



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

NCT Number: NCT03131895

Protocol Approve Date: 06 June 2017

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

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

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

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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

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

Contact Type / Role	Contact
Serious adverse event and pregnancy reporting	Personal Protected Data
Primary Medical Monitor (primary medical monitor for the study providing medical advice on protocol and compound)	Personal Protected Data
Takeda Medical Monitor (medical advice on protocol and compound if primary medical monitor not available)	Personal Protected Data
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Personal Protected Data

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

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

Personal Protected Data



INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the 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 Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- [Appendix B](#) - Responsibilities of the Investigator.

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

Signature of Investigator

Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment 02. The primary reason for this amendment is to allow the replacement of subjects who are discontinued or withdrawn.

For specific descriptions of the changes listed below and where these changes are located, see [Appendix F](#).

Changes in Amendment 02

1. Allow the replacement of subjects who are discontinued or withdrawn.
2. Correct the dose shown in Part 2 of the crossover study design schematic.
3. Remove all reference to the subject's legally acceptable representative.
4. Update the definitions of women of (and not of) childbearing potential.
5. Update the subject replacement information based on the allowance for replaced subjects.
6. Clarify that an 8-hour fast may not be possible at Early termination.
7. Correct the sequence numbers in [Table 8.b](#) for Part 2 of the study.

TABLE OF CONTENTS

1.0	ADMINISTRATIVE INFORMATION	2
1.1	Contacts.....	2
1.2	Approval.....	3
1.3	Protocol Amendment 02 Summary of Changes	5
2.0	STUDY SUMMARY	11
3.0	STUDY REFERENCE INFORMATION	15
3.1	Study-Related Responsibilities.....	15
3.2	Principal Investigator	15
3.3	List of Abbreviations	16
3.4	Corporate Identification	17
4.0	INTRODUCTION.....	18
4.1	Background	18
4.2	Rationale for the Proposed Study	18
5.0	STUDY OBJECTIVES AND ENDPOINTS.....	19
5.1	Objectives.....	19
5.1.1	Primary Objective(s)	19
5.1.2	Additional Objectives.....	19
5.2	Endpoints.....	19
5.2.1	Primary Endpoints.....	19
5.2.2	Additional Endpoints	19
5.2.3	Safety Endpoints	19
6.0	STUDY DESIGN AND DESCRIPTION.....	20
6.1	Study Design	20
6.2	Justification for Study Design, Dose, and Endpoints	22
6.3	Premature Termination or Suspension of Study or Investigational Site.....	23
6.3.1	Criteria for Premature Termination or Suspension of the Study	23
6.3.2	Criteria for Premature Termination or Suspension of Investigational Sites ..	23
6.3.3	Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s).....	23
7.0	SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS	24
7.1	Inclusion Criteria	24
7.2	Exclusion Criteria	24
7.3	Excluded Medications and Dietary Products	26
7.4	Diet, Fluid and Activity Control.....	27

7.4.1	Confinement	27
7.4.2	Diet and Fluid	27
7.4.3	Activity Control	28
7.5	Criteria for Discontinuation or Withdrawal of a Subject	28
7.6	Procedures for Discontinuation or Withdrawal of a Subject	29
8.0	CLINICAL TRIAL MATERIAL MANAGEMENT	30
8.1	Study Medication	30
8.1.1	Dosage Form, Manufacturing, Packaging, and Labeling	30
8.1.2	Storage	30
8.1.3	Dose and Regimen	30
8.1.4	Overdose	31
8.2	Investigational Drug Assignment and Dispensing Procedures	32
8.3	Randomization Code Creation and Storage	32
8.4	Accountability and Destruction of Sponsor-Supplied Drugs	32
8.5	Reserve Study Medication Samples for Retention	34
9.0	STUDY PLAN	35
9.1	Study Procedures	35
9.1.1	Informed Consent Procedure	35
9.1.1.1	Pharmacogenomic Informed Consent Procedure	35
9.1.2	Demographics, Medical History, and Medication History Procedure	35
9.1.3	Physical Examination Procedure	35
9.1.4	Weight, Height and BMI	36
9.1.5	Vital Sign Procedure	36
9.1.6	Documentation of Concomitant Medications	37
9.1.7	Documentation of Concurrent Medical Conditions	37
9.1.8	Procedures for Clinical Laboratory Samples	37
9.1.9	Contraception and Pregnancy Avoidance Procedure	39
9.1.10	Pregnancy	40
9.1.11	ECG Procedure	40
9.1.12	Pharmacogenomic Sample Collection	40
9.1.13	PK Sample Collection	41
9.1.13.1	Collection of Blood for PK Sampling	41
9.1.14	PK Parameters	42
9.1.15	Documentation of Screen Failure	42
9.1.16	Documentation of Randomization	43

9.2	Monitoring Subject Treatment Compliance.....	43
9.3	Schedule of Observations and Procedures.....	43
9.3.1	Screening.....	43
9.3.2	Check-in (Day -1).....	44
9.3.3	Treatment Phase (Day 1).....	44
9.3.4	Day 2 (Period 1).....	45
9.3.5	Day 2 (Period 2)/Study Exit.....	45
9.3.6	Early Termination.....	45
9.3.7	Follow-up.....	46
9.3.8	Unscheduled Visit.....	46
9.4	Biological Sample Retention and Destruction.....	46
9.5	Blood Volume.....	47
10.0	PRETREATMENT EVENTS AND ADVERSE EVENTS.....	48
10.1	Definitions.....	48
10.1.1	Pretreatment Events.....	48
10.1.2	AEs.....	48
10.1.3	Additional Points to Consider for PTEs and AEs.....	48
10.1.4	SAEs.....	50
10.1.5	Severity of PTEs and AEs.....	51
10.1.6	Causality of AEs.....	51
10.1.7	Relationship to Study Procedures.....	51
10.1.8	Start Date.....	52
10.1.9	Stop Date.....	52
10.1.10	Frequency.....	52
10.1.11	Action Concerning Study Medication.....	52
10.1.12	Outcome.....	52
10.2	Procedures.....	53
10.2.1	Collection and Reporting of AEs.....	53
10.2.1.1	PTEs and AEs Collection Period.....	53
10.2.1.2	PTEs and AEs Reporting.....	53
10.2.2	Collection and Reporting of SAEs.....	54
10.2.3	Reporting of Abnormal LFTs.....	54
10.3	Follow-up of SAEs.....	54
10.3.1	Safety Reporting to Investigators, IRBs and Regulatory Authorities.....	55
11.0	STUDY-SPECIFIC COMMITTEES.....	56

