



Title: A Phase 3 Double Blind Study to Evaluate the Efficacy and Safety of Dexlansoprazole (30 mg QD) compared to Placebo on Heartburn Relief in Subjects With Symptomatic Nonerosive Gastroesophageal Reflux Disease (GERD)

NCT Number: NCT02873689

Protocol Approve Date: 20 February 2017

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**PROTOCOL AMENDMENT**

**A Phase 3 Double Blind Study to Evaluate the Efficacy and Safety of Dexlansoprazole (30 mg QD) compared to Placebo on Heartburn Relief in Subjects With Symptomatic Nonerosive Gastroesophageal Reflux Disease (GERD)**

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

**Study Number:** TAK-390MR\_302

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

**Compound:** Dexlansoprazole Capsules

**Date:** 20 February 2017      **Amendment Number:** 03

**Amendment History:**

<b>Date</b>	<b>Amendment Number</b>	<b>Amendment Type</b>	<b>Region</b>
17 June 2011	Initial Protocol	Not applicable	China
26 January 2016	1	Nonsubstantial	China
09 June 2016	02	Nonsubstantial	China
20 February 2017	03	Nonsubstantial	China

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## 1.0 ADMINISTRATIVE INFORMATION

### 1.1 Contacts

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

TDC Asia sponsored Asia Pacific investigators will be provided with emergency medical contact information cards to be carried by each subject.

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

Issue	Asia Pacific Contact
Serious adverse event, pregnancy, and special interest adverse event reporting	Personally Protected Data
Medical Monitor (medical advice on protocol, compound, and medical management of subjects)	
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	

## 1.2 Approval

### REPRESENTATIVES OF TAKEDA

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

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

### SIGNATURES

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

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

Personally Protected Data	Date	Personally Protected Data	Date
Personally Protected Data	Date		

## INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also 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.
- Responsibilities of the Investigator ([Appendix B](#)).

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

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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 03 Summary of Main Changes

This section describes the changes in reference to the protocol incorporating Amendment No. 03. The primary reason for this amendment is to clarify acceptable windows for some screening procedures. Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

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

1. Update contract research organization (CRO) contact information.
2. Remove the requirement that the Screening Period be a minimum of 7 days.
3. Change the appropriate contact for confirming available brands of rescue medication.
4. Gastrin levels will be blinded to both investigators and medical monitors during the study period.
5. Clarify acceptable windows for screening labs and endoscopy.
6. Update one of the definitions of an SAE.

## TABLE OF CONTENTS

1.0	ADMINISTRATIVE INFORMATION .....	2
1.1	Contacts.....	2
1.2	Approval.....	3
1.3	Protocol Amendment 03 Summary of Main Changes .....	5
2.0	STUDY SUMMARY .....	11
3.0	STUDY REFERENCE INFORMATION .....	14
3.1	Study-Related Responsibilities.....	14
3.2	Coordinating Investigator.....	14
3.3	List of Abbreviations .....	15
3.4	Corporate Identification .....	16
4.0	INTRODUCTION.....	17
4.1	Background .....	17
4.2	Rationale for the Proposed Study .....	19
5.0	STUDY OBJECTIVES AND ENDPOINTS.....	20
5.1	Objectives.....	20
5.1.1	Primary Objective .....	20
5.1.2	Secondary Objective .....	20
5.1.3	Additional Objectives.....	20
5.2	Endpoints.....	20
5.2.1	Primary Endpoint .....	20
5.2.2	Secondary Endpoint .....	20
5.2.3	Additional Endpoints .....	20
6.0	STUDY DESIGN AND DESCRIPTION.....	21
6.1	Study Design .....	21
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 Treatments.....	26

7.4	Diet, Fluid, Activity Control .....	27
7.5	Criteria for Discontinuation or Withdrawal of a Subject .....	28
7.6	Procedures for Discontinuation or Withdrawal of a Subject .....	30
8.0	CLINICAL TRIAL MATERIAL MANAGEMENT .....	31
8.1	Study Medication and Materials .....	31
8.1.1	Dosage Form, Manufacturing, Packaging, and Labeling .....	31
8.1.2	Storage .....	33
8.1.3	Dose and Regimen .....	33
8.1.4	Overdose .....	34
8.2	Investigational Drug Assignment and Dispensing Procedures .....	34
8.3	Randomization Code Creation and Storage .....	34
8.4	Investigational Drug Blind Maintenance .....	35
8.5	Unblinding Procedure .....	35
8.6	Accountability and Destruction of Sponsor-Supplied Drugs .....	35
9.0	STUDY PLAN .....	37
9.1	Study Procedures .....	37
9.1.1	Informed Consent Procedure .....	37
9.1.2	Demographics, Medical History, and Medication History Procedure .....	37
9.1.3	Physical Examination Procedure .....	37
9.1.4	Weight, Height .....	38
9.1.5	Vital Sign Procedure .....	38
9.1.6	GERD Symptoms Investigator Assessment .....	38
9.1.7	Daily eDiary .....	39
9.1.8	Documentation of Concomitant Medications .....	39
9.1.9	Documentation of Concurrent Medical Conditions .....	39
9.1.10	Procedures for Clinical Laboratory Samples .....	39
9.1.11	Contraception and Pregnancy Avoidance Procedure .....	41
9.1.12	Pregnancy .....	42
9.1.13	ECG .....	43
9.1.14	Documentation of Screen Failure .....	43
9.1.15	Documentation of Study Randomization .....	44
9.1.16	Endoscopy .....	44
9.2	Monitoring Subject Treatment Compliance .....	44
9.3	Schedule of Observations and Procedures .....	45
9.3.1	Screening .....	45



9.3.2	Study Randomization.....	46
9.3.3	Treatment Period.....	47
9.3.4	Final Visit or Early Termination ( $\pm 3$ Days) .....	47
9.3.5	Unscheduled Visit.....	48
9.3.6	Follow-up .....	48
9.3.7	Post Study Care.....	48
10.0	PRETREATMENT EVENTS AND ADVERSE EVENTS .....	49
10.1	Definitions.....	49
10.1.1	Pretreatment Events .....	49
10.1.2	AEs.....	49
10.1.3	Additional Points to Consider for PTEs and AEs.....	49
10.1.4	SAEs.....	51
10.1.5	Severity of PTEs and AEs .....	52
10.1.6	Causality of AEs .....	52
10.1.7	Relationship to Study Procedures.....	52
10.1.8	Start Date.....	53
10.1.9	Stop Date.....	53
10.1.10	Frequency .....	53
10.1.11	Action Concerning Study Medication.....	53
10.1.12	Outcome.....	53
10.2	Procedures.....	54
10.2.1	Collection and Reporting of AEs.....	54
10.2.2	Collection and Reporting of SAEs.....	55
10.2.3	Reporting of Abnormal Liver Function Tests .....	56
10.3	Follow-up of SAEs .....	56
10.3.1	Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities .....	56
11.0	STUDY-SPECIFIC COMMITTEES .....	57
12.0	DATA HANDLING AND RECORDKEEPING.....	58
12.1	eCRF.....	58
12.2	Record Retention .....	58
13.0	STATISTICAL METHODS.....	60
13.1	Statistical and Analytical Plans .....	60
13.1.1	Analysis Sets.....	60
13.1.2	Analysis of Demographics and Other Baseline Characteristics .....	60
13.1.3	Efficacy Analysis.....	60

