capsules or other drugs with the same mechanism of action (including lansoprazole, omeprazole, rabeprazole, pantoprazole, or esomeprazole), or related compounds; or any significant results from physical examination or clinical laboratory results that make the subject unsuitable for the study.

Main Criteria for Evaluation and Analyses:

The primary endpoints of the study are the following plasma PK parameters of dexlansoprazole derived on Day 1 of each period:

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

Additional Endpoints

In addition, the following plasma PK parameters for dexlansoprazole will be calculated:

- time to first occurrence of C_{max} (t_{max}),
- terminal disposition phase half-life ($t_{1/2z}$),
- terminal disposition phase rate constant (λ_z),
- apparent clearance after extravascular administration (CL/F),
- apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).

Safety Endpoints

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

Statistical Considerations:

For each regimen of each part, dexlansoprazole plasma concentrations and PK parameter estimates will be tabulated and descriptive statistics computed.

For each part, analysis of variance (ANOVA) will be performed on natural logarithms of dexlansoprazole C_{max} and area under the plasma concentration-time curve (AUC) with factors for sequence, subject nested within sequence, period, and regimen. The factor of the subject nested within sequence will be the error term for testing the sequence effect. Other factors will be tested with the residual as the error term. For the relative BA determination, pairwise comparisons will be performed to assess the relative BA of dexlansoprazole via point estimates and 90% confidence intervals (CI) for the ratio of C_{max} and AUC central values of the dexlansoprazole 30 or 60 mg capsules manufactured at TOB compared to the respective 30 or 60 mg capsules manufactured at TPC. A conclusion of BE in the PK of dexlansoprazole between test regimen (dexlansoprazole capsule - TOB) and the reference regimen (dexlansoprazole capsule - TPC) will be reached if the 90% CIs for C_{max} and AUC are within the (0.80–1.25) interval.

Statistical analyses of other plasma PK parameters will be performed, if appropriate.

Sample Size Justification:

For each part, a sample size of 60 (30 per sequence) will be used in this study. This sample size will allow for up to 6 dropouts (10% dropout rate) and provide 90% probability of concluding equivalence on dexlansoprazole C_{max} between the 2 regimens if the true difference between dexlansoprazole C_{max} central values from 2 regimens is no more than 5%. The power for concluding equivalence on dexlansoprazole AUC between 2 regimens would be over 95%. This sample size was based on the intrasubject variance of 0.0884 for log(C_{max}) and 0.0365 for log(AUC) from Part 1 (30 mg) of the TAK-390MR-1001 study. Part 1 was used because the intrasubject variance of log(C_{max}) was higher than in Part 2 (60 mg).

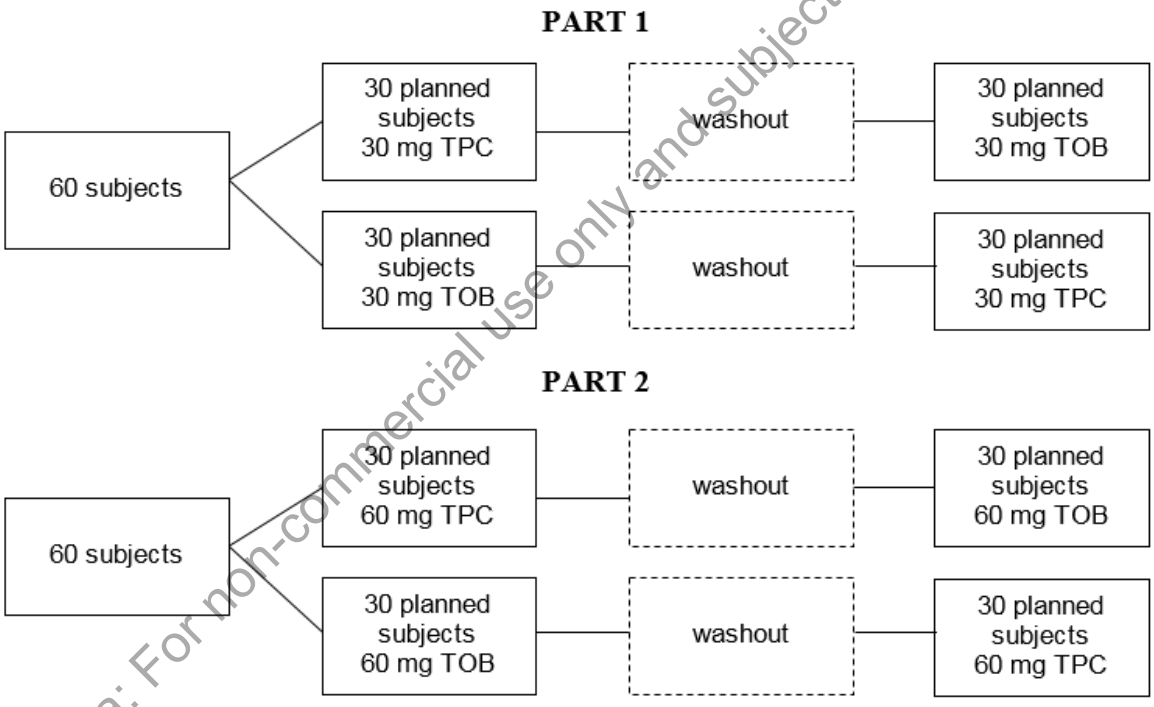
2.0 STUDY SCHEMATIC

Figure 2.a Schematic of Study Design

Screening Period	Check-in (Periods 1 and 2)	Treatment Periods 1 and 2		Study Exit (Period 2)	Follow-up Phone Call
		Dexlansoprazole 30 and 60 mg capsule Single Dose PK	Discharge (Period 1)		
Days -28 to -2	Day -1	Day 1	Day 2 Period 1	Day 2	Day 10 (±2 days)
		←——Confinement ——→			

Note: There is a minimum 5-day washout period between the dose in Period 1 and the dose in Period 2. A follow-up phone call will be made for collection of AEs, SAEs, and concomitant medications taken since the final dose.

Figure 2.b Schematic of Crossover Design



3.0 SCHEDULE OF STUDY PROCEDURES

Study Day:	Pretreatment Period	Treatment Periods 1 and 2 (a)			Study Exit (Day 2 of Period 2)/ Early Termination (c)	Follow-up Phone Call (d)
	Days -28 to -2 (screening) (b)	Day -1 (Check-in)	Day 1	Day 2 (Period 1)		
Confinement		X	X	X (e)	X (c)	
Informed consent	X					
Inclusion/exclusion criteria	X	X (f)				
Demographics and medical history	X					
Medication history	X					
Physical examination	X	X			X	
Height, Weight, and BMI (g)	X					
Vital signs (h)	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X
Clinical laboratory tests (i)	X	X		X	X	
HIV and Hepatitis panel	X					
Pregnancy test (hCG) (j)	X	X			X	
FSH (k)	X					
Urine drug and alcohol screen	X	X				
Urine cotinine test	X	X				
ECG (l)	X	X		X	X	
Administration of study drug (m)			X			
PK blood collection (n)			X	X	X (o)	
AE assessment (p)	X	X	X	X	X	X

Footnotes are on following page.