12.0	DATA HANDLING AND RECORDKEEPING.....	57
12.1	CRFs (Electronic).....	57
12.2	Record Retention.....	57
13.0	STATISTICAL METHODS.....	59
13.1	Statistical and Analytical Plans.....	59
13.1.1	Analysis Sets.....	59
13.1.2	Analysis of Demographics and Other Baseline Characteristics.....	59
13.1.3	PK Analysis.....	59
13.1.4	Safety Analysis.....	60
13.2	Interim Analysis and Criteria for Early Termination.....	60
13.3	Determination of Sample Size.....	60
14.0	QUALITY CONTROL AND QUALITY ASSURANCE.....	61
14.1	Study-Site Monitoring Visits.....	61
14.2	Protocol Deviations.....	61
14.3	Quality Assurance Audits and Regulatory Agency Inspections.....	62
15.0	ETHICAL ASPECTS OF THE STUDY.....	63
15.1	IRB Approval.....	63
15.2	Subject Information, Informed Consent, and Subject Authorization.....	64
15.3	Subject Confidentiality.....	65
15.4	Publication, Disclosure, and Clinical Trial Registration Policy.....	65
15.4.1	Publication and Disclosure.....	65
15.4.2	Clinical Trial Registration.....	66
15.4.3	Clinical Trial Results Disclosure.....	66
15.5	Insurance and Compensation for Injury.....	66
16.0	REFERENCES.....	67

LIST OF IN-TEXT TABLES

Table 6.a	Part 1 Sequences.....	20
Table 6.b	Part 2 Sequences.....	21
Table 7.a	Prohibited Medications, Supplements, and Dietary Products.....	27
Table 8.a	Study Medication – Sponsor Supplied.....	30
Table 8.b	Dose and Regimen.....	31
Table 9.a	Clinical Laboratory Tests.....	38
Table 9.b	Collection of Blood Samples for PK Analysis.....	41
Table 9.c	Approximate Blood Volume.....	47

Table 10.a	Takeda Medically Significant AE List.....	51
Table 14.a	Windows for PK Sample Collection.....	61

LIST OF IN-TEXT FIGURES

Figure 6.a	Schematic of Study Design	22
Figure 6.b	Schematic of Crossover Design.....	22

LIST OF APPENDICES

Appendix A	Schedule of Study Procedures	68
Appendix B	Responsibilities of the Investigator.....	70
Appendix C	Elements of the Subject Informed Consent.....	72
Appendix D	Investigator Consent to Use of Personal Information.....	75
Appendix E	Collection, Storage, and Shipment of Bioanalytical Samples	76
Appendix F	Detailed Description of Amendments to Text.....	79

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.		Compound: Dexlansoprazole Delayed-Release Capsules													
Title of 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		IND No.: 069927	EudraCT No.: Not applicable												
Study Number: TAK-390MR-1001		Phase: 1													
<p>Study Design:</p> <p>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 or 60 mg dexlansoprazole capsules manufactured at Takeda Pharmaceutical Company Ltd. (TPC) plant in Osaka, Japan. The study will be conducted in 2 parts. In Part 1, 52 healthy subjects will receive dexlansoprazole 30 mg capsules manufactured by TOB and TPC in a crossover fashion. In Part 2, an additional 52 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. If bioequivalence (BE) is not achieved with the first TOB formulation, the study may be repeated for one or both dose strengths in new subjects who will receive the same TOB formulation or a different TOB formulation. The same study design will be used if additional formulation assessments are needed.</p> <p>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 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.</p> <p>Part 1 Sequences</p> <table border="1"> <thead> <tr> <th>Sequences</th> <th>Number of Subjects</th> <th>Period 1</th> <th>Period 2</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>26</td> <td>A</td> <td>B</td> </tr> <tr> <td>2</td> <td>26</td> <td>B</td> <td>A</td> </tr> </tbody> </table> <p>Regimen A (test): A single dexlansoprazole 30 mg capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast. Regimen B (reference): A single dexlansoprazole 30 mg capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.</p>				Sequences	Number of Subjects	Period 1	Period 2	1	26	A	B	2	26	B	A
Sequences	Number of Subjects	Period 1	Period 2												
1	26	A	B												
2	26	B	A												

Part 2 Sequences																									
Sequences	Number of Subjects	Period 1		Period 2																					
3	26	C		D																					
4	26	D		C																					
<p>Regimen C (test): A single dexlansoprazole 60 mg capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast.</p> <p>Regimen D (reference): A single dexlansoprazole 60 mg capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.</p> <p>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 on Day 1 of each period at approximately 0800 hours, following a 10-hour fast. 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. On Day 1 of each period, breakfast will not be served. During Periods 1 and 2 of each part, blood samples will be collected over 24 hours postdose to measure dexlansoprazole plasma concentrations.</p> <p>A blood sample for pharmacogenomics (PGx) will also be collected on Day 1 of Period 1 of each part. The cytochrome P-450 (CYP)2C19 isozyme is a polymorphic enzyme that is involved in the metabolism of dexlansoprazole. A genotype test for CYP2C19 will determine the subject's metabolizer status.</p> <p>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.</p> <p>A follow-up phone call will be made 10 (\pm2) days post last dose of study drug to inquire for any ongoing adverse events (AEs) or serious adverse events (SAEs), new AEs or SAEs, and concomitant medications taken since final dose. Subjects who withdraw their consent will still be contacted for a safety follow-up call. The contact will only be recorded in their source documents and the electronic case report forms (eCRFs), according to data protection regulations.</p> <p>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.</p> <p>A schematic of the study design is shown below.</p> <p>Schematic of Study Design</p> <table border="1"> <thead> <tr> <th rowspan="2">Screening Period</th> <th rowspan="2">Check-in (Periods 1 and 2)</th> <th colspan="2">Treatment Periods 1 and 2</th> <th rowspan="2">Study Exit (Period 2)</th> <th rowspan="2">Follow-up Phone Call</th> </tr> <tr> <th>Dexlansoprazole 30 and 60 mg capsule Single Dose PK</th> <th>Discharge (Period 1)</th> </tr> </thead> <tbody> <tr> <td>Days -28 to -2</td> <td>Day -1</td> <td>Day 1</td> <td>Day 2 Period 1</td> <td>Day 2</td> <td>Day 10 (\pm2 days)</td> </tr> <tr> <td></td> <td></td> <td colspan="2" style="text-align: center;">←—Confinement—→</td> <td></td> <td></td> </tr> </tbody> </table> <p>PK=Pharmacokinetic.</p> <p>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.</p> <p>Primary Objectives:</p> <ul style="list-style-type: none"> 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. <p>Additional Objectives:</p> <ul style="list-style-type: none"> To evaluate the safety and tolerability of dexlansoprazole following oral administration of a single 						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 (\pm 2 days)			←—Confinement—→			
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 (\pm 2 days)																				
		←—Confinement—→																							