13.1.4	Safety Analysis .....	60
13.2	Interim Analysis and Criteria for Early Termination .....	61
13.3	Determination of Sample Size.....	61
14.0	QUALITY CONTROL AND QUALITY ASSURANCE.....	62
14.1	Study-Site Monitoring Visits .....	62
14.2	Protocol Deviations.....	62
14.3	Quality Assurance Audits and Regulatory Agency Inspections .....	62
15.0	ETHICAL ASPECTS OF THE STUDY .....	63
15.1	IRB and/or IEC 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 7.a	Excluded Medications.....	27
Table 8.a	Study Drugs .....	31
Table 8.b	Rescue Medications .....	32
Table 8.c	Sponsor-Supplied Drug.....	33
Table 9.a	Clinical Laboratory Tests .....	40
Table 10.a	Takeda Medically Significant AE List.....	52

**LIST OF IN-TEXT FIGURES**

Figure 6.a	Schematic of Study Design .....	22
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**LIST OF APPENDICES**

Appendix A	Schedule of Study Procedures .....	69
Appendix B	Responsibilities of the Investigator.....	71
Appendix C	Elements of the Subject Informed Consent.....	73

Appendix D Investigator Consent to Use of Personal Information..... 76  
Appendix E GERD Symptoms Investigator Assessment ..... 77  
Appendix F Definition of Heartburn Severity (Daytime/Nighttime)..... 78  
Appendix G eDiary ..... 79  
Appendix H Detailed Description of Amendments to Text..... 80

## 2.0 STUDY SUMMARY

<b>Name of Sponsor(s):</b> Takeda Development Center Asia, Pte. Ltd.		<b>Compound:</b> Dexlansoprazole	
<b>Title of Protocol:</b> A Phase 3 Double Blind Study to Evaluate the Efficacy and Safety of Dexlansoprazole (30 mg QD) compared to Placebo on Heartburn Relief in Subjects With Symptomatic Nonerosive Gastroesophageal Reflux Disease (GERD)		<b>IND No.:</b> Not applicable	<b>EudraCT No.:</b> Not applicable
<b>Study Number:</b> TAK-390MR_302		<b>Phase:</b> 3b	
<b>Study Design:</b> This is a phase 3, randomized, double-blind, multicenter, placebo-controlled, 2-arm study with a 4-week treatment period. The study is designed to evaluate heartburn relief in subjects with symptomatic nonerosive gastroesophageal reflux disease (GERD).			
<b>Primary Objectives:</b> To compare the efficacy of dexlansoprazole capsule (30 mg once daily [QD]) with placebo in relief of daytime and nighttime heartburn over 4 weeks in Chinese subjects with symptomatic nonerosive GERD as assessed by daily electronic diary (eDiary).			
<b>Secondary Objectives:</b> To compare the efficacy of dexlansoprazole capsules (30 mg QD) with placebo in relief of nighttime heartburn over 4 weeks in Chinese subjects with symptomatic nonerosive GERD as assessed by daily eDiary.			
<b>Subject Population:</b> Subjects $\geq 18$ years with symptomatic nonerosive GERD.			
<b>Number of Subjects:</b> Estimated total: 200 subjects Per treatment group: <ul style="list-style-type: none"> <li>100 subjects/dexlansoprazole 30 mg capsules</li> <li>100 subjects/placebo</li> </ul>		<b>Number of Sites:</b> Estimated total: 20 sites in China	
<b>Dose Level(s):</b> Dexlansoprazole 30 mg capsules (QD) Placebo (QD)		<b>Route of Administration:</b> Oral	
<b>Duration of Treatment:</b> 4 weeks		<b>Period of Evaluation:</b> 11 weeks	
<b>Main Criteria for Inclusion:</b> The subject is capable of understanding and complying with protocol requirements. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures. The subject is male or female and aged $\geq 18$ years. Subjects identifying their main symptom as a burning feeling in the mid-epigastric area and/or chest area (ie, heartburn). The subject must have a history of symptomatic GERD for 6 months or longer prior to Screening with GERD symptoms that were responsive to acid-suppressive therapy. The subject must have episodes of heartburn for any 4 or more days during the 7 days prior to Day -1 as recorded in the eDiary. All women of childbearing potential, or men who are sexually active, agree to use adequate contraception from signing of informed consent form (ICF) throughout the duration of the study and for 30 days after the last dose of study medication.			

**Main Criteria for Exclusion:**

The subject has a history or clinical manifestations of serious neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine, hematologic, dermatologic, immunologic, psychiatric disorders, or other abnormality which may impact the ability of the subjects to participate or potentially confound the study results. The subject is required to take excluded medications, or it is anticipated that the subject will require treatment with at least 1 of the disallowed concomitant medications during the study evaluation period as specified in the exclusion medication section (Section 7.3). Within 30 days prior to the Screening Visit, the subject has received any investigational drug or participate another clinical study (other than study TAK-390MR\_301). The subject has a hypersensitivity to any proton pump inhibitor (PPI) (including, but not limited to, lansoprazole, omeprazole, rabeprazole, pantoprazole, esomeprazole or ilaprazole), any component of dexlansoprazole capsules, or antacid (eg, magnesium trisilicate or similar antacid). The subject has a history of cancer, (except basal cell carcinoma of the skin), that has not been in remission for at least 5 years prior to Screening. The subject has a known history of Barrett's esophagus with dysplastic changes or any changes suspicious of Barrett's seen during screening endoscopy. The subject developed acute upper gastrointestinal bleeding, gastric ulcer (a mucosal defect with white coating) or duodenal ulcer (a mucosal defect with white coating), within 30 days before the start of the Screening Visit (with the possible inclusion of those with gastric or duodenal erosion). The subject requires chronic use (>12 doses per month) of nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 (COX-2) NSAIDs within 30 days prior to the Screening Period and throughout the study. The subject has comorbidities that could affect the esophagus (eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal strictures); a history of radiotherapy or cryotherapy of the esophagus; and a history of corrosive or physiochemical injury (with the possible inclusion in the study of those with Schatzki's ring). The subject has a history of surgical procedures that may affect the esophagus (eg, fundoplication and mechanical dilatation for esophageal strictures) or a history of gastric or duodenal surgery other than endoscopic removal of benign polyps. Subjects with erosive esophagitis (EE) as shown by endoscopy, during the Screening Period. The subject has any abnormal laboratory value during screening or Day-1 that suggests a clinically significant underlying disease or condition that may prevent the subject from entering the study, based on the medical judgment of the investigator; or the subject has creatinine >1.5 mg/dL or alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2.5 times the upper limit of normal ( $\times$ ULN) or total bilirubin >2.0 mg/dL. The subject is known to have acquired immunodeficiency syndrome (AIDS) or hepatitis, including hepatitis virus carriers: hepatitis B surface antigen (HBsAg) positive or hepatitis C virus (HCV) antibody positive. The subject has current Zollinger-Ellison syndrome (gastric acid hypersecretion) or a history of gastric acid hypersecretion. The subject is scheduled for surgery that requires hospitalization or requires surgical treatment during his/her participation in the study. The subject has donated or lost >300 mL blood volume, undergone plasmapheresis, or has had a transfusion of any blood product within 90 days prior to the first dose of study drug. The subject has a history of alcohol or drug abuse (defined as any illicit drug use), or drug addiction in the 12 months prior to Screening. If the subject is a pregnant or lactating woman; is intending to become pregnant before, during, or within 30 days after participating in this study; is intending to donate ova during this time period; or is a man who is intending to donate sperm. Any subject who, in the opinion of the investigator, is unable to comply with the requirements of the study or is unsuitable for any reason. The subject with positive serology result of *Helicobacter pylori* (*H. pylori*) that needs eradication therapy during the study participation period as anticipated by the investigator. The subject is an immediate family member, study site employee, is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling), or may consent under duress.