(a) There will be at least 5 days between the dose in 1 period and the dose in a subsequent period.
(b) Screening procedures must be performed within 28 days prior to first administration of investigational product.
(c) Following study procedure completion on Day 2 of Period 1, subjects will be discharged from the clinic for the washout period.
(d) Follow-up phone call will be made 10±2 days after last dose of study drug (including any subject who received at least one dose of study drug and terminated from the study early) to inquire about any TEAE or SAEs, as well as new AEs 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/SAE.
(e) Following study procedure completion on Day 2 of Period 2, subjects will be discharged from the clinic. Early termination procedures are explained in Section7.5.
(f) Assessment of inclusion and exclusion criteria will be done on Day -1, Period 1 only.
(g) The BMI is calculated using metric units as follows: Metric: BMI = weight (kg)/[height (m)]^2.
(h) Vital signs: oral body temperature, sitting blood pressure (after resting 5 minutes), respiratory rate, and pulse (beats per minute) at Screening. Only blood pressure and pulse will be collected in each period on Check-in (Day -1), prior to dosing and at 8 hours postdose on Day 1, and prior to discharge from the clinic on Day 2, or if the subject terminates early from the study. 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 30 minutes before or after the scheduled blood draw.
(i) Hematology, serum chemistries, and urinalysis tests. Clinical laboratory samples will be collected after a minimum of an 12 hour fast on Screening, Check-in (Day -1) of Periods 1 and 2; Day 2 of Period 1, and Study Exit (Day 2 of Period 2)/Early termination. If a 12-hour fast is not possible at Early Termination or due to re-checks, laboratory samples will still be collected.
(j) A serum pregnancy test will be done on all female subjects at Screening and Day -1 of each period, Study Exit (Day 2 of Period 2), or if a subject prematurely terminates from the study.
(k) For women where menopause is suspected (see Appendix D).
(l) ECG will be performed at Screening, Check-in (Day -1 of Period 1), and Study Day 2 of each period or if a subject terminates early from the study.
(m) Study drug will be administered in the morning of Day 1 of each period 30 minutes following the beginning of a high-fat/high-calorie breakfast. Dosing may be staggered to help facilitate logistics at the site.
(n) Blood samples for PK obtained predose (within 1 hour prior to dose), and at 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 10, 12, 14, 16, and 24 hours post Day 1 dosing in each period.
(o) The PK sample should not be collected at Early Termination if a PK collection is not scheduled at that time
(p) Pretreatment AEs will be captured immediately following the signing of the informed consent at Screening until dosing on Day 1 of Period 1. The routine collection of AEs will continue after dosing through the follow-up phone call.

4.0 INTRODUCTION

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, is currently marketed in over 90 countries and has a well-established safety profile.

Takeda Development Center Americas, Inc. (TDC Americas) 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) and adolescents (12 to 17 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 (US) in January 2009. The international birth date (IBD) is 30 January 2009.

The dual delayed-release capsule formulation of dexlansoprazole consists of 2 types of enteric-coated granules contained within a single capsule. Each type of granule has a different pH-dependent release profile. The formulation has been designed to have drug released within 1 to 2 hours of administration, followed by a second release phase within 4 to 5 hours of the dose. This dual delayed-release formulation is designed to extend the duration of drug exposure and maintain pharmacologically active levels of drug over a longer period of time, resulting in prolonged elevation of intragastric pH.

The pharmacokinetic (PK), pharmacodynamic, efficacy, and safety profiles of dexlansoprazole capsules following administration of dexlansoprazole 30, 60, and 90 mg capsules in adults have been extensively studied. Dexlansoprazole 60 mg capsules are approved for the healing of EE and dexlansoprazole 30 mg capsules are approved for the treatment of symptomatic nonerosive GERD, and the maintenance of healed EE. Currently, dexlansoprazole granules (Granules-LL and Granules-H for 30 mg and Granules-LS and Granules-H for 60 mg) are manufactured and encapsulated into capsule product at Takeda Pharmaceutical Company, Ltd. (TPC) located in Osaka, Japan.

4.1 Rationale for the Proposed Study

The rationale for conducting this study is to qualify an additional production site (Takeda GmbH Plant Oranienburg [TOB]) for the manufacture of dexlansoprazole capsules by establishing the bioequivalence (BE) of dexlansoprazole 30 and 60 mg capsules manufactured by TOB with dexlansoprazole 30 and 60 mg capsules manufactured by the TPC plant in Osaka. Clinical studies in healthy subjects receiving dexlansoprazole (DEXILANT®) under various fed conditions compared to fasting conditions, demonstrated increases in C_{max} ranging from 12 to 55%, increases in AUC ranging from 9 to 37%, and T_{max} varied (ranging from a decrease of 0.7 hours to an increase of three hours) [1]. As the dual stage bioavailability of the drug is based on the solubility of the different excipients in different pH levels and as DEXILANT® is prescribed to be administered with or without food [1], it is important to confirm the BE under both fasted and fed

conditions. This study will complement study TAK-390MR-1001 which assessed the BE of the drug produced in the 2 plants under fasted conditions.

4.2 Benefit/Risk Profile

The dose of dexlansoprazole administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, as it is a single dose administered according to the dosing recommendations found in the full prescribing information for DEXILANT® (dexlansoprazole) delayed-release capsules.

The safety monitoring practices employed by this protocol (ie, 12-lead ECG, vital signs, clinical laboratory tests, adverse events (AE) questioning, and physical examination) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this study is the free medical tests received at screening and during the study.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Hypothesis

A conclusion of BE in the PK of dexlansoprazole between test product (dexlansoprazole capsule - TOB) and the reference product (dexlansoprazole capsule - TPC) will be reached if the 90% confidence intervals (CIs) for C_{max} and AUC are within the (0.80–1.25) interval.

5.2 Trial Objectives

5.2.1 Trial Primary Objective

The primary objectives of the study are:

- To assess the BA of dexlansoprazole from a 30 mg capsule manufactured at TOB relative to that of dexlansoprazole from a 30 mg capsule manufactured at TPC.
- To assess the BA of dexlansoprazole from a 60 mg capsule manufactured at TOB relative to that of dexlansoprazole from a 60 mg capsule manufactured at TPC.

5.2.2 Trial Secondary Objective

The secondary objective of the study is:

To evaluate the safety and tolerability of dexlansoprazole following oral administration of a single dexlansoprazole 30 or 60 mg capsule.

5.3 Endpoints

5.3.1 Primary Endpoint

The primary endpoint of the study is following plasma PK parameters of dexlansoprazole derived on Day 1 of each period:

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

5.3.2 Additional Endpoints

The following plasma PK parameters for dexlansoprazole will be calculated:

- time to first occurrence of C_{max} (t_{max}),
- terminal disposition phase half-life ($t_{1/2z}$),
- terminal disposition phase rate constant (λ_z),
- apparent clearance after extravascular administration (CL/F),

- apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F).

5.3.3 Safety Endpoints

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

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase 1, randomized, open-label, single-center, single-dose, 2-part, 2-way crossover study in healthy subjects to assess the BA of 30 or 60 mg dexlansoprazole capsules manufactured at TOB relative to the corresponding 30 or 60 mg dexlansoprazole capsules manufactured at TPC under fed conditions. The study will be conducted in 2 parts. In Part 1, 60 healthy subjects will receive dexlansoprazole 30 mg capsules manufactured by TOB and TPC in a crossover fashion. In Part 2, an additional 60 healthy subjects will receive dexlansoprazole 60 mg capsules manufactured by TOB and TPC in a crossover fashion. Due to the difference between the Granules-L used in the 30 mg (Granules-LL) and 60 mg (Granules-LS) capsules, the relative BA of both dosage strengths will be assessed.

At Check-in (Day -1 of Period 1), approximately 120 subjects in total (60 in Part 1, 60 in Part 2), including both men and women, aged 18 to 55 years, inclusive, will be selected to participate in the study. Subjects who satisfy the Screening evaluation and selection criteria may be enrolled in the study. For each part, eligible subjects will be randomized on Day 1 of Period 1 in a 1:1 ratio to 1 of 2 sequences, which defines the order in which they will receive dexlansoprazole regimens in Periods 1 and 2. The dosing between periods will be separated by a minimum 5-day washout interval. During Periods 1 and 2, blood samples will be collected predose and over 24 hours postdose to measure dexlansoprazole plasma concentrations.