dexlansoprazole 30 or 60 mg capsule.	
Subject Population: Healthy subjects aged 18 to 55 years, inclusive, who have a body mass index between 18 and 30 kg/m ² .	
Number of Subjects: Per dose level: 52 Estimated Total: 104 If additional formulation assessments are required, up to an additional 104 subjects will be enrolled.	Number of Sites: Estimated total: 1 in the United States
Dose Level(s): 30 mg dexlansoprazole 60 mg dexlansoprazole	Route of Administration: Oral
Duration of Treatment: 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.	Period of Evaluation: 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 periods: 5 days. Follow-up phone call: 10 days (±2) after last dose. Total Study Duration including Screening: Approximately 48 days
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 8 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:

Primary Endpoints

The primary endpoints for this 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: 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 52 (26 per sequence) will be used in this study. This sample size will allow for up to 6 dropouts (11.5% 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 90%. This sample size was based on the intrasubject variance of 0.075 for $\log(C_{max})$ and 0.024 for $\log(AUC)$ from the TAK-390MR_107 study.

If BE is not achieved with the first TOB formulation assessed, the study may be repeated for one or both dose strengths in new subjects who will receive the same TOB formulation or a different TOB formulation. The same study design will be used if additional formulation assessments are needed.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

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

3.2 Principal Investigator

Personal Protected Data



3.3 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
CRO	contract research organization
CS	clinically significant
CYP	cytochrome P-450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDTA	ethylenediamine tetraacetic acid
eCRF	electronic case report form
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
LFT	liver function test
MAV	markedly abnormal value
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	United Kingdom Medicines and Healthcare products Regulatory Agency
NCS	not clinically significant
NDA	New Drug Application
PGx	pharmacogenomics
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency (of Japan)
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.
WHODRUG	World Health Organization Drug Dictionary

3.4 Corporate Identification

Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
TDC Americas	Takeda Development Center Americas, Inc.
TOB	Takeda GmbH Plant Oranienburg, Germany
TPC	Takeda Pharmaceutical Company Ltd. (Osaka, Japan)

4.0 INTRODUCTION

4.1 Background

Dexlansoprazole is a proton-pump inhibitor (PPI) with prolonged elevation of intragastric pH. PPIs inhibit the secretion of H⁺ ions in the stomach by inhibiting the (H⁺, K⁺)-ATPase enzyme (proton pump) at the secretory surface of the gastric parietal cell [1]. Dexlansoprazole is the *R*-enantiomer of the racemate lansoprazole. Lansoprazole, initially approved in France in 1990, 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.

4.2 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.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

- To assess the bioavailability (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.

5.1.2 Additional Objectives

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

5.2 Endpoints

5.2.1 Primary Endpoints

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_{∞}).

5.2.2 Additional Endpoints

- 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).

5.2.3 Safety Endpoints

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

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study 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. The study will be conducted in 2 parts. In Part 1, 52 healthy subjects will receive dexlansoprazole 30 mg capsules manufactured by TOB and TPC in a crossover fashion. In Part 2, an additional 52 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. If BE is not achieved with the first TOB formulation, the study may be repeated for one or both dose strengths in new subjects who will receive the same TOB formulation or a different TOB formulation. The same study design will be used if additional formulation assessments are needed.

At Check-in (Day -1 of Period 1), approximately 104 subjects in total (52 in Part 1, 52 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 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	26	A	B
2	26	B	A

Regimen A (test): A single dexlansoprazole 30 mg capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast.

Regimen B (reference): A single dexlansoprazole 30 mg capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.

Table 6.b Part 2 Sequences

Sequences	Number of Subjects	Period 1	Period 2
3	26	C	D
4	26	D	C

Regimen C (test): A single dexlansoprazole 60 mg capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast.

Regimen D (reference): A single dexlansoprazole 60 mg capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.

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 on Day 1 of each period at approximately 0800 hours, following a 10-hour fast. 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. On Day 1 of each period, breakfast will not be served. During Periods 1 and 2, blood samples will be collected over 24 hours postdose to measure dexlansoprazole plasma concentrations.

A blood sample for pharmacogenomics (PGx) will also be collected on Day 1 of Period 1. The cytochrome P-450 (CYP)2C19 isozyme is a polymorphic enzyme that is involved in the metabolism of dexlansoprazole. A genotype test for CYP2C19 will determine the subject's metabolizer status.

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 (\pm 2) days post last dose of study drug to inquire for any ongoing AEs or serious adverse events (SAEs), new AEs or SAEs, and concomitant medications taken since final dose. Any spontaneously reported AEs will continue to be collected for 30 days after the last dose of study drug. Subjects who withdraw their consent will still be contacted for a safety follow-up call. The contact will only be recorded in their source documents and the electronic case report forms (eCRFs), 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.