**Main Criteria for Evaluation and Analyses:**

Primary Endpoint: The percentage of days with neither daytime nor nighttime heartburn during treatment as assessed by daily eDiary.

Secondary Endpoint: The percentage of days without nighttime heartburn during treatment as assessed by daily eDiary.

Additional Endpoints: The severity of GERD symptoms at Week 2 and Week 4 as assessed by the investigator. The percentage of days without rescue medication over 4 weeks as assessed by daily eDiary. Safety will be assessed by summarizing the incidence of adverse events (AEs), ECG results, physical examinations, clinical laboratory values, gastrin levels, and vital signs.

**Statistical Considerations:**

**Efficacy Assessments**

The primary efficacy variable will be the percentage of days with neither daytime nor nighttime heartburn over 4 weeks as assessed by daily eDiary. Comparisons between dexlansoprazole capsules and placebo will be made using a Wilcoxon rank-sum test.

The secondary efficacy variable will be the percentage of days without nighttime heartburn over 4 weeks as assessed by daily eDiary. Comparisons between dexlansoprazole capsules and placebo will be made using a Wilcoxon rank-sum test.

**Safety Assessments**

Safety will be assessed by summarizing the incidence of AEs, clinical laboratory values, physical examinations, gastrin levels, ECG, and vital signs using the safety analysis set.

**Sample Size Justification:**

A total of 200 subjects are planned to be enrolled into this study to ensure 160 subjects with symptomatic nonerosive GERD will complete the study (assuming a 20% dropout rate). The sample size of 80 subjects per treatment group will provide at least 95% power at the 0.05 two-sided significance level to detect a difference of 25% in the mean percentage of days without daytime or nighttime heartburn over 4 weeks between dexlansoprazole capsules (50%) and placebo (25%). The dexlansoprazole capsules and placebo rates were estimated from prior dexlansoprazole Study T-GD05-137. The common standard deviation was assumed to be 35%.

### **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 in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

#### **3.2 Coordinating Investigator**

TDC Asia will select a signatory coordinating investigator (CI) from the investigators who participate in the study and enroll at least 1 subject. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The signatory CI will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

### 3.3 List of Abbreviations

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BID	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CI	coordinating investigator
C <sub>max</sub>	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COX-2	cyclo-oxygenase-2
CRO	contract research organization
CYP	cytochrome P450
ECG	electrocardiogram
ECL	enterochromaffin-like
eCRF	electronic case report form
EE	erosive esophagitis
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GGT	$\gamma$ -glutamyl transferase
(H <sup>+</sup> , K <sup>+</sup> )-ATPase	hydrogen, potassium adenosine triphosphatase
H2RA	histamine2-receptor antagonist
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
<i>H. pylori</i>	<i>Helicobacter pylori</i>
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board



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IUD	intrauterine device
IWRS	interactive web response system
LA	Los Angeles
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MR	modified-release
NSAID	nonsteroidal anti-inflammatory drug
OE	over encapsulated
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency of Japan
PPI	proton pump inhibitor
PTE	pretreatment event
QD	once daily
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
TCM	traditional Chinese medicine
TEAE	treatment-emergent adverse event
$t_{\max}$	time to reach $C_{\max}$
Total CO <sub>2</sub>	bicarbonate
TRAE	treatment-related adverse event
ULN	upper limit of normal
US	United States
WHODRUG	World Health Organization Drug Dictionary

### **3.4 Corporate Identification**

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

## 4.0 INTRODUCTION

### 4.1 Background

Gastroesophageal reflux disease (GERD) is a common recurring medical problem in the adult population with a prevalence between 10% to 20% in the Western world and less than 5% in Asia [1]. Prevalence of GERD-related symptoms ranges from at least once a month in approximately 40%, once a week in 20%, to daily in 14% of patients [1,2]. A number of risk factors, such as advancing age, obesity, smoking, and alcohol and caffeine consumption have all been associated with the development of GERD [1]. Gastroesophageal reflux disease affects men and women in nearly equal proportions; however, men develop erosive esophagitis (EE) and Barrett's esophagus more often than women [1], and women develop nonerosive GERD more often than men [3]. GERD results in substantial morbidity due to the occurrence of serious complications [4,5] and its adverse impact on quality of life (QOL) [6].

Gastroesophageal reflux disease comprises a spectrum of acid-related disorders, including nonerosive GERD and EE. Nonerosive GERD is defined as the presence of symptoms caused by intraesophageal acid reflux in patients with absence of endoscopically observed injury to the esophageal mucosa [7]. EE is defined as the presence of superficial esophageal erosions in patients with or without typical GERD symptoms.

Patients who do not receive treatment, or in whom acid reflux is not effectively controlled, are at risk of developing significant complications, such as bleeding, strictures, and Barrett's esophagus [4]. Other complications of gastroesophageal reflux, such as dysphagia, chronic cough, laryngitis, and sleep disturbance can be troublesome or painful for the patient, thereby impairing well-being.