The treatment sequences are outlined in Table 6.a (Part 1) and Table 6.b (Part 2).

Table 6.a Part 1 Sequences

Sequences	Number of Subjects	Period 1	Period 2
1	30	A	B
2	30	B	A

Regimen A (test): A single dexlansoprazole 30 mg capsule manufactured at TOB administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen B (reference): A single dexlansoprazole 30 mg capsule manufactured at TPC administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.

Table 6.b Part 2 Sequences

Sequences	Number of Subjects	Period 1	Period 2
3	30	C	D
4	30	D	C

Regimen C (test): A single dexlansoprazole 60 mg capsule manufactured at TOB administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen D (reference): A single dexlansoprazole 60 mg capsule manufactured at TPC administered orally on Day 1 30 minutes following the beginning of a high-fat/high calorie breakfast.

In each period of each part, subjects will be confined from Check-in Day -1 until all study procedures have been completed on Day 2. Study drug will be administered in the morning of Day 1 of each period 30 minutes following the beginning of a high-fat/high calorie breakfast. The entire standardized breakfast is to be consumed within 25 minutes. Dosing may be staggered to help facilitate logistics at the site. Subjects will be instructed to swallow the intact capsule with 240 mL of water.

Subjects will be discharged from the study site on Day 2 of each period (subjects will exit the study on Day 2 of Period 2 within each part).

A follow-up phone call will be made 10 (±2) days post last dose of study drug to inquire for any ongoing AEs or serious adverse events (SAEs), as well as new AEs or SAEs and concomitant medications taken since final dose. Subjects who received at least one dose of study drug and terminate from the study early will still be contacted for a safety follow-up call. The contact will only be recorded in their source documents and the case report forms (CRFs), according to data protection regulations.

Primary completion date will be based on the final data collection for the primary endpoint, Day 2 of Period 2. End of trial (study completion date) will be based on the final data collection date for the entire study, which is the follow-up phone call.

A schematic of the study design is included in Section 2.0. A schedule of assessments is listed in Section 3.0.

6.2 Dose Escalation

NA

6.3 Rationale for Trial Design, Dose, and Endpoints

6.3.1 Rationale of Trial Design

This phase 1 randomized, open-label, single-dose, 2-part, 2-way crossover relative BA study is designed in accordance with Health Canada Guidance Document - Comparative Bioavailability Standards: Formulations Used for System Effects (July 2018) [2].

A single-dose study under fed conditions for assessing the relative BA between formulations is recommended in the guidance referenced above for some dosage forms and will be used for comparison of the capsule formulations from each manufacturing site. The crossover design is appropriate for the objectives of this study because each subject receives both regimens and serves as his or her own control.

In humans, dexlansoprazole has a mean $t_{1/2z}$ of approximately 1 to 2 hours. Therefore, a minimum 5-day washout interval between the doses is sufficient to ensure that there is no drug carryover effect, and collection of PK blood samples for 24 hours postdose is appropriate to characterize the PK of dexlansoprazole. The primary PK endpoints, C_{max} and area under the concentration-time curve (AUC) are standard parameters to assess BA. The safety endpoints, including TEAEs, vital

signs, 12-lead ECGs, clinical laboratory tests and physical examination data, are standard methods for assessing safety and tolerability in clinical pharmacology studies.

6.3.2 Rationale for Dose

Due to the difference between the Granules-L used in the 30 mg (Granules-LL) and 60 mg (Granules-LS) capsules, the relative BA of both dosage strengths will be assessed.

6.3.3 Rationale for Endpoints

The primary PK endpoints, C_{max} and AUC are standard parameters to assess BA. The safety endpoints, including TEAEs, vital signs, 12-lead ECGs, clinical laboratory tests and physical examination data, are standard methods for assessing safety and tolerability in clinical pharmacology studies.

6.3.4 Critical Procedures Based on Trial Objectives: Timing of Procedures

For this study, the blood collection for plasma dexlansoprazole concentrations is the critical procedure and is required to be collected as close to the scheduled times defined in this protocol as possible.

6.4 Trial Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

The dose and administration of the study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 7.5.

6.5 Trial Beginning and End/Completion

6.5.1 Definition of Beginning of the Trial

The beginning of the trial will be defined as the beginning of the screening (ie, signing of the ICF) of the first subject.

6.5.2 Definition of End of the Trial

The end of study is defined as the date of the last scheduled study procedure as outlined in the Schedule of Study Procedures (Section 3.0).

6.5.3 Definition of Trial Completion

The end of the study is scheduled after completion of the evaluations in the follow-up phone call for the last subject in the study.

This time period may change in the event that the study is terminated early or the last subject is lost to follow-up.

6.5.4 Definition of Trial Discontinuation

Celerion reserves the right to terminate the study in the interest of subject welfare.

The Sponsor reserves the right to suspend or terminate the study at any time.

6.5.5 Criteria for Premature Termination or Suspension of the Trial

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 product, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.5.6 Criteria for Premature Termination or Suspension of a Site

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.

6.5.7 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), 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

7.1 Inclusion Criteria

Attempts will be made to enroll an equal number of men and women. 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 signs and dates a written, ICF 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 in good health as determined by a physician based upon medical history, vital signs, ECG, and physical examination findings at Screening and Check-in.
4. The subject is a man or woman aged 18 to 55 years, inclusive, at the time of informed consent and first study medication dose.
5. The subject has a body mass index (BMI) from 18 to 30 kg/m^2, inclusive, at Screening.
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. A woman of childbearing potential* who is sexually active with a nonsterilized* male partner 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.

   *Definitions and acceptable methods of contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Appendix D.

8. Women must have a negative serum pregnancy test at Screening and Check-in (Day -1 of Period 1) and they must not be nursing.
9. Subject has clinical chemistry, hematology, and complete urinalysis (after fasting for at least 12 hours) at Screening and Check-in (Day -1 of Period 1) results within the reference range for the testing laboratory unless the out-of-range results are deemed not clinically significant by the investigator.
10. The subject is willing and able to consume the high-fat/high-calorie breakfasts administered during the study.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 30 days prior to the first dose of study medication.

2. 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).
3. The subject has a history of drug abuse (defined as any illicit drug use) or drug addiction in the 12 months prior to Screening or a history of alcohol abuse (defined as regular consumption exceeding 21 units per week [1 unit = 12 ounces (oz) beer, 1.5 oz hard liquor, or 5 oz wine]) within 1 year prior to the Screening Visit, or is unwilling to agree to abstain from alcohol and drugs throughout the study.
4. The subject has a positive test result for drugs of abuse (defined as any illicit drug use) or alcohol at Screening or Check-in (Day -1 of Period 1).
5. Subject has received any known hepatic or renal clearance altering agents (eg, erythromycin, cimetidine, barbiturates, phenothiazines, fluvoxamine, etc) for a period of 28 days prior to Day 1 of Period 1.
6. Subject has had an acute, clinically significant illness within 30 days prior to Day 1 of Period 1.
7. Subject has a systolic blood pressure >140 mm Hg or has a diastolic blood pressure >90 mm Hg at Screening or Check-in (Day -1 of Period 1).
8. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus infection (HIV) at Screening.
9. Subject has abnormal Screening or Day -1 of Period 1 clinical laboratory test result that suggests a clinically significant underlying disease or subject with the following laboratory abnormalities: creatinine >1.5 mg/dL, alanine aminotransferase (ALT) and or aspartate aminotransferase (AST) >2.5 x the upper limit of normal (ULN) or total bilirubin >2.0 mg/dL.
10. Subject has an abnormal (clinically significant) ECG at Screening or Check-in (Day -1 of Period 1). Entry of any subject with an abnormal (not clinically significant) ECG must be approved, and documented by the signature of the principal investigator.
11. Subject has donated blood products (such as plasma) within 30 days or has donated whole blood or lost 450 mL or more of his or her blood volume, or had a transfusion of any blood product within 56 days prior to Day 1 of Period 1.
12. With the exception of acetaminophen, the subject has taken any excluded medication, supplements, or food products listed in Section 7.3. Hormonal contraception (see Appendix D) and hormone replacement therapy are allowed, as long as the subject has been on a stable dose for a minimum of 90 days prior to Day 1 of Period 1.
13. Subject has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch nicotine gum, e-cigarettes) within 28 days prior to

Check-in (Day -1 of Period 1), or has a positive cotinine test at Screening or Check-in (Day -1 of Period 1), or is unwilling to abstain from these products for the duration of the study.