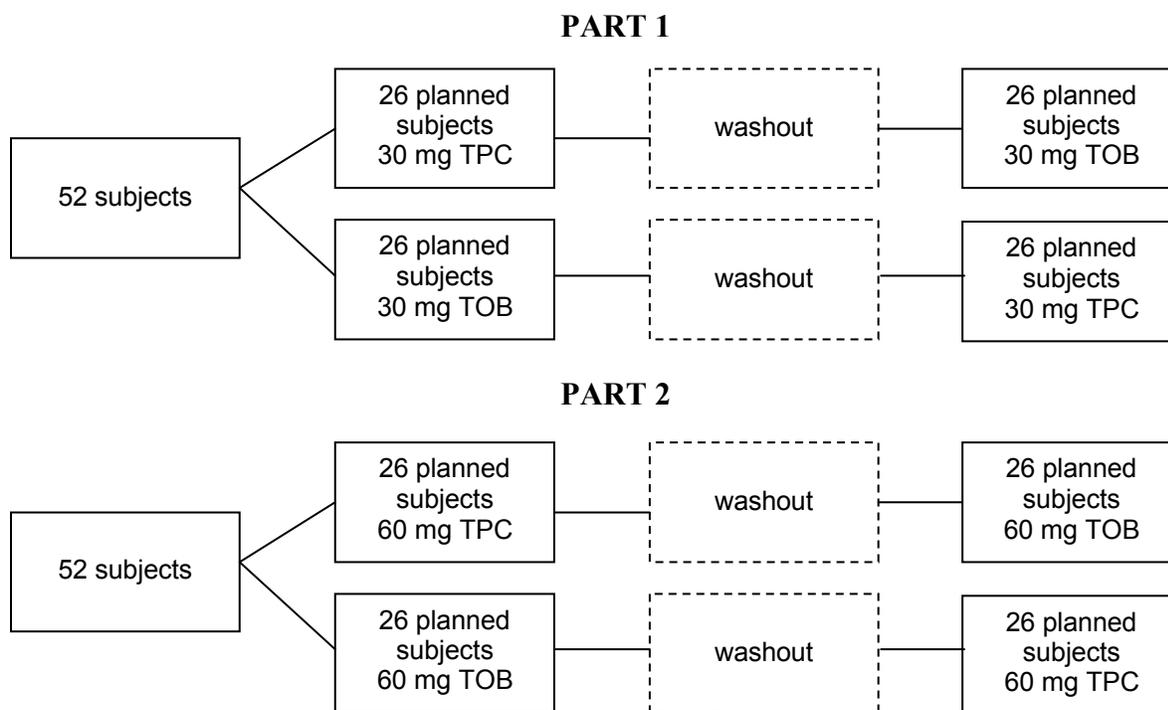
A schematic of the study design is included as [Figure 6.a](#) and [Figure 6.b](#). A schedule of assessments is listed in [Appendix A](#).

Figure 6.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
		← 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 6.b Schematic of Crossover Design



6.2 Justification for Study Design, Dose, and Endpoints

This phase 1 randomized, open-label, single-dose, 2-part, 2-way crossover relative BA study is designed in accordance with the Bioavailability and Bioequivalence Studies Submitted in New Drug Applications (NDAs) or Investigational New Drug (INDs) – General Considerations Guidance for Industry (March 2014) [2], and The Committee for Medicinal Products for Human Use Guideline on the Investigation of Bioequivalence (January 2010) [3].

A single-dose study under fasting conditions for assessing the relative BA between formulations is recommended in the guidances referenced above 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 treatment-emergent adverse events (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.

The CYP2C19 isozyme is a polymorphic enzyme that is involved in the metabolism of dexlansoprazole. Therefore, the CYP2C19 metabolizer status of the subjects will be determined and, if appropriate, the effect of metabolizer status on the PK of dexlansoprazole will be assessed. As this is a crossover study and each subject will be his/her own control, inclusion of CYP2C19 poor metabolizers is not expected to affect the overall results of the study.

6.3 Premature Termination or Suspension of Study or Investigational Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

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

- New information or other evaluation regarding the safety or efficacy of the study medication that indicates a change in the known risk/benefit profile for the 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.

6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

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, informed consent form and any required privacy authorization prior to the initiation of any study procedures including requesting that a subject fast for any laboratory evaluations.
3. The subject is 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/m², 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. Women of childbearing potential* must have a negative serum pregnancy test at Screening and Check-in (Day -1 of Period 1) and they must not be nursing.

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

8. Subject has clinical chemistry, hematology, and complete urinalysis (after fasting for at least 8 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.

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 at Screening or a known history of human immunodeficiency virus infection (HIV).
9. Subject has abnormal Screening or Day -1 of Period 1 laboratory values that suggest a clinically significant underlying disease or subject with the following lab abnormalities: creatinine >1.5 mg/dL, alanine aminotransferase (ALT) and or aspartate aminotransferase (AST) >2.5 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 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, gastrointestinal, 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. 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.
 20. If a man, the subject intends to donate sperm during the course of this study or for 30 days thereafter.
 21. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

7.3 Excluded Medications and Dietary Products

Use of the agents in [Table 7.a](#) (prescription or nonprescription) is prohibited from the time points specified 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 Immunization/Vaccines (c)	Intake of known OTC inhibitors/inducers of CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6 (d)	Poppy seeds

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.

(b) Occasional use of acetaminophen (≤ 2 g/day) is allowed or other medication as approved by Takeda on a case-by-case basis. Acetaminophen is not allowed on Day 1.

(c) Inclusive of but not limited to H1N1 and flu vaccinations.

(d) Lansoprazole, esomeprazole, omeprazole, cimetidine, ranitidine, and chlorpheniramine.

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator during the Washout Period, as well as during confinement.

7.4 Diet, Fluid and Activity Control

7.4.1 Confinement

Subjects enrolled in this study will be confined in the clinical research unit for 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.

7.4.2 Diet and Fluid

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

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

Subjects will fast for a minimum of 10 hours prior to dosing on Day 1 of each period. On Day 1 of each period, breakfast will not be served. 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 eCRF. Subjects will be fasting for a minimum of 8 hours prior to collection of safety labs and 24 hour PK sample on Day 2 of Periods 1 and 2.