Therapy for GERD is largely focused on the prevention of reflux of gastric acid into the esophagus, either by pharmacological or surgical means, with surgery usually reserved for intractable cases. Pharmacological management of GERD includes treatment with antacids, histamine<sub>2</sub>-receptor antagonists (H<sub>2</sub>RA), prokinetic agents, and proton pump inhibitors (PPIs). PPIs, which are labeled for once daily (QD) dosing, are the most effective medications for relieving GERD symptoms, healing the injured mucosa, maintaining a healed mucosa, and preventing the development of complications [8].

However, significant challenges remain in the treatment of patients with endoscopically negative GERD, moderate to severe esophageal erosions (Los Angeles [LA] Classification Grades C and D) [9] or ulcers, and other GERD-related symptoms. This is reflected by the high number of prescriptions written for twice daily (BID) dosing of currently available PPIs [10]. BID dosing with PPIs in itself represents a current challenge in treatment, because a dosing frequency for a PPI greater than QD has been shown to increase the probability of discontinuation of treatment and to reduce the rate of adherence to therapy [11]. In addition, concomitant antacid use has been reported by 37% of patients receiving PPIs [12]. This concomitant antacid use among some PPI users suggests that currently available PPIs may not achieve sufficient acid control when used as monotherapy for symptom relief. In addition, 79% of individuals with weekly heartburn also report nighttime heartburn. Approximately 60% of individuals with nighttime symptoms experience interference with sleep, which may affect daytime activities and quality-of-life [13].

To further enhance the potential for dexlansoprazole capsules to demonstrate clinical benefit, especially in treating patients with unmet medical needs, Takeda Global Research & Development Center, Inc. now known as Takeda Development Center Americas, Inc. (TDC Americas) developed a dual delayed-release formulation of dexlansoprazole, referred to as dexlansoprazole modified-release (MR). This novel formulation consists of 2 types of granules contained within a single capsule. Each type of granule has a different pH-dependent release profile. The first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours. This dual delayed release formulation is designed to extend the duration of drug exposure and maintain pharmacologically active levels of drug over a longer time period. As a result, the pharmacokinetic (PK) profile of dexlansoprazole following the administration of dexlansoprazole capsules is characterized by a concentration-time profile with 2 distinct peaks. In order to achieve this 2-peak, prolonged PK profile, dexlansoprazole MR releases drug substance over a longer period of time, thus requiring higher daily doses and consequently higher area under the plasma concentration-time curves (AUCs), without a commensurate increase in maximum observed plasma concentration ( $C_{max}$ ), compared with that following administration of the conventional lansoprazole formulation.

Dexlansoprazole 30 mg capsules are approved for use in adults in over 30 countries for treatment of heartburn associated with symptomatic nonerosive GERD, and maintenance of healed EE, and 60 mg capsules are approved for healing of EE.

In the United States (US) registration trials, dexlansoprazole capsules were evaluated in 5072 subjects in many phase 1 studies and in the phase 3 healing of EE, maintenance of healed EE, symptomatic nonerosive GERD, and long-term safety studies. A total of 282 subjects were exposed to doses of either 60 or 90 mg for  $\geq 52$  weeks, 382 subjects were exposed to doses of either 60 or 90 mg for  $\geq 48$  weeks and 863 subjects to doses of 30, 60, or 90 mg for 6 months ( $\geq 24$  weeks). No safety concerns were noted in phase 1 studies of dexlansoprazole capsules in healthy volunteers and selected patient groups. No prolongation of QT interval was observed using doses up to 300 mg (T-P104-092). Five separate drug-drug interaction studies using dexlansoprazole capsule 60 mg or 90 mg (in which no PK interactions were seen with diazepam, phenytoin, theophylline, or warfarin and no pharmacodynamic interactions were seen with warfarin or clopidogrel) revealed no trends in adverse events (AEs) (T-P105-134, T-P105-133, T-P105-132, T-P105-139, and TAK-390MR\_101). As expected with PPI therapy, mean serum gastrin levels increased 1- to 2-fold during the first 3 months of receiving dexlansoprazole capsules in 2 6-month maintenance studies (T-EE04-086 and T-EE05-135) and a long-term (12-month) safety study (T-GI04-088), and then generally stabilized for the remainder of treatment. These increases in gastrin levels were not dependent on the dose of dexlansoprazole capsules. In a phase 1 study in healthy volunteers, gastrin levels returned to Baseline within 7 days of last dose of dexlansoprazole capsules [14]. In the maintenance of healed EE studies, and in the long term safety study, no clinically important differences in gastric biopsy results were observed between any of the dexlansoprazole capsule treatment groups and placebo. In the long-term safety study, chronic gastritis (in either antral or fundic tissue) was the most commonly reported abnormality in 31% and 36% of patients in the dexlansoprazole capsules 60 and 90 mg groups respectively. There

were no reports of enterochromaffin cell-like (ECL) hyperplasia in the phase 3 studies of 6 months to 1 year duration.

Gender had no effect on either the rate (time to reach  $C_{max}$  [ $t_{max}$ ]) or extent ( $C_{max}$  and AUC) of dexlansoprazole absorption following the administration of dexlansoprazole capsules (T-P105-119). Although mean  $t_{max}$  values were approximately 2 hours shorter in subjects 18 to 40 years of age compared with subjects 65 to 80 years of age, the extent of absorption as measured by  $C_{max}$  and AUC was not statistically significantly different between young and elderly subjects (T-P105-119). While hepatic impairment had no effect on the rate of absorption, dexlansoprazole  $C_{max}$  and AUC values in subjects with moderate hepatic impairment were approximately 2 times higher compared with those in subjects who have normal hepatic function, likely due to decreased clearance (T-P105-115).

Dexlansoprazole is extensively metabolized in the liver to inactive metabolites by oxidation, reduction, and subsequent formation of sulfate, glucuronide, and glutathione conjugates. Oxidative metabolites are formed by the cytochrome P450 (CYP) enzyme system, including hydroxylation mainly by CYP2C19 and oxidation by CYP3A4. Following the administration of a [ $^{14}C$ ]dexlansoprazole dose, the major circulating component in plasma was dexlansoprazole regardless of CYP2C19 metabolizer status, and no single metabolite accounted for more than 10% of the plasma total radioactivity through 6 hours postdose (T-P106-141). Although 51% of the administered [ $^{14}C$ ]dexlansoprazole dose was excreted in the urine, no unchanged dexlansoprazole was present in the urine. The remaining 48% of the radioactive dose was recovered in the feces.

All dexlansoprazole capsule doses were well tolerated and demonstrated an acceptable safety profile similar to that of lansoprazole 30 mg.