14. The subject has received dexlansoprazole or lansoprazole in a previous clinical study or as a therapeutic agent within 6 months of screening.
15. The subject has a history (within 6 months) or clinical manifestations of clinically significant metabolic, hematologic, pulmonary, cardiovascular, GI, neurologic, hepatic, renal, urologic, immunologic, musculoskeletal or psychiatric disorder as defined by the investigator, which may impact the ability of the subject to participate or potentially confound the study results.
16. Subject has a history of cancer, except basal cell carcinoma that has been in remission for at least 5 years prior to Day 1 of Period 1.
17. The subject has poor peripheral venous access.
18. Subject has a known hypersensitivity to any component of the formulation of dexlansoprazole capsules or other drugs with the same mechanism of action (including lansoprazole, omeprazole, rabeprazole, pantoprazole, or esomeprazole), or related compounds.
19. The subject is lactose intolerant.
20. If a woman, the subject is pregnant or lactating or intending to become pregnant before, during, or within 30 days after participating in this study, or intending to donate ova during such time period.
21. If a man, the subject intends to donate sperm from first dosing and during the course of this study or for 30 days thereafter.
22. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse/partner, parent, child, sibling) or may consent under duress.

7.3 Excluded Medications, Supplements, Dietary Products

Use of the agents in Table 7.a (prescription or nonprescription) is prohibited from the time points specified and for the duration of the subject's participation in the study.

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

28 days prior to Check-in (Day -1 of Period 1)	7 days prior to Check-in (Day -1 of Period 1)	72 hours prior to Check-in (Day -1 of Period 1)
Prescription medications including oral contraceptives (a)	OTC medications (b)	Alcohol-containing products
Nicotine-containing products	Vitamin supplements	
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	Products containing caffeine and/or xanthine
Hepatic or renal clearance altering agents	Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 (d).	Poppy seeds
Immunization/Vaccines (c)		

OTC=over-the-counter.
(a) Hormonal contraception and hormone replacement therapy (HRT) are allowed, as long as the subject has been on a stable dose for a minimum of 90 days prior to Day 1 of Period 1.
(b) Occasional use of acetaminophen (≤2 g/day) is allowed or other medication as approved by the investigator and Takeda on a case-by-case basis. Acetaminophen is not allowed on Day 1 of each period.
(c) Inclusive of but not limited to H1N1 and flu vaccinations.
(d) Inclusive of but not limited to esomeprazole, omeprazole, cimetidine, ranitidine, and chlorpheniramine.
Subjects must be instructed not to take any medications including OTC products, without first consulting with the investigator during the Washout Period, as well as during confinement.

7.4 Diet, Fluid, Activity

7.4.1 Diet and Fluid

During each day of the confinement period, subjects will receive standardized meals and an evening snack, each of which contains approximately 30% fat (caloric value), with the exception of the high-fat/high-calorie breakfast served on Day 1 of each period. The clinical research site will ensure the same meals are served to all subjects on Day 1 of both study periods. All subjects may consume water ad libitum except for 1 hour before and 1 hour after drug administration.

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.

On Day 1 of each period, subjects will fast for a minimum of 10 hours until 30 minutes prior to their scheduled morning dose, when they will be given a high-fat/high-calorie breakfast which will be entirely consumed within 25 minutes. The high-fat/high-calorie breakfast will have approximately 50 percent of total caloric content of the meal come from fat and a total of approximately 800 to 1000 kilocalories (kcal). This meal will derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal will include a description of the protein, carbohydrate and fat content (specified in grams, calories and

relative caloric content (%). An example of high-fat/high-calorie breakfast will include approximately 910 kcal consisting of approximately 55% fat, 25% carbohydrates, and 18% protein, and would consist of 2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 240 mL of whole milk. Subjects will fast for at least 4 hours postdose on these days. 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 of each period. The start and stop times of meals on Day 1 of each period, along with whether the meal was completely consumed, will be recorded in the source documentation and on the CRF. Subjects will be fasting for a minimum of 12 hours prior to collection of scheduled safety laboratory assessments.

7.4.2 Activity

Subjects should be instructed to refrain from strenuous exercise starting approximately 48 hours prior to confinement on Day -1 of Period 1 and up to release from the clinic on Day 2 of Period 2.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the CRF using the following categories.

1. Pretreatment event or AE. The subject has experienced a pretreatment event 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 pretreatment event or AE.

   - Liver Function Test (LFT) Abnormalities

     Study medication should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a subject's laboratory profile has returned to normal/baseline status, see Section 9.2.8), if the following circumstances occur at any time during study medication treatment:

     – ALT or AST >8 × ULN, or

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

     – ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalized ratio (INR) >1.5, or ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. Significant protocol deviation. The discovery after the first dose of study medication 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 wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the CRF.

   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).

5. Study termination. The Sponsor, contract research organization, IRB, 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 Appendix D.

7. Other.

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

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination. Discontinued or withdrawn subjects may be replaced.

7.7 Subject Replacement

Discontinued or withdrawn subjects may be replaced. Any subjects that replace withdrawn or discontinued subjects will maintain the same treatment sequence as the discontinued subject.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

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

8.1 Clinical Study Drug

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

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

Table 8.a Study Medication – Sponsor Supplied

Formulation	Investigational Product	Dosage	Manufacturer and Location
A (test)	Dexlansoprazole capsule	30 mg	Capsules manufactured at TOB
B (reference)	Dexlansoprazole capsule	30 mg	Capsules manufactured at TPC
C (test)	Dexlansoprazole capsule	60 mg	Capsules manufactured at TOB
D (reference)	Dexlansoprazole capsule	60 mg	Capsules manufactured at TPC

The study site will be supplied with 30-count bottles of dexlansoprazole delayed-release capsules 30 mg manufactured at TOB (containing Granules-LL and Granules-H), and 30 mg capsules manufactured at TPC (containing Granules-LL and Granules-H). Also supplied will be 30-count bottles of dexlansoprazole delayed-release capsules 60 mg manufactured at TOB (containing Granules-LS and Granules-H), and 60 mg capsules manufactured at TPC (containing Granules-LS and Granules-H).

8.1.1 Clinical Study Drug Labeling

The bottles containing the study medication will be packaged in an open label manner. The bottles will bear a single-panel computer-generated label containing the required information, including the Federal caution statement "CAUTION: New Drug-Limited by Federal (or United States) Law to Investigational Use."

8.1.2 Clinical Study Drug Inventory and Storage

All drug supplies used to conduct this study must be kept in an appropriate, limited-access, secure place until it is used or returned to the Sponsor or designee for destruction. Drug supplies must be stored at controlled room temperature 20°C to 25°C (68°F to 77°F; see US Pharmacopeia); excursions allowed between 15°C and 30°C (59°F to 86°F), protected from moisture and in a secure location until dispensed to study subjects or returned to Takeda or its designee. Drug supplies will be counted and reconciled at the site before disposition or return to Takeda or designee. Each unused drug supply must be returned in its original container.