7.4.3 Activity Control

Subjects should be instructed to refrain from strenuous exercise starting approximately 48 hours prior to confinement on Day -1 of Period 1 and for the duration of their participation in the study.

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study medication should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section [9.1.15](#).

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 [9.1.8](#)), if the following circumstances occur at any time during study medication treatment:
 - ALT or AST $>8 \times$ ULN, or
 - ALT or AST $>5 \times$ ULN and persists for more than 2 weeks, or
 - ALT or AST $>3 \times$ ULN in conjunction with elevated total bilirubin $>2 \times$ ULN or international normalized ratio (INR) >1.5 , or ALT or AST $>3 \times$ 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 eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE).

5. Study termination. The sponsor, 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 Section 9.1.10.

7. Other.

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

7.6 Procedures for Discontinuation or Withdrawal of a Subject

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

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Study Medication

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

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

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). The bottles 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.”

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

8.1.2 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 drug supply must be returned in its original container.

8.1.3 Dose and Regimen

Subjects will fast for a minimum of 10 hours prior to dosing in Periods 1 and 2. On Day 1 at approximately 0800 hours, subjects will be instructed to swallow the intact capsule 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 8.b](#)).

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 8.b Dose and Regimen

Study Part	Sequence	Number of Subjects	Period 1 Regimen	Period 2 Regimen
Part 1	1	26	A	B
30 mg	2	26	B	A
Part 2	3	26	C	D
60 mg	4	26	D	C

Regimen A: A single 30 mg dexlansoprazole capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast.

Regimen B: A single 30 mg dexlansoprazole capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.

Regimen C: A single 60 mg dexlansoprazole capsule manufactured at TOB administered orally on Day 1 following a 10-hour fast.

Regimen D: A single 60 mg dexlansoprazole capsule manufactured at TPC administered orally on Day 1 following a 10-hour fast.

Note: If the study is repeated in the same or new formulations, the regimens will be labeled AA, BB, CC, and DD, as needed.

8.1.4 Overdose

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

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

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

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

8.2 Investigational Drug Assignment and Dispensing Procedures

Subjects will be assigned, in the order in which they are randomized into the study, to receive their treatment according to the randomization schedule allocated to the site. The Randomization Sequence Number will be entered onto the eCRF.

Subjects will be assigned to receive a 4-digit randomization sequence number by the clinic site personnel in sequential order. For Part 1, men will be assigned in ascending order starting from 1001 and women will be assigned in descending order starting from 1052. For Part 2, men will be assigned in ascending order starting from 2001 and women will be assigned in descending order starting from 2052. Additional schedules will be generated if the second formulations are assessed. This 4-digit number will be used by the clinical site to facilitate the prelabeling of PK samples, and will be the only subject identifier used on all PK sample collections. It should also be contained on the PK transport vials shipped to the bioanalytical laboratory, and will be used by the laboratory to report the subject data results. This 4-digit number should only be used for the purposes described in this section. It does not replace the 3-digit subject number which is assigned at the time the informed consent is obtained and which is used for all other procedures to identify the subjects throughout the study.

8.3 Randomization Code Creation and Storage

The randomization schedule will be generated 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.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

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

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 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.

In the event of expiry date extension of supplies already at the study site, clinical study material may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will

prepare additional labels, and all necessary documentation for completion of the procedure at the sites.

8.5 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 PLAN

9.1 Study Procedures

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

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section [15.2](#).

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

A unique subject identification number (subject 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.

9.1.1.1 Pharmacogenomic Informed Consent Procedure

PGx informed consent is a component of the overall study informed consent. The requirements are described in Section [15.2](#). The PGx sample collection is mandatory.

9.1.2 Demographics, Medical History, and Medication History Procedure

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 (see Section [9.1.7](#)).

9.1.3 Physical Examination Procedure

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 eCRF 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 eCRF. All CS findings/changes will be recorded as a pretreatment event (PTE) or concurrent medical condition in the source document and on the appropriate eCRF described in Section 10.0 or Section 9.1.7.

On subsequent examinations, any abnormal change from the pretreatment physical examination assessment occurring immediately prior to the start of the study drug must be assessed as NCS or CS by the investigator and recorded in the source document and eCRF. Any CS change or new diagnosis as a result of a CS change, as determined by the investigator, will be recorded as an AE in source documentation and on the PTE/AE eCRF described in Section 10.0.

9.1.4 Weight, Height and BMI

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

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

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 meters), then $\text{BMI} = 79.2 / 1.76^2 = 25.56818 \text{ kg/m}^2$.

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.

9.1.5 Vital Sign Procedure

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 (Appendix A).

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

9.1.6 Documentation of Concomitant Medications

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 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 eCRF. All medications taken from Screening through to the end of the study will be recorded in the source document and Concomitant Medication eCRF.

9.1.7 Documentation of Concurrent Medical Conditions

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

9.1.8 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Laboratory samples will be taken following a minimum 8-hour overnight fast at the time points stipulated in the Schedule of Study Procedures ([Appendix A](#)).

[Table 9.a](#) lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC	Alanine aminotransferase	Specific gravity
WBC with differential	Albumin	pH
Hemoglobin	Alkaline phosphatase	Protein
Hematocrit	Aspartate aminotransferase	Ketones
Platelets	Glucose	Glucose
	Total bilirubin	Bilirubin
	Total protein	Red blood cells and white blood cells
	Total cholesterol	
	Triglycerides	Microscopic battery (RBCs, WBCs, epithelial cells, casts) if significant findings on dipstick urinalysis
	Serum creatinine	
	Blood urea nitrogen	
	Uric acid	
	gamma-glutamyl transferase	
	Calcium	
	Phosphorus	
	Potassium	
	Sodium	
	Chloride	
	Bicarbonate or carbon dioxide	
Diagnostic Screenings:		
Serum	Urine/Blood	Breath
Hepatitis panel, including HBsAg and anti-HCV	Drug screen, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine and opiates.	Alcohol
<i>Women subjects only:</i>		
Serum hCG for pregnancy		
Serum FSH <i>If postmenopausal women defined as amenorrhea >1 year</i>		

FSH=follicle stimulating hormone, hCG= human chorionic gonadotropin, RBC=red blood cells, WBC=white blood cells.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis as referenced in [Appendix A](#). 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 eCRF.