#### 4.2 Rationale for the Proposed Study

Phase 3 studies performed in the United States have demonstrated positive results using dexlansoprazole capsules on the relief of heartburn in subjects with symptomatic nonerosive GERD. This study will be the first to examine the effectiveness and safety of dexlansoprazole capsules in Chinese subjects with symptomatic nonerosive GERD. Takeda has developed dexlansoprazole in a dual delayed-release capsule formulation (dexlansoprazole capsules) as a new therapy for treating acid related disorders including symptomatic nonerosive GERD, healing of EE, and maintenance of healed EE. All tested dexlansoprazole doses were effective in controlling and preventing the return of heartburn and other GERD symptoms, healing EE, preventing relapse of EE and maintaining QOL.

## **5.0 STUDY OBJECTIVES AND ENDPOINTS**

### **5.1 Objectives**

#### **5.1.1 Primary Objective**

The primary objective is to compare the efficacy of dexlansoprazole capsule (30 mg QD) and placebo in relief of daytime and nighttime heartburn over 4 weeks in Chinese subjects with symptomatic nonerosive GERD as assessed by daily electronic diary (eDiary).

#### **5.1.2 Secondary Objective**

To compare the efficacy of dexlansoprazole capsules (30 mg QD) and placebo in relief of nighttime heartburn over 4 weeks in Chinese subjects with symptomatic nonerosive GERD as assessed by daily eDiary.

#### **5.1.3 Additional Objectives**

- To compare the efficacy of dexlansoprazole capsule (30 mg QD) with placebo as measured by the severity of GERD symptoms at Week 2 and Week 4 as assessed by the investigator.
- To compare the efficacy of dexlansoprazole capsule (30 mg QD) with placebo in Chinese subjects with symptomatic nonerosive GERD as measured by the percentage of days without rescue medication over 4 weeks as assessed by daily eDiary.
- To compare the safety of dexlansoprazole capsule (30 mg QD) with placebo in Chinese subjects with symptomatic nonerosive GERD.

### **5.2 Endpoints**

#### **5.2.1 Primary Endpoint**

The primary endpoint is the percentage of days with neither daytime nor nighttime heartburn over 4 weeks as assessed by daily eDiary.

#### **5.2.2 Secondary Endpoint**

The secondary endpoint is the percentage of days without nighttime heartburn over 4 weeks as assessed by daily eDiary.

#### **5.2.3 Additional Endpoints**

- The severity of GERD symptoms at Weeks 2 and 4 as assessed by the investigator.
- The percentage of days without rescue medication over 4 weeks as assessed by daily eDiary.
- Safety will be assessed by summarizing the incidence of AEs, electrocardiogram (ECG) results, clinical laboratory values, gastrin levels, physical examinations, and vital signs.

## 6.0 STUDY DESIGN AND DESCRIPTION

### 6.1 Study Design

This is a phase 3, randomized, double-blind, multicenter, placebo-controlled, 2-arm study with a 4-week treatment period. This study will compare the efficacy of dexlansoprazole capsule (30 mg QD) with that of placebo when administered orally as a single daily dose in the morning, without regard to food. The study is designed to evaluate heartburn relief in subjects with symptomatic nonerosive GERD. Approximately 200 subjects, 18 years and above will be enrolled at approximately 20 sites across China.

The study consists of 2 periods: a Screening Period, which will last a maximum of 21 days, and a Treatment Period, which will last 4 weeks.

After signing an informed consent form (ICF), subjects will undergo a Screening Period. Subjects will be instructed that lifestyle or behavioral modifications designed to treat their symptoms of GERD should not be altered throughout the study.

During the Screening Period, subjects will undergo various procedures to determine eligibility for the Treatment Period. Screening evaluations will include the following: demographics, medical and social history, physical examination including vital signs, height and weight, ECG, endoscopy, clinical laboratory evaluations including hepatitis panel, urine and serum pregnancy test (all women subjects of childbearing potential), and concomitant medication assessment. The screening clinical laboratory tests, hepatitis panel, and endoscopy must be performed within 14 days prior to randomization. Subjects will be given rescue medication and eDiary on the first day of the Screening Period. Throughout the Screening Period, subjects will record their usage of rescue medication and document the presence and maximum severity of daytime and nighttime heartburn symptoms each day in their eDiary. Endoscopy data will be collected to exclude subjects with EE. Endoscopic pictures will be taken by the study site and kept in the site's source document files according to the site's practice. It may be collected by Takeda as necessary.

Subjects who satisfy the screening evaluation and selection criteria may be entered into the study. Subjects who identified heartburn as their primary symptom, had a history of heartburn episodes for 6 months or longer, experienced heartburn on at least 4 of the 7 days preceding Study Day -1, and showed macroscopically normal esophageal mucosa at the Screening endoscopy, will be eligible for the Treatment Period in this study. Subjects having an esophageal stricture will be excluded from the study. The endoscope must pass freely into the stomach during the endoscopy. The rescue medication will be supplied during the screening period.

All subjects will return to the investigative site on Day -1, which will be deemed as the Baseline. Subjects who have completed all of the Screening procedures and met all eligibility requirements and none of the exclusion criteria will have routine fasting laboratory evaluations including fasting serum gastrin, a urine pregnancy test (all women subjects of childbearing potential), a physical examination and vital signs measurements to assure continued eligibility. In addition, subjects will be assessed for GERD symptoms such as heartburn, acid regurgitation, dysphagia, belching, and epigastric pain by investigator assessment.

Subjects will be dispensed study drug on Day -1 according to an Interactive Web Response System (IWRS) and will begin taking study drug at the following day (Day 1). Rescue medication will continue to be supplied during the Treatment Period.

Subjects will be randomized in a 1:1 ratio to one of the following 2 treatment groups during the 4-week Treatment Period:

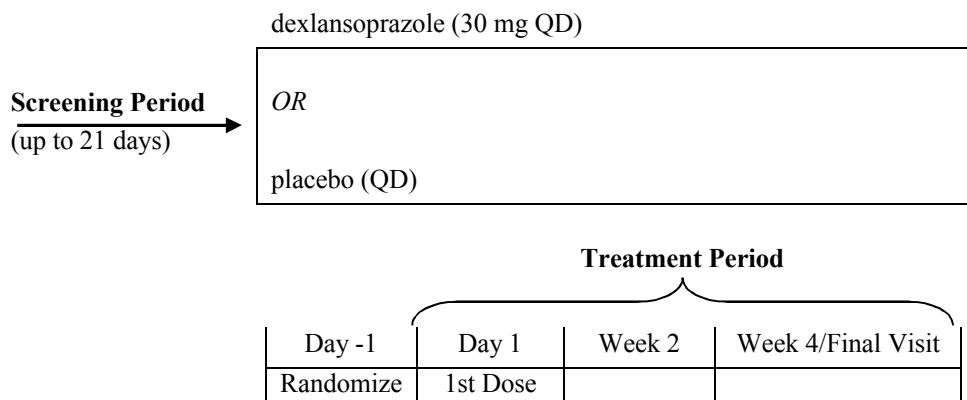
Group I: dexlansoprazole capsules (30 mg QD)

Group II: placebo (QD)

During this 4-week Treatment Period, study drug will be self-administered, orally, once a day, in the morning, without regard to food. Subjects will continue to document the presence and maximum severity of daytime and nighttime heartburn symptoms and record usage of rescue medication using an eDiary. Subject visits will be conducted at Weeks 2 and 4 of the Treatment Period to collect and/or dispense study drug, assess GERD symptoms, review concomitant medication use, assess adverse events and subject will undergo a physical examination including vital signs. In addition, at the Week 4/ Final Visit, all subjects will undergo laboratory evaluations, ECG, fasting serum gastrin and urine pregnancy test (all women of childbearing potential). Subjects who prematurely discontinue during the study after the randomization should undergo Week 4/Final Visit procedures no later than 5 days after the last dose of study drug.