8.1.3 Clinical Study Drug Blinding

This is an open-label study.

8.1.4 Randomization Code Creation and Storage

The randomization schedule will be generated by Celerion prior to the start of the study, and will be provided to the site pharmacist prior to the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.1.5 Clinical Trial Blind Maintenance/Unblinding Procedure

NA

8.1.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the Sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation, 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 the bottom half of the packing list and faxing per instructions provided on the form. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- 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 or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed, including initials of the person

dispensing the drug, and the date and amount returned to the site by the subject, including the initials of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

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

Prior to site closure or at appropriate intervals, a representative from the Sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the Sponsor or its designee for destruction. The CRO may be designated by the Sponsor to destruct any unused sponsor-supplied drug. The investigator or designee will retain the original documentation regarding sponsor-supplied drug accountability, return, and/or 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 sponsor-supplied drug during the study conduct. On expiry date notification from the Sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the Sponsor or its designee for destruction.

8.1.6.1 Reserve Study Medication Samples for Retention

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

9.0 STUDY 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 Section 3.0.

9.1 Administrative Procedures

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 13.2.

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.

9.1.1.1 Assignment of Screening and Randomization Numbers

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

9.1.1.2 Study Drug Assignment

All subjects will receive the same treatments as detailed in Section 9.2.6.

9.1.2 Inclusion and Exclusion

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

9.1.3 Medical History/Demography

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

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.

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

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

9.1.4 Concomitant Medications

Subjects will be instructed not to take any medications during the study, including over-the-counter products, without first consulting with the investigator. Use of concomitant medications will not be allowed during the study unless deemed necessary in cases of medical emergency or approved by the Sponsor and the investigator on a case-by-case basis. Occasional use of acetaminophen (up to 2 g/day) is allowed. Acetaminophen is not allowed on Day 1 of each period. Hormonal contraception and HRT are allowed, as long as a subject has been on a stable dose for a minimum of 90 days prior to Day 1.

All medications used within 28 days prior to Screening will be recorded in the source document and Medication History CRF. All medications taken from Screening through to the end of the study will be recorded in the source document and Concomitant Medication CRF.

9.2 Clinical Procedures and Assessments

9.2.1 Full Physical Exam

Physical exams will be performed at Screening, Check-in (Day -1 of Periods 1 and 2), Day 2 Study Exit for Period 2 only, Early Termination, and during Unscheduled Visits. A baseline physical examination (defined as the pretreatment assessment immediately prior to the start of study drug) will be performed at Check-in (Day -1) of Period 1. The exams 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; (11) genitourinary system; and (12) other. The genitourinary examination will not be required for this protocol but will be listed on the CRF page for physical examination and hard-coded as "not done."

All physical examinations subsequent to Check-in (Day -1) of Period 1 should assess clinically significant changes from the Baseline Check-in (Day -1) of Period 1 examination. If a body system is not examined, "not done" should be indicated.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant (NCS) or clinically significant (CS) by the investigator and recorded in the source document and CRF. All CS findings/changes will be recorded as a pretreatment event (PTE) or concurrent medical condition in the source document and on the appropriate CRF described in Section 9.1.4 or Section 10.0.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the study drug must be assessed as NCS or CS by the investigator and recorded in the source document and CRF. 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 CRF described in Section 10.0.

9.2.2 Height and Weight

A subject should have weight and height measured while wearing indoor clothing and with shoes off. The Takeda standard for collecting height is centimeters (cm) without decimal places and for weight it is kilograms (kg) with 1 decimal place.

9.2.3 BMI

The BMI is calculated using metric units with the formula provided below:

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

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

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

9.2.4 Vital Signs

Vital signs will include oral body temperature, sitting blood pressure (resting 5 minutes), and pulse (beats per minute). Only blood pressure and pulse will be taken on Check-in (Day -1) through Day 2. Vital signs will be obtained at the time points stipulated in Schedule of Study Procedures (Section 3.0).

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.

9.2.5 12-Lead ECG

A standard 12-lead ECG will be recorded at Screening, Check-in (Day -1) of Period 1, and Day 2 Study Exit of Periods 1 and 2 or if a subject terminates early from the study. 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 CRF 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. The following parameters will be recorded on the CRF from the subject's ECG trace: heart rate, QT interval, and QRS interval.

9.2.6 Study Drug Administration

Subjects will fast for a minimum of 10 hours until 30 minutes prior to their scheduled morning dose in Periods 1 and 2, when they will be given a high-fat/high-calorie breakfast which will be entirely consumed within 25 minutes. In the morning of Day 1, subjects will be instructed to swallow the intact capsule with 240 mL of water. Dosing may be staggered to help facilitate

logistics at the site. All subjects may consume water ad libitum, except for 1 hour prior to and 1 hour post drug administration. Subjects must drink all of the water provided with the dose.

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

On each dosing day (Day 1 of Periods 1 and 2) subjects will be administered dosing regimens according to the sequence group they are assigned to (See Table 9.a).

The 4 dosing regimens are:

Regimen A: A single 30 mg dexlansoprazole capsule manufactured at TOB.

Regimen B: A single 30 mg dexlansoprazole capsule manufactured at TPC.

Regimen C: A single 60 mg dexlansoprazole capsule manufactured at TOB.

Regimen D: A single 60 mg dexlansoprazole capsule manufactured at TPC.

On Day 2 of Period 1, subjects will be discharged from the study site for a minimum washout interval of 5 days between the dose in the first period and the dose in the second period.

Table 9.a Dose and Regimen

Study Part	Sequence	Number of Subjects	Period 1 Regimen	Period 2 Regimen
Part 1	1	30	A	B
30 mg	2	30	B	A
Part 2	3	30	C	D
60 mg	4	30	D	C

Regimen A: A single 30 mg dexlansoprazole capsule manufactured at TOB administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen B: A single 30 mg dexlansoprazole capsule manufactured at TPC administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen C: A single 60 mg dexlansoprazole capsule manufactured at TOB administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.
Regimen D: A single 60 mg dexlansoprazole capsule manufactured at TPC administered orally on Day 1, 30 minutes following the beginning of a high-fat/high calorie breakfast.

9.2.7 AE Monitoring

Subjects will be monitored throughout the study for adverse reactions to the study formulations and/or procedures as described in Section 10.0.

9.2.8 Laboratory Procedures and Assessments

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following a minimum 12-hour overnight fast at the time points stipulated in

the Schedule of Study Procedures (Section 3.0). If a 12-hour fast is not possible at early termination or due to re-checks, laboratory samples will still be collected.

Clinical Laboratory Tests

Hematology

Hematology will consist of the following tests:

RBC	Hematocrit
WBC with differential	Platelets
Hemoglobin	

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

ALT	Blood urea nitrogen
Albumin	Uric acid
ALP	gamma-glutamyl transferase
AST	Calcium
Glucose	Phosphorus
Total bilirubin	Potassium
Total protein	Sodium
Total cholesterol	Chloride
Triglycerides	Bicarbonate or carbon dioxide
Serum creatinine	

ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase

Urinalysis

Urinalysis will consist of the following tests:

Specific gravity	Glucose
pH	Bilirubin
Protein	Red blood cells and white blood cells
Ketones	Urobilinogen
Nitrite	Leukocyte esterase

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of RBC/high-power field, WBC/high-power field, bacteria, and casts.