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 eCRF 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.

9.1.9 Contraception and Pregnancy Avoidance Procedure

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

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

*Women of childbearing potential are defined as any female who has experienced menarche and who are NOT permanently sterile or postmenopausal. Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as 12 consecutive months with no menses without an alternative medical cause).**Sterilized men should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

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

Barrier methods (each time the subject has intercourse):

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

Intrauterine devices (IUDs):

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

Hormonal contraceptives:

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

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

At Screening, serum hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and ova and sperm donation as part of the study procedures ([Appendix A](#)). In addition, subjects

must also have a negative serum hCG pregnancy test 1 day prior to receiving first dose of study medication.

9.1.10 Pregnancy

If any subject is found to be pregnant during the study, she should be withdrawn and any sponsor-supplied drug should be immediately discontinued. In addition, any pregnancies in the partner of a 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 pregnancy occurs during administration of active study medication, eg, after Check-in (Day -1 of Period 1) or within 30 days of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

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

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

9.1.11 ECG Procedure

A standard 12-lead ECG will be recorded at 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 eCRF and the original hard copies should be kept as source documentation. ECGs on thermal paper must be photocopied and the copy should be kept in the subjects' source documents. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, QT interval, and QRS interval.

9.1.12 Pharmacogenomic Sample Collection

When sampling of whole blood for PGx analysis occurs, every subject must sign an informed consent/be consented in order to participate in the study.

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

- Identifying genetic reasons certain people respond differently to dexlansoprazole.

- Finding out more information about how dexlansoprazole works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to dexlansoprazole.
- Identifying variations in genes related to the biological target of dexlansoprazole.

This information may be used to develop a better understanding of the safety and efficacy of dexlansoprazole and other study medications, and for improving the efficiency, design, and study methods of future research studies.

One 6 mL whole blood sample for DNA isolation will be collected before dosing on Day 1 of Period 1 from each subject in the study, into plastic K2 ethylenediamine tetraacetic acid (EDTA) spray-coated tubes, and stored under frozen conditions. If necessary and feasible, a second aliquot of blood may be taken at any time after randomization if isolation of DNA from the first sample was not successful or possible.

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

The CYP2C19 isozyme is a polymorphic enzyme that is involved in the metabolism of dexlansoprazole. Therefore, the CYP2C19 metabolizer status of the subjects will be determined.

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

9.1.13 PK Sample Collection

9.1.13.1 Collection of Blood for PK Sampling

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.b](#).

Instructions for sample processing and shipment are provided in [Appendix E](#).

Table 9.b Collection of Blood Samples for PK Analysis

Sample Type	Dosing Day	Time (hours)
	(Periods 1 and 2)	
Plasma	1	Predose (within 15 minutes prior to dose) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours postdose.

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

9.1.14 PK Parameters

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.

Symbol/Term	Definition
Plasma	
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.

9.1.15 Documentation of Screen Failure

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

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

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

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

9.1.16 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the study. Any subjects that replace withdrawn or discontinued subjects will maintain the same treatment sequence as the discontinued subject.

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

9.2 Monitoring Subject Treatment Compliance

Study medication will be administered while subjects are under observation in the clinical research unit. Following administration of the study medication, appropriate mouth and/or hand checks will be performed to ensure that the dose is swallowed and noted in the source document. The date and time of each dose will be recorded to the nearest minute on the source document and the eCRFs. The exact dose time of consecutive subjects may be staggered to facilitate logistics at the site.

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening

Subjects will be screened within 28 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.15 for procedures for documenting screening failures.

Procedures to be completed at Screening include:

- Informed consent.
- Demographics, medical history, and medication history.
- Physical examination.
- Vital signs.
- Weight, height, and BMI.
- Concomitant medications.
- Concurrent medical conditions.
- Fasting Screening clinical laboratory tests (hematology, serum chemistry, urine analysis, hepatitis panel, urine drug screen).
- 12-lead ECG procedure.
- Assessment of inclusion/exclusion criteria.
- Pregnancy test (women of childbearing potential).

- FSH (only performed if menopause is suspected).
- Pretreatment event assessment.

9.3.2 Check-in (Day -1)

Subjects will be admitted to the clinic on Check-in (Day -1). The following procedures will be performed; all results must be available prior to administration of study drug on Day 1:

- Confinement.
- Assessment of inclusion/exclusion criteria (Period 1 only).
- Complete physical examination.
- 12-lead ECG.
- Vital signs.
- Fasting laboratory evaluations (after a minimum 8-hour fast).
- Serum pregnancy test (females of childbearing potential only).
- Urine drug screen, alcohol screen, and cotinine screen.
- AEs: Pretreatment events are assessed on Day -1 of Period 1 and TEAEs are assessed on Day -1 of Period 2.
- Concomitant medication assessment.

9.3.3 Treatment Phase (Day 1)

The following procedures will be performed at Day 1:

- Randomization (Period 1 only).
- Confinement.
- Vital signs (blood pressure and pulse only) prior to dose and 8 hours postdose.
- Concomitant medication assessment.
- Administration of study drug.
- PK blood sampling.
- Pharmacogenomic sample collection (Period 1 only).
- Pretreatment event/AE assessment.

For Period 1, if the subject has satisfied all of the inclusion criteria and met none of the exclusion criteria for randomization, the subject should be randomized as described in Section 8.3. The procedure for documenting screening failures is provided in Section 9.1.15.

9.3.4 Day 2 (Period 1)

The following procedures will be performed at Day 2 (Period 1):

- Confinement.
- PK blood sampling.
- AE assessment.
- Concomitant medication assessment.
- 12-lead ECG.
- Vital signs (blood pressure and pulse only).
- Fasting laboratory evaluations (after a minimum 8-hour fast).