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

**Figure 6.a Schematic of Study Design**



## 6.2 Justification for Study Design, Dose, and Endpoints

Subjects with history of heartburn episodes for 6 months or longer and endoscopically proven normal esophageal mucosa is an appropriate population to evaluate efficacy and safety of dexlansoprazole 30 mg capsules QD compared with that of placebo when administered orally as a single daily dose in the morning. The study is designed to evaluate symptom relief in subjects with symptomatic nonerosive GERD. The study design, endpoints and dose of dexlansoprazole 30 mg capsules QD has been selected based on the results of completed multicenter controlled

registration phase 3 studies, where 30 mg of dexlansoprazole capsules (QD) was found to be the lowest effective dose tested.

The efficacy and safety measurements and the clinical and routine laboratory procedures used in this study are considered standard and generally accepted.

### **6.3 Premature Termination or Suspension of Study or Investigational Site**

#### **6.3.1 Criteria for Premature Termination or Suspension of the Study**

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

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

#### **6.3.2 Criteria for Premature Termination or Suspension of Investigational Sites**

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

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

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



## 7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

### 7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is a man or woman and aged at least 18 years.
4. Subjects identifying their main symptom as a burning feeling in the mid epigastric area and/or chest area (ie, heartburn).
5. The subject must have a history of symptomatic GERD for 6 months or longer prior to Screening with GERD symptoms that were responsive to acid-suppressive therapy.
6. The subject must have episodes of heartburn for any 4 or more days during the 7 days prior to Day -1 as recorded in the eDiary.
7. All women subjects of child bearing potential who are sexually active agree to routinely use adequate contraception from signing of the informed consent throughout the duration of the study and for 30 days after the last dose of study medication.
8. All men subjects who are nonsterilized\* and sexually active with women partner of childbearing potential\* agree to use adequate contraception\* from signing of informed consent throughout the duration of the study and for 30 days after the last dose of study medication.

\*Definitions and acceptable methods of contraception are defined in Section 9.1.11 Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 9.1.12 Pregnancy.

### 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 a history or clinical manifestations of serious neurologic, cardiovascular, pulmonary, hepatic, renal, metabolic, gastrointestinal, urological, endocrine, hematologic, dermatologic, immunologic, psychiatric disorders, or other abnormality which may impact the ability of the subjects to participate or potentially confound the study results.
2. The subject is required to take excluded medications, or it is anticipated that the subject will require treatment with at least 1 of the disallowed concomitant medications during the study evaluation period as specified in the exclusion medication section (section 7.3).

3. The subject has received any investigational drug or participated in another clinical study (other than study TAK-390MR\_301) within 30 days prior to the Screening Visit.
4. The subject has a hypersensitivity to any PPI (including, but not limited to, lansoprazole, omeprazole, rabeprazole, pantoprazole, esomeprazole or ilaprazole), any component of dexlansoprazole, or antacid (eg, magnesium trisilicate or similar antacid).
5. The subject has a history of cancer, (except basal cell carcinoma of the skin), that has not been in remission for at least 5 years prior to Screening.
6. The subject has a known history of Barrett's esophagus with dysplastic changes or any changes suspicious of Barrett's seen during screening endoscopy.
7. The subject developed acute upper gastrointestinal bleeding, gastric ulcer (a mucosal defect with white coating) or duodenal ulcer (a mucosal defect with white coating), within 30 days before the start of the Screening Visit (with the possible inclusion of those with gastric or duodenal erosion). The subject requires chronic use (>12 doses per month) of nonsteroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 (COX-2) NSAIDs within 30 days prior to the Screening Period and throughout the study.
8. The subject has comorbidities that could affect the esophagus (eosinophilic esophagitis, esophageal varices, scleroderma, viral or fungal infection, esophageal strictures); a history of radiotherapy or cryotherapy of the esophagus; and a history of corrosive or physiochemical injury (with the possible inclusion in the study of those with Schatzki's ring).
9. The subject has a history of surgical procedures that may affect the esophagus (eg, fundoplication and mechanical dilatation for esophageal strictures) or a history of gastric or duodenal surgery other than endoscopic removal of benign polyps.
10. Subjects with EE as shown by endoscopy, during the Screening Period.
11. The subject has any abnormal laboratory value during screening or Day-1 that suggests a clinically significant underlying disease or condition that may prevent the subject from entering the study, based on the medical judgment of the investigator, or the subject has:
  - a) Creatinine >1.5 mg/dL or
  - b) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >2.5 times the upper limit of normal ( $\times$ ULN) or
  - c) Total bilirubin >2.0 mg/dL
12. The subject is known to have acquired immunodeficiency syndrome (AIDS) or hepatitis, including hepatitis virus carriers: (ie, hepatitis B surface antigen HBs-antigen (HBsAg) positive or hepatitis C virus (HCV)-antibody positive).
13. The subject has current Zollinger-Ellison syndrome or a history of gastric acid hypersecretion.
14. The subject is scheduled for surgery that requires hospitalization or requires surgical treatment during his/her participation in the study.

15. The subject has donated or lost >300 mL blood volume, undergone plasmapheresis, or has had a transfusion of any blood product within 90 days prior to the first dose of study drug.
16. The subject has a history of alcohol or drug abuse (defined as any illicit drug use), or drug addiction in the 12 months prior to Screening.
17. If the subject is a pregnant or lactating woman; is intending to become pregnant before, during, or within 30 days after participating in this study; is intending to donate ova during this time period; or is a man who is intending to donate sperm.
18. Any subject who, in the opinion of the investigator, is unable to comply with the requirements of the study or is unsuitable for any reason.
19. The subject with positive serology result of *Helicobacter pylori* (*H. pylori*) that needs eradication therapy during the study participation period as anticipated by the investigator.
20. The subject is an immediate family member, study site employee, is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling), or may consent under duress.

### 7.3 Excluded Medications and Treatments

The substances listed in [Table 7.a](#) are excluded from the time points indicated and for the duration of subject's participation in the study. Subjects must be instructed not to take any medications, including over-the-counter products or traditional Chinese medicines (TCM) without first consulting with the investigator.