Other

HIV	Urine drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine and opiates.
Hepatitis panel, including HBsAg and anti-HCV	Urine alcohol screen
Serum hCG for pregnancy (female subjects only)	
Serum FSH (postmenopausal women defined as amenorrhea >1 year)	

FSH=follicle stimulating hormone, hCG= human chorionic gonadotropin, HBsAg=hepatitis B specific antibodies, HCV=hepatitis C virus, HIV=human immunodeficiency virus, RBC=red blood cells, WBC=white blood cells.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis as referenced in Section 3.0. The results of laboratory tests will be returned to the investigator, who is responsible for filing and reviewing these results for clinical significance together with the data in the CRF.

Laboratory reports must be signed and dated by the principal investigator or subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. All clinically significant laboratory abnormalities must be recorded as an AE in the subject's source documents and on the appropriate CRF unless they are the result of pathology for which there is an overall diagnosis. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used. 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.

9.3 Biomarker, PK, PD, and PGx, Samples

Primary specimen collection parameters are provided in Table 9.b.

Table 9.b Primary Specimen Collections

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for PK	Plasma		Plasma sample for PK analysis	Mandatory

9.3.1 PK Measurements

Plasma PK parameters of dexlansoprazole will be derived using noncompartmental analysis methods. The PK parameters of dexlansoprazole will be determined from the concentration-time data for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all PK computations involving blood sampling times. The following PK parameters for dexlansoprazole will be determined. Additional PK parameters may be calculated as appropriate.

The following PK parameters will be calculated from plasma concentrations of dexlansoprazole, unless otherwise specified:

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

9.3.1.1 Plasma for PK Measurements

Blood samples (4 mL) for dexlansoprazole plasma concentrations will be collected beginning on Day 1 of each period of each part, as shown in Table 9.c.

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

Table 9.c Collection of Blood Samples for PK Analysis

Sample Type	Dosing Day (Periods 1 and 2)	Time (hours)
Plasma	1	Predose (within 1 hour prior to dose) and at 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 10, 12, 14, 16, and 24 hours postdose.

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

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 CRF. However, blood samples not collected as displayed in Table 9.d should be reported (see Section 12.2).

Table 9.d Windows for PK Sample Collection

Minutes	Nominal Sampling Time
No more than 1 hour predose	0 hour
±5	Immediately postdose to ≤6 hours
±10	>6 hours to ≤12 hours postdose
±15	>12 hours to ≤24 hours

9.3.2 Biomarker Measurements

NA

9.3.3 PGx Measurements

NA

9.3.4 Confinement

Subjects enrolled in this study will be confined in the clinical research unit for 2 consecutive nights in each period, beginning at Check-in (Day -1) to Day 2. There will be a minimum 5-day washout interval between the dose in the first period and the dose in the second period. Subjects will be released from the clinic during the washout interval.

10.0 ADVERSE EVENTS

10.1 Definitions and Elements of AEs

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

An untoward finding generally may:

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

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 an AE(s).

Laboratory values and ECG findings:

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

Pre-existing conditions:

- A pre-existing condition (present at the time of signing of informed consent) is considered a concurrent medical history condition and should NOT be recorded as an AE. A baseline evaluation (eg, laboratory test, ECG, X-ray, etc) should NOT be recorded as an AE unless related to a study procedure. However, if the subject experiences a worsening or complication

of such a concurrent medical history condition, the worsening or complication should be recorded appropriately as an AE (worsening or complication occurs after informed consent is signed). 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 an AE if the episodes become more frequent, serious, or severe in nature, that is, investigators should ensure that the AE term recorded captures the change from Baseline in the condition (eg "worsening of…").
- If a subject has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as an AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after the first administration of study medication or 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:

- If the subject experiences a change in the severity of an AE that is not associated with a change in study medication, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

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. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.
- All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the (e)CRF, in order to capture this important safety information consistently in the

database. AEs associated with an overdose will be documented on AE CRF(s) according to Section 10.0.

- Serious adverse events (SAEs) of overdose should be reported according to the procedure outlined in Section 10.2.8.
- In the event of drug overdose, the subject should be treated symptomatically.

10.1.1 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 seizures	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

AEs that fulfill 1 or more of the serious criteria above are to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.1 and 10.1.1).

10.1.2 Special Interest AEs

NA

10.2 AE Procedures

10.2.1 Assigning Severity/Intensity of AEs

The different categories of severity/intensity are:

Mild: An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.2.2 Assigning 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 a causal relationship is at least a reasonable possibility, ie, the relationship 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 medications and concurrent treatments.

10.2.3 Start Date

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

10.2.4 End Date

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

10.2.5 Pattern of Adverse Event (Frequency)

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

10.2.6 Action Taken With Study Treatment

- 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 had not yet started or 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 increased – the dose was increased due to the particular AE.
- Drug interrupted – the dose was interrupted due to the particular AE.

10.2.7 Outcome

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

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

10.2.8 Collection and Reporting of AEs, SAEs, Special Interest AEs, and Abnormal LFTs

10.2.8.1 Collection Period

Collection of AEs (ie, AEs, SAEs, Special Interest AEs, and Abnormal LFTs) will commence at the time the subject signs the informed consent. Routine collection of AEs will continue until the follow-up phone call on Day 10 (± 2 days) of Period 2, approximately 10 days after the last dose of investigational product. For subjects who discontinue prior to the administration of study medication, AEs will be followed until the subject discontinues study participation.

10.2.8.2 Reporting AEs

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 an SAE prior to the first exposure to investigational product 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. Nonserious AEs that begin prior to the first exposure to investigational product, related or unrelated to the study procedure, need not 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 AEs will be documented in the AE page of the CRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term.
- Start and end date and time.
- Pattern of AE (frequency).
- Severity/Intensity.
- Causality (Investigator's opinion of the causal relationship between the event and administration of study drug[s]).
- Action taken with trial drug.
- Outcome of event.
- Seriousness.

10.2.8.3 Reporting SAEs

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

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 14.1.1.

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

Reporting of SAEs that begin before first administration of investigational product will follow the same procedure for SAEs occurring on treatment.

SAE Follow-Up

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.

10.2.8.4 Reporting Special Interest AEs

NA

10.2.8.5 Reporting of Abnormal LFTs

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 CRF 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 10.2.8.3. 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. Follow-up laboratory tests as described in Section 9.2.8 must also be

performed. In addition, an LFT Increases CRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.9).

10.2.9 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 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 STATISTICAL METHODS

11.1 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.

A targeted data review 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.

11.1.1 Analysis Sets

11.1.1.1 Safety Set

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

11.1.1.2 PK Set

All subjects in the safety set who have at least 1 valid plasma concentration of dexlansoprazole at scheduled sample collection time will be included in the PK set.

11.1.2 Analysis of Demography and Other Baseline Characteristics

For each part, demographic and baseline characteristics will be summarized by sequence and overall. Summary statistics (number of subjects, mean, median, standard deviation and range) will be generated for continuous variables (eg, age, weight, and BMI) and the number and percentage of subjects within each category will be presented for categorical variables (eg, gender, race, and ethnicity).

11.1.3 PK Analysis

For each regimen of each part, dexlansoprazole plasma concentrations and PK parameter estimates will be tabulated and descriptive statistics computed.

For each part, analysis of variance (ANOVA) will be performed on natural logarithms of dexlansoprazole C_{max} and AUC with factors for sequence, the subject nested within sequence, period and regimen. The factor of the subject nested within sequence will be the error term for testing the sequence effect. Other factors will be tested with the residual as the error term. For the relative BA determination, pairwise comparisons will be performed to assess the relative BA of dexlansoprazole via point estimates and 90% CI for the ratio of C_{max} and AUC central values of the dexlansoprazole 30 mg or 60 mg capsules manufactured at TOB compared with the respective dexlansoprazole 30 mg or 60 mg capsules manufactured at TPC. A conclusion of BE in the PK of dexlansoprazole between test regimen (dexlansoprazole capsule - TOB) and the reference regimen (dexlansoprazole capsule - TPC) will be reached if the 90% CIs for C_{max} and AUC are within the (0.80-1.25) interval.