9.3.5 Day 2 (Period 2)/Study Exit

The Final Visit will be performed on Day 2 of Period 2 or at the Early Termination Visit. The following procedures will be performed and documented on Day 2 of Period 2:

- Confinement.
- Complete physical examination (excluding genitourinary examination).
- 12-Lead ECG.
- Vital signs (blood pressure and pulse only).
- Fasting laboratory evaluations (after a minimum 8-hour fast).
- Serum pregnancy test (females of childbearing potential only).
- PK blood sampling.
- AE assessment.
- Concomitant medication assessment.

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

9.3.6 Early Termination

- Complete physical exam (excluding genitourinary examination).
- 12-Lead ECG.
- Vital signs.
- Fasting laboratory evaluations. (If an 8-hour fast is not possible at Early termination, laboratory samples will still be collected.)
- Serum pregnancy test (females of childbearing potential only).

- Pretreatment event/AE assessment.
- Concomitant medication assessment.

9.3.7 Follow-up

At 10±2 days following the last dose of study drug, a follow-up phone call will be made to inquire about any ongoing or new AEs, any SAEs, and concomitant medications taken since final dose. Any spontaneously reported AEs will continue to be collected for 30 days after the last dose of study drug. Subjects who withdraw their consent should still be contacted for a safety follow-up call. The contact should only be recorded in their source documents and the eCRFs, according to data protection regulations.

9.3.8 Unscheduled Visit

1. Complete physical examination.
2. Vital signs.
3. AE assessment.
4. Concomitant medication assessment.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.12. The genetic material will be preserved and retained at Covance Biorepository for up to, but not longer than, 15 years, or as required by applicable law. The sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

The samples will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sponsor and researchers working with the sponsor will have access to the samples collected and any test results. All samples collected during the study will be stored securely with limited access and the sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

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

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

9.5 Blood Volume

Total blood sampling volume for an individual subject is shown in [Table 9.c](#).

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Approximate Blood Volume			Total Volume (mL)
		Number of Samples			
		Screening	Period 1	Period 2	
Clinical Laboratory Test Samples	20	1	2	2	100
PK Samples	4	0	15	15	120
PGx DNA	6	0	1	-	6
Total Blood Sampling Volume					226

The maximum volume of blood at any single day is approximately 96 mL, and the approximate total volume of blood for the study is 226 mL.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

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

Diagnoses vs signs and symptoms:

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

Laboratory values and ECG findings:

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

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

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

Pre-existing conditions:

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

Worsening of PTEs or AEs:

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

Changes in severity of AEs /Serious PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Overdose:

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

10.1.4 SAEs

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

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

Table 10.a Takeda Medically Significant AE List

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

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

10.1.5 Severity of PTEs and AEs

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

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

10.1.6 Causality of AEs

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

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

10.1.7 Relationship to Study Procedures

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

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

10.1.8 Start Date

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

10.1.9 Stop Date

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

10.1.10 Frequency

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

10.1.11 Action Concerning Study Medication

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

10.1.12 Outcome

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

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTEs and AEs Collection Period

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

Collection of AEs will commence from the time that the subject is first administered study medication (Day 1). Routine collection of AEs will continue until 5 to 10 days after the last dose of study drug is completed. Any spontaneously reported AEs will continue to be reported for 30 days after the last dose of study drug.

10.2.1.2 PTEs and AEs Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change. Nonserious PTEs, 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 PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Severity.
5. Investigator’s opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
6. Investigator’s opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.

7. Action concerning study medication (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

10.2.2 Collection and Reporting of SAEs

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

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

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

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

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

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

10.2.3 Reporting of Abnormal LFTs

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

If a subject is noted to have ALT or AST $>3 \times \text{ULN}$ and total bilirubin $>2 \times \text{ULN}$ for which an alternative etiology has not been identified, the event should be recorded as an SAE and reported as per Section 10.2.2. The investigator must contact the Medical Monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. Follow-up laboratory tests as described in Section 9.1.8 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

10.3 Follow-up of SAEs

If information that is not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation

and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

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

10.3.1 Safety Reporting to Investigators, IRBs and Regulatory Authorities

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

11.0 STUDY-SPECIFIC COMMITTEES

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

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 CRFs (Electronic)

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

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

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

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, 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), and detailed records of drug disposition to enable evaluations or audits from regulatory authorities,

the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Phase 1 Site Specifications document for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

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.

13.1.1 Analysis Sets

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.

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.

13.1.2 Analysis of Demographics 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).

13.1.3 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% confidence interval (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.

13.1.4 Safety Analysis

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.

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

Shift tables for character ECG results will be provided overall to tabulate the number and percentage of subjects who changed status after dosing.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

For each part, a sample size of 52 (26 per sequence) will be used in this study. This sample size will allow for up to 6 dropouts (11.5% 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 90%. This sample size was based on the intrasubject variance of 0.075 for $\log(C_{max})$ and 0.024 for $\log(AUC)$ from the TAK-390MR_107 study.

If BE is not achieved with the first TOB formulation assessed, the study may be repeated in new subjects who will receive the same TOB formulation or a different TOB formulation. The same study design will be utilized if additional formulation assessments are needed.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

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

Every attempt will be made to collect each PK blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF. However, blood samples not collected as displayed in [Table 14.a](#) should be reported to Takeda using the Protocol Deviation Form.

Table 14.a Windows for PK Sample Collection

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

Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

The sponsor or designee contact information for communicating protocol deviations is provided in Section 1.1.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB Approval

IRBs must be constituted according to the applicable state and federal requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. 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, package insert, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB’s written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site of drug shipment once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives notification to proceed with the study, no protocol activities, including screening, may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

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

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

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

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

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

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

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

15.4.2 Clinical Trial Registration

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

15.4.3 Clinical Trial Results Disclosure

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

1. Dexilant (dexlansoprazole) Delayed Release Capsules. Full Prescribing Information. Deerfield, IL: Takeda Pharmaceuticals America, Inc., Revised October 2016.
2. Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs - General Considerations. US Dept of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). March 2014.
3. Guideline on the Investigation of Bioequivalence. European Medicines Agency, Committee for Medicinal Products for Human Use. 20 January 2010. Publication No. CPMP/EWP/QWP/1401/98 Rev. 1.