**Table 7.a Excluded Medications**

<b>Excluded Medications</b>	<b>Period of Exclusion</b>
Prescription or nonprescription H2RA	During Screening and throughout the study.
Antacids (except the rescue medications or similar antacid)	During Screening and throughout the study.
PPIs (except study-supplied dexlansoprazole)	During Screening and throughout the study.
NSAIDs, chronic use (>12 doses/month) including COX 2 NSAIDs	Within 30 days prior to Screening and throughout the study.
Drugs with significant anticholinergic effects such as tricyclic antidepressants or drugs with CNS effects that could mask perception of symptoms (eg, SSRI, benzodiazepines).	During Screening and throughout the study. However, subjects who have remained on a stable regimen and dose of these medications for 30 days prior to Day -1 and who agree to maintain the same regimen and dose during the trial including the screening and treatment period will qualify. Also, short-term use of anticholinergics for trial-related procedures is not exclusionary.
Misoprostol	During Screening and throughout the study.
Prokinetics (including metoclopramide, cisapride, tegaserod)	During Screening and throughout the study.
Anticoagulant or antiplatelet therapy	During Screening and throughout the study.
Medications with pH-dependent absorption*	During Screening and throughout the study
Methotrexate **	During Screening and throughout the study
Other: bethanechol	During Screening and throughout the study

H2RA=histamine 2-receptor antagonist, SSRI=selective serotonin reuptake inhibitor.

\*Consideration of coadministration is based on clinically meaningful differences in efficacy or safety of medication due to pH dependent absorption.

\*\*The investigator or designee should discuss methotrexate use with the medical monitor on a case by case basis if the methotrexate treatment is necessary throughout the study.

#### **7.4 Diet, Fluid, Activity Control**

The principal investigator, the coinvestigators, and the study collaborators are to explain, and give instructions on, the following before the start of the study or during the study, as well as to check to see if the subjects keep to the instructions at the time of their scheduled visits.

- Every subject should keep to the scheduled visits, seek medical consultation, and undergo predetermined laboratory tests.
- The subject should ensure that all study medications are swallowed with approximately 240 mL water according to the administration, and dosing schedule. Subjects should be instructed according to Section 8.1.3.1 (Missed Doses) and 9.2 (Compliance). Details of any missed or forgotten doses should be reported to the Investigator or designee at the subsequent study visit.
- The subject should store all medications in a cool, dry, safe place which is out of reach of children and to bring all study supplies (empty / used / unused drug packets and diaries alike) to each study visit.

- The subject should record his/her nighttime (during sleep) subjective symptoms and the previous daytime subjective symptoms in his/her subject eDiary upon rising in the morning on a daily basis. The subject should also record the use of rescue medication during Screening Period and his/her rescue medication and study medication compliance status during the Treatment Phase.
- The subject will be required to fast for at least 8 hours before each visit at which fasted blood tests will be drawn and/or endoscopy will be performed, after the ICF is signed. Fasting is defined as no food or nutritional drinks for 8 hours before the blood draw. Water is allowed. Any medication that needs to be taken with food and any study medications should be held until after the fasting blood has been drawn and/or the endoscopy has been performed. Medication that does not need to be taken with food should be continued. The investigator must instruct the subject accordingly prior to visits in which serum gastrin is measured and endoscopy is performed.
- After the first dose of study drug during the Treatment Phase, the subject should present to the clinic in the morning as scheduled.
- The subject should consult with the study investigator or designee prior to being treated by physicians other than the study investigator. All other medications such as over-the-counter drugs beyond those prescribed for the study should be reported at the next study visit.
- The subject should report on all subjective or objective symptoms experienced (ie, including details of day of onset, severity, outcome, and day of outcome) at every visit. In case of emergency such as occurrence of a serious adverse event (SAE), the subject, family, or legal designee should contact the principal investigator as soon as possible.
- The subject should use contraception without fail. A woman of childbearing potential will agree to use contraception from signing of informed consent throughout the duration of the study and 30 days after the final dose of the study medication. Pregnancy in a female subject, if found, should be reported immediately.
- The subject should not donate blood during the study.
- The subject should refrain from excessive drinking and eating, and any extreme diet change (eg, change to an extremely high-fat diet) or excessive exercise throughout the study. Subjects will be instructed to maintain usual food intake, sleep habits, consistent activity, and caffeine intake throughout the study.

### **7.5 Criteria for Discontinuation or Withdrawal of a Subject**

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

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

- Liver Function Test 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 9.1.10), 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 postrandomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject’s health.
- 3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject’s source documents.
- 4. Voluntary withdrawal. The subject (or subject’s legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE or lack of efficacy should not be recorded in the “voluntary withdrawal” category).
- 5. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
- 6. Pregnancy. The subject is found to be pregnant.

Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.12.
- 7. Lack of efficacy. The investigator has determined that the subject is not benefiting from investigational treatment; and, continued participation would pose an unacceptable risk to the subject.
- 8. Other.

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

## 7.6 Procedures for Discontinuation or Withdrawal of a Subject

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

## 8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

### 8.1 Study Medication and Materials

Once a subject meets all eligibility criteria, the site will randomize the subject via IWRS, which will assign a unique study drug identification number. The subject will be randomized in a 1:1 ratio into 1 of 2 treatment groups in the study:

- Dexlansoprazole 30 mg capsules.
- Placebo capsules.

Subjects will receive study drug for 4 Weeks.

#### 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 sites will be supplied with double-blind study medication containing dexlansoprazole 30 mg capsules or matching placebo blister cards, as shown in [Table 8.a](#).

**Table 8.a Study Drugs**

Study Drugs	Dosage Strength/Dosage Form	Manufacturer
Dexlansoprazole	30 mg capsules	Takeda Pharmaceutical Company Ltd.
Placebo	capsules (dose is not applicable)	Takeda Pharmaceutical Company Ltd.

The study sites will be supplied with study medication that is blinded via over encapsulation (OE) of dexlansoprazole 30 mg capsules and placebo. The study drug will be foil/foil blistered and packaged in 7-day child resistant blister cards containing 7 OE capsules. Each card will have a single-panel multilingual label that will contain, but will not be limited to: protocol number, medication identification (ID) number, name and strength of the product, quantity of dosage unit, directions for use, storage conditions, country specific regulatory caution statement, and name and address of the sponsor. The matching placebo capsules will be manufactured by Takeda Pharmaceutical Company Ltd. The study medication is overencapsulated, foil/foil blistered, packaged, labeled and distributed by Fisher Clinical Services.

##### 8.1.1.1 Investigational Drug

The investigational drugs are manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan. The active capsule contains drug substance and excipients. The placebo capsules contain excipients only. The study medication is overencapsulated, foil/foil blistered, packaged, labeled, and distributed by Fisher Clinical Services.