Statistical analyses of other plasma PK parameters will be performed if appropriate.

11.1.4 PD Analysis

NA

11.1.5 Safety Analysis

11.1.5.1 AEs

AEs will be summarized using the safety analysis set. AEs that started or worsened in severity after the first dose of study drug will be summarized by regimen. AEs will be classified according to MedDRA® system organ class, high-level term and preferred term. Summary tables for AEs will include numbers and percentages of subjects experiencing AEs by system organ class and preferred term. The following summary tables will be included in the report by intervals: summary of AEs, drug-related AEs, relationship of AEs to study drug, severity of AEs and related AEs. AEs leading to study drug discontinuation and SAEs will be listed.

11.1.5.2 Clinical Laboratory Evaluation

Baseline, postdose, and change from Baseline to postdose laboratory values will be summarized by regimen utilizing descriptive statistics. Criteria for markedly abnormal laboratory values (markedly abnormal values [MAVs]) will be presented and the number and percentage of subjects with at least 1 markedly abnormal laboratory test result will also be summarized by regimen.

11.1.5.3 Vital Signs

Baseline, postdose, and change from Baseline to postdose vital sign values will be summarized by regimen utilizing descriptive statistics. Criteria for markedly abnormal vital sign values (MAVs) will be presented.

11.1.5.4 Other Safety Parameters

Physical examination findings will be presented in the data listings.

ECGs will be summarized by treatment and point of time of collection. Shift tables for character ECG results will be provided overall to tabulate the number and percentage of subjects who changed status after dosing.

11.2 Interim Analysis and Criteria for Early Termination

NA

11.3 Determination of Sample Size

For each part, a sample size of 60 (30 per sequence) will be used in this study. This sample size will allow for up to 6 dropouts (10.0% dropout rate) and provide 90% probability of concluding equivalence on dexlansoprazole C_{max} between the 2 regimens if the true difference between dexlansoprazole C_{max} central values from 2 regimens is no more than 5%. The power for

concluding equivalence on dexlansoprazole AUC between 2 regimens would be over 95%. This sample size was based on the intrasubject variance of 0.0884 for log(C_{max}) and 0.0365 for log(AUC) from the Part 1 (30 mg) of the TAK-390MR-1001 study. Part 1 was used because the intrasubject variance of log(C_{max}) was higher than in Part 2 (60 mg).

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 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 CRFs. Source documents are defined as original documents, data, and records. The investigator and study site guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the Sponsor or the Sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, trial drug, subject medical records, informed consent documentation, and review of CRFs 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.

12.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial 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.

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.

12.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency , the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 12.1.

13.0 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 International Council for Harminsation (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 A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

13.1 IRB and/or IEC Approval

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

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

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

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

13.2 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 ICF, 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 ICF 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 ICF 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 ICF and, if applicable, the subject authorization form. The ICF, 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 ICF, 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 ICFand 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 ICF 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 ICF, 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 ICFs 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 ICF.

13.3 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 13.2).

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 CRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 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.

13.4.2 Clinical Trial Registration

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

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

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

13.4.3 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.

13.5 Insurance and Compensation for Injury

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

14.0 ADMINISTRATIVE AND REFERENCE INFORMATION

14.1 Administrative Information

14.1.1 Study Contact Information

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Pharmacovigilance Takeda Development Center Americas, Inc. Fax: 224-554-1052 Email: PVSafetyAmericas@tpna.com

14.1.2 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert 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 Council for 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 10.2.9 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix A).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C 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)

14.1.3 Study-Related Responsibilities

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

14.1.4 Protocol Amendment 01 Summary of Changes

Rationale for Amendment No. 01

The purpose of this amendment is to update the protocol to exclude true abstinence as an acceptable method of contraception. For specific descriptions of text changes and where the changes are located, see Appendix F.

14.1.5 List of Abbreviations

λ_z	terminal disposition phase rate constant
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{∞}	AUC from time 0 to infinity
AUC_{last}	AUC from time 0 to time of the last quantifiable concentration
BA	bioavailability
BE	bioequivalence
BMI	body mass index
CI	confidence interval
CL/F	apparent clearance after extravascular administration
C_{max}	maximum observed concentration
CRF	case report form
CRO	contract research organization
CS	clinically significant
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDTA	ethylenediamine tetraacetic acid
EE	erosive esophagitis
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HBsAg	hepatitis B surface antigen

hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IBD	international birth date
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
kcal	kilocalories
LFT	liver function test
MAV	markedly abnormal value
MedDRA®	Medical Dictionary for Regulatory Activities
NCS	not clinically significant
NDA	New Drug Application
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PPI	proton-pump inhibitor
PTE	pretreatment event
SAE	serious adverse event
SAP	statistical analysis plan
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 to first occurrence of C_{max}
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution during the terminal disposition phase after extravascular administration, calculated using the observed value of the last quantifiable concentration.
WHO	World Health Organization Drug Dictionary

15.0 DATA HANDLING AND RECORD KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan.

15.1 CRFs

The Sponsor or its designee will supply investigative sites with access to CRFs. The Sponsor or its designee will train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. CRFs 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.

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

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

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

CRFs 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 CRFs. The completed CRFs 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.

15.2 Record Retention

The investigator agrees to keep the records stipulated in Section 15.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), copy of CRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified

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

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

16.0 REFERENCES

1. Dexilant (dexlansoprazole) Delayed Release Capsules. Full Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc., Revised October 2016.
2. Guidance Document - Comparative Bioavailability Standards: Formulations Used for System Effects, Health Canada. July 2018.

17.0 APPENDICES

Appendix A Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigator(s) by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff that will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. 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.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. 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.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. 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.
10. Prepare and maintain adequate case histories of all persons entered into the study, including CRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of

2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied drugs, and return all unused Sponsor-supplied drugs to the Sponsor.
13. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix B Elements of the Subject Informed Consent

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

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

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx 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.

f) Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from signing the informed consent and throughout the duration of the study, and for 30 days after the last dose of study drug. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.

g) Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study and for 30 after the last dose of study drug. 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.

25. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix C Investigator Consent to the 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 D Pregnancy and Contraception

Contraception and Pregnancy Avoidance Procedure

Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 30 days after last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Females of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 30 after last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use a highly effective/effective method of contraception (from the list below).

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

Definitions and Procedures for Contraception and Pregnancy Avoidance

* A woman is considered a woman of childbearing potential (WOCBP), ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/L) may be used to confirm a post-menopausal state in younger women (eg, those <45 year old) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

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

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included , the only acceptable methods of contraception are:
    - Non-Hormonal Methods:
        - Intrauterine device (IUD).
        - Bilateral tubal occlusion.
        - Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.

- Hormonal Methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, concomitant medications, which may reduce the efficacy of the contraception method (Evaluate on compound-by-compound and protocol – by-protocol basis and obtain clinical pharmacology justification).
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 90 days prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if for shorter duration until she has been on contraceptive for 90 days;
    - Oral †.
    - Intravaginal † (eg, ring).
    - transdermal †.
  - Progestogen-only hormonal contraception associated with inhibition of ovulationinitiated at least 90 days prior to the first dose of study drug OR combined with a barrier method (male condom, female condom or diaphragm) if shorter till she has been on contraceptive for 90 days;
    - oral †.
    - Injectable.
    - Implantable.

2. Effective methods of contraception (there may be a higher than 1% failure rate) are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams PLUS male condom).
   - Progestogen only hormonal contraception, where inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
3. Unacceptable methods of contraception are:
   - Sexual abstinence is NOT an acceptable method of contraception.
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.
4. Subjects will be provided with information on highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, {and sperm donation} during the course of the study.