Appendix A Schedule of Study Procedures

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

Footnotes are on last table 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 administration of investigational product.
- (c) Day 1 of each treatment period.
- (d) Follow-up phone call will be made 10±2 days after last dose of study drug to inquire about any TEAE or SAEs, and concomitant medications taken since final dose. Any TEAE/SAE spontaneously reported within 30 days postdose will be included within the database as a TEAE.
- (e) Following study procedure completion on Day 2 of Period 1, subjects will be discharged from the clinic to begin the washout period.
- (f) Following study procedure completion on Day 2 of Period 2, subjects will be discharged from the clinic. Early termination procedures are explained in Section 9.3.6.
- (g) Assessment of inclusion and exclusion criteria will be done on Day -1, Period 1 only.
- (h) The BMI is calculated using metric units as follows: Metric: $BMI = \text{weight (kg)} / [\text{height (m)}]^2$.
- (i) Vital signs: oral body temperature, sitting blood pressure (after resting 5 minutes), respiratory rate, and pulse (beats per minute) at Screening. Only blood pressure and pulse will be collected on Check-in (Day -1) through Day 2 of each period prior to dose and 8 hours postdose, or if the subject terminated early from 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.
- (j) Hematology, serum chemistries, and urinalysis tests. Clinical laboratory samples will be collected after a minimum of an 8 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 an 8-hour fast is not possible at Early termination, laboratory samples will still be collected.
- (k) A serum pregnancy test will be done at Screening and Day -1 of each period, Study Exit (Day 2 of Period 2), or if a subject prematurely terminates from the study.
- (l) For women where menopause is suspected (see Section 9.1.9).
- (m) ECG 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.
- (n) Study drug will be administered on Day 1 of each period at approximately 0800 hours, following a 10-hour fast. Dosing may be staggered to help facilitate logistics at the site.
- (o) One 6 mL whole-blood sample will be collected for DNA analysis prior to dosing on Day 1 of Period 1 only.
- (p) Blood samples for PK obtained predose (within 15 minutes prior to dose), and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours post Day 1 dosing in each period.
- (q) The PK sample should not be collected at the Early Termination Visit if a PK collection is not scheduled.
- (r) 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.

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

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

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

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

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject 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, IRB/IEC, and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

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

20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject 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.

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

Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

Appendix E Collection, Storage, and Shipment of Bioanalytical Samples

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-1001], 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 PPD Development, Middleton, WI. 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-1001), 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:

Personal Protected Data



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.

Personally Protected Data



16. 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 sections of the protocol affected by the changes in Amendment No. 02 are indicated.

Change 1: Allow the replacement of subjects who are discontinued or withdrawn.

The change occurs in Section [7.6 Procedures for Discontinuation or Withdrawal of a Subject](#).

Initial wording:	The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5 . In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.
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Amended or new wording:	The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5 . In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not may be replaced.
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Rationale for Change:

This change was made because a greater number of subjects were discontinued or withdrawn from the study than was originally expected.

Change 2: Correct the dose shown in Part 2 of the crossover study design schematic.

The change occurs in [Figure 6.b Schematic of Crossover Design](#) in Section [6.1 Study Design](#).

Initial wording:	[Dose level for Part 2 was indicated to be 30 mg.]
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Amended or new wording:	[Dose level for Part 2 is indicated to be 60 mg.]
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Rationale for Change:

This was corrected for consistency with the study design.

Change 3: Remove all reference to the subject’s legally acceptable representative.

The primary change occurs in Section [15.2 Subject Information, Informed Consent, and Subject Authorization](#).

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

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

Rationale for Change:

This change was requested by the IRB for consistency with the language in the inclusion criterion regarding subject informed consent.

The following sections also reflect this change:

- Section [7.5 Criteria for Discontinuation or Withdrawal of a Subject](#).
 - [Appendix B Responsibilities of the Investigator](#).
 - [Appendix C Elements of the Subject Informed Consent](#).
-

Change 4: Update the definitions of women of (and not of) childbearing potential.

The change occurs in Section 9.1.9 Contraception and Pregnancy Avoidance Procedure.

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

Amended or new wording: * **Women of childbearing potential are defined as any female who has experienced menarche and who are NOT permanently sterile or postmenopausal.** Women NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (eg, defined as ~~at least 1 year since last regular menses with an FSH>40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented~~ **12 consecutive months with no menses without an alternative medical cause**).

Rationale for Change:

This was changed to reflect requested wording from the IRB during previous IRB review.

Change 5: Update the subject replacement information based on the allowance for replaced subjects.

The change occurs in Section 9.1.16 Documentation of Randomization.

Initial wording: Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the study.

Amended or new wording: Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the study. **Any subjects that replace withdrawn or discontinued subjects will maintain the same treatment sequence as the discontinued subject.**

Rationale for Change:

The new text was added to reflect the allowance for replacement subjects.

Change 6: Clarify that an 8-hour fast may not be possible at Early termination.

The primary change occurs in Section 9.3.6 Early Termination.

Initial wording: Fasting laboratory evaluations.

Amended or new wording: Fasting laboratory evaluations. **(If an 8-hour fast is not possible at Early termination, laboratory samples will still be collected.)**

Rationale for Change:

This text clarifies that laboratory samples should still be collected even though subjects who discontinue may not have had the opportunity to fast for 8 hours prior to the visit.

This change is also reflected in footnote j of [Appendix A Schedule of Study Procedures](#).

Change 7: Correct the sequence numbers in Table 8.b for Part 2 of the study.

The change occurs in [Table 8.b Dose and Regimen](#).

Initial wording: [Sequence numbers for Part 2 were listed as 1 and 2.]

Amended or new wording: [Sequence numbers for Part 2 are now listed as 3 and 4.]

Rationale for Change:

This was corrected for consistency with the information presented in [Table 6.b Part 2 Sequences](#).

Amendment 02 to Phase 1 Bioequivalence Study of Dexlansoprazole Capsules from Two Manufacturing Plants

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Data	Clinical Pharmacology Approval	07-Jun-2017 14:44 UTC
	Quality Control Approval	07-Jun-2017 14:49 UTC
	Clinical Science Approval	07-Jun-2017 18:24 UTC