5. During the course of the study, regular serum human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women and all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   a) contraceptive requirements of the study
   b) reasons for use of barrier methods (ie, condom) in males with pregnant partners
   c) assessment of subject compliance through questions such as
      i. Have you used the contraception consistently and correctly since the last visit?
      ii. Have you forgotten to use contraception since the last visit?
      iii. Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")
      iv. Is there a chance you could be pregnant?
6. In addition to a negative serum hCG pregnancy test at Screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses), a negative serum hCG pregnancy test within 2 daysprior to receiving any dose of study medication. In addition, subjects must also have a negative serumhCG pregnancy test within 2 days prior to receiving first dose of investigational drug as close as possible and prior to first dose of investigational drug, preferably on the same day.

General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- contraceptive requirements of the study.
- reasons for use of barrier methods (ie, condom) in males with pregnant partners.
- assessment of subject compliance through questions such as:
  - Have you used the contraception consistently and correctly since the last visit?
  - Have you forgotten to use contraception since the last visit?
  - Are your menses late (even in women with irregular or infrequent menstrual cycles a pregnancy test must be performed if the answer is "yes")?
  - Is there a chance you could be pregnant?

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 male subject during the study or for 30 days after the last dose, should also be recorded following authorization from the subject's partner.

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

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

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

1. Collect 4 mL of venous blood into a chilled Becton-Dickinson Vacutainer. All dexlansoprazole blood samples should be collected into Vacutainers containing K2EDTA.
2. Gently invert the Vacutainer several times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
3. Centrifuge the Vacutainers for 10 minutes at a relative centrifugal force of approximately 1100 to 1300 in a refrigerated centrifuge. Note: if using a collection device other than the Becton-Dickinson Vacutainer, 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 0.6 mL needs to be obtained for each sample. Labeling may include protocol number [TAK-390MR-1002], sample matrix (ie, plasma), randomization number, period, nominal day and time, analyte (dexlansoprazole), and either "SET 1" (for original sample) or "SET 2" (for duplicate sample).
5. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -20°C or lower until shipment to CCI [redacted]. No more than 45 minutes will elapse between blood collection and freezing the plasma sample.

Shipping of Plasma Samples

The following instructions are recommended unless they differ from the site's standard operating procedures (SOPs) for labeling, packaging, or shipping of PK samples.

1. Biological samples should be shipped on sufficient dry ice to prevent thawing during transit. Samples should be shipped to arrive at the destination during normal business hours (local time). For US domestic shipments, 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, and for international shipments, 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.
2. Before shipping, make sure the sample tubes are tightly sealed. Separate each subject's samples as follows:
3. Separate the duplicate SET 2 samples from the SET 1 samples.
4. Place SET 1 samples for each subject into a self-sealing bag (eg, Ziploc) containing additional absorbent material.
5. Using a permanent marker, write the 4-digit randomization sequence number, sample matrix (ie, plasma), number of samples, and "SET 1" on each self-sealing bag.

6. Place the bags of individual subject's samples into a larger plastic bag so that samples are double bagged. Duplicate SET 2 samples should be returned to the freezer for storage. Repeat steps 3 through 6 above when preparing duplicate samples for shipment, except self-sealing bags should be marked "SET 2".
7. An inventory of individual samples should accompany each shipment and should include the Sponsor's name (Takeda), study medication (dexlansoprazole delayed-release capsule), protocol number (TAK-390MR-1002), investigator's name, sample type (ie, plasma), randomization number, period, nominal day and time, and intended sample storage conditions. When duplicate SET 2 samples are being shipped, make a copy of the original SET 1 sample inventory and mark as "SET 2." Place the inventory paperwork into a large self-sealing bag. SET 1 samples will be shipped first on dry ice, followed by shipment of duplicate SET 2 samples after SET 1 samples have been received by the analytical laboratory.
8. For sample packing, utilize dry ice generously (eg, 20 to 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 polystyrene plastic (eg, Styrofoam) container (or other suitable container) and fill the excess space with dry ice slabs or ice pellets (preferably the latter). Make a note of the estimated weight of the dry ice used per shipping container.
9. Place the inventory paperwork (in a large self-sealing bag) on top of the dry ice in the polystyrene plastic container. Place the lid on the polystyrene plastic container and seal completely with strapping tape. Place the polystyrene plastic container in a cardboard shipping carton and seal securely with strapping tape.
10. Mark the outside of shipping carton(s) with a tally number (eg, 1 of 5, 2 of 5).
11. Affix an address label to each shipping carton. Complete the address label with the following information:

    Plasma Samples for dexlansoprazole delayed-release capsules:

    PPD

12. Affix a carbon dioxide label on each carton, specifically:

    Carbon Dioxide Solid UN-1845

    Class 9 PKG GR III

    Quantity _____ (fill in weight to nearest lb/kg and specify unit of measure used)

13. Affix 2 dry ice symbol labels on opposite sides of the carton. Mark KEEP FROZEN on each carton. Specify a return address and contact person on the carton.
14. Obtain the airway bill number and a receipt of shipment from the carrier.
15. After shipping of the samples, please contact the following to notify them of next day delivery.

PPD

When calling, provide the following information:

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

Appendix F Detailed Description of Amendments to Text

The primary change occurs in Appendix D - Pregnancy and Contraception under Definitions and Procedures for Contraception and Pregnancy Avoidance.

Change 1. Removal of true abstinence from the list of highly effective non-hormonal methods of contraception.

The primary change occurs in Appendix D - Pregnancy and Contraception under Definitions and Procedures for Contraception and Pregnancy Avoidance, Item number 1, Bullet 1.

Initial wording:

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included , the only acceptable methods of contraception are:
   - Non-Hormonal Methods:
     - Intrauterine device (IUD).
     - Bilateral tubal occlusion.
     - Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.
     - True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 30 days after last dose.

Amended or new wording:

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly). In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are:
   - Non-Hormonal Methods:
     - Intrauterine device (IUD).
     - Bilateral tubal occlusion.
     - Vasectomised partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.
     - ~~True sexual abstinence, only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from~~

	~~heterosexual intercourse during the entire period of the study, from 1 month prior to the first dose until 30 days after last dose.~~
Rational for Change: Clarifies that true abstinence is not an acceptable method of contraception.	

Change 2. Update of the list of unacceptable methods of contraception to include all types of abstinence.

The primary change occurs in Appendix D - Pregnancy and Contraception under Definitions and Procedures for Contraception and Pregnancy Avoidance, Item number 3.

Initial wording:

3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.

Amended or new wording:

3. Unacceptable methods of contraception are:
   - ~~Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods).~~
   - **Sexual abstinence is NOT an acceptable method of contraception**
   - Spermicides only.
   - Withdrawal.
   - No method at all.
   - Use of female and male condoms together.
   - Cap/diaphragm/sponge without spermicide and without condom.

Rationale for Change:

Clarifies that all types of abstinence is considered an unacceptable methods of contraception and not only periodic abstinence.

Amendment 01 to A Phase 1, Randomized, Open-Label, Single-Center, Single-Dose, Two-Period, Two-Part Crossover Study in Healthy Subjects to Compare the Bioavailability of Dexlansoprazole from Dexlansoprazole Delayed-Release Capsules 30 mg and 60 mg Manufactured by Takeda Pharmaceutical Company Limited Osaka Plant Following a High-Fat Meal

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	15-Jan-2019 21:14 UTC
	Clinical Pharmacology Approval	16-Jan-2019 16:38 UTC
	Clinical Pharmacology Approval	18-Jan-2019 22:14 UTC