- OE dexlansoprazole 30 mg capsules.
- OE placebo.

#### 8.1.1.2 Rescue Medication

During the study, including the during Screening Period, over-the-counter medications such as Talcid chewable tablets (hydrotalcite) or Gaviscon tablets can be used as rescue medication if the symptoms caused by acid reflux cannot be tolerated by the subjects. The investigator or designee will give medical instructions to the subject regarding the use of rescue medication during the dispensing visits. Subjects shall be instructed to refrain from using rescue medication unless necessary to manage symptoms. Proper documentation of use is required. Subjects shall contact the investigators if they would like to take the rescue medication at a dose higher than approved in the local package insert.

The use of rescue medication shall be recorded in the subject daily eDiary.

The institution or its designee will help to source the rescue medication for the subjects as necessary, or alternatively, subject may buy the rescue medication from the pharmacy and be reimbursed.

Rescue medications include those listed in [Table 8.b](#):

**Table 8.b Rescue Medications**

Rescue Medication (Active Ingredients in Each Tablet)	Dosage Strength (mg)	Manufacturer
Talcid chewable tablets (hydrotalcite)	500 mg	Bayer China Ltd.
Gaviscon Tablets	aluminum hydroxide 0.05 g magnesium trisilicate 0.0125 g alginic acid 0.25g	Local China domestic companies

If the listed rescue medications are not available, the subject should contact the subject's responsible investigator for confirmation of available brand. During the rescue medication administration, the following should be noted:

1. The administration of rescue medication shall be in accordance with the local package insert;
2. For aluminum based medications, an interval of at least 2 hours must be maintained between administration of study medication (or placebo) and rescue medication;
3. When rescue medication has been taken for more than 7 consecutive days, or more than 25% of the days in whole study period, the investigator should discuss with CRO/sponsor and decide whether to withdraw the subject.

### 8.1.1.3 Sponsor-Supplied Drug

- OE dexlansoprazole 30 mg capsules.
- OE placebo capsules.

### 8.1.2 Storage

All clinical trial material must be kept in an appropriate, limited-access, secure location until it is used or returned to the sponsor or designee for destruction. All sponsor-supplied drugs must be stored under the conditions specified on the label, and remain in the original container until dispensed.

All study medication supplied for the study must be stored as follows:

Store at: 20°C to 25°C; excursions allowed between 15°C and 30°C.

A daily temperature log of the drug storage area must be maintained every working day.

Temperature excursions must be reported to the sponsor or designee.

The investigator should ensure that study drug is used only in accordance with the approved protocol. Study drug shall be dispensed only to subjects enrolled in the study.

### 8.1.3 Dose and Regimen

Once a subject meets all inclusion criteria and none of the exclusion criteria, the site will randomize the subject on Study Day -1 via the IWRS, which will assign a study drug kit number. The study drug kit number will encode the subject's randomization to 1 of the 2 arms (dexlansoprazole 30 mg capsules QD or placebo QD) of the study at a ratio of 1:1, according to the randomization schedules generated prior to study start.

Subjects will receive three 7-day cards on Study Day -1 and Week 2. All subjects will self-administer 1 dexlansoprazole capsule QD or placebo QD at approximately the same time each morning without regard to food. The dose of study drug will be taken with a sip of water on the day of the fasting lab visit. Subjects should continue taking study drug so that the last dose is taken in the morning of the day before the Final Visit (Visit 4).

**Table 8.c Sponsor-Supplied Drug**

<b>Investigational Product</b>	<b>Formulation</b>	<b>Dosage</b>	<b>Mode of Administration</b>	<b>Manufacturer and Location</b>
Dexlansoprazole	30 mg capsule	30 mg QD AM	Oral	Takeda Pharmaceutical Company Ltd.
Placebo	0 mg capsule	0 mg QD AM	Oral	Takeda Pharmaceutical Company Ltd.

### 8.1.3.1 Missed Doses

Subjects should be instructed that all doses of study medication (dexlansoprazole capsules or placebo) should be taken on time. Subjects should also be instructed that if any dose is missed inadvertently it is acceptable for that dose to be taken within 12 hours of the time that it was due. If more than 12 hours have passed since the dose was due, it should not be taken, but instead subjects should be instructed to report the missed dose to the investigator or designee during the next visit.

### 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. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0, Pretreatment Events and Adverse Event.

Serious adverse events (SAEs) of 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

An IWRS will be used for the study.

The investigator or investigator's designee will access the IWRS at Screening to obtain the subject identification number. The investigator or the investigator's designee will utilize the IWRS to enroll the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. The medication ID number of the investigational drug to be dispensed will then be provided by the IWRS. If sponsor-supplied drug is lost or damaged, the site can request a replacement from IWRS. (Refer to IWRS manual provided separately). At subsequent drug-dispensing visits, the investigator or designee will again contact the IWRS to request additional investigational drug for a subject.

## 8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor or designee will generate the randomization schedule prior to the start of the study.

Once a subject meets all admission criteria, the site will randomize the subject via the IWRS, which will assign a study drug kit number for the Treatment Period. The study drug kit number will encode the subject's randomization to 1 of the 2 arms (dexlansoprazole 30 mg QD, or placebo QD) at a ratio of 1:1, according to the randomization schedules generated prior to study start.

All randomization information will be stored in a secured area, accessible only by authorized personnel.

#### **8.4 Investigational Drug Blind Maintenance**

The investigational drug blind will be maintained using the IWRS.

#### **8.5 Unblinding Procedure**

The investigational drug blind shall not be broken by the investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational drug blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational drug blind can be obtained by the investigator, by accessing the IWRS.

The sponsor must be notified as soon as possible if the investigational drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

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

#### **8.6 Accountability and Destruction of Sponsor-Supplied Drugs**

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

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug (dexlansoprazole 30 mg capsules, placebo), the investigator must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

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

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

- Frequently verifying that actual inventory matches documented inventory.

- Verifying that the log is completed for the drug lot (or medication ID number) used to prepare each dose.
- Verifying that all containers used and unused are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

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

The investigator must record the current inventory of all sponsor-supplied drugs (dexlansoprazole 30 mg capsules, placebo) on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, 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.

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

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

## 9.0 STUDY PLAN

### 9.1 Study Procedures

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

#### 9.1.1 Informed Consent Procedure

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

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

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

#### 9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include: date of birth, sex, race as described by the subject, smoking status, history of use of alcohol and caffeine-containing drinks, history of *H. pylori* eradication therapy (eg, triple therapy with PPI + amoxicillin + clarithromycin), and date of completion of such therapy (within the past 1 year/more than 1 year) of the subject at Screening Period.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that stopped at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section [9.1.9](#)). Medical history will include the following:

- Nonerosive GERD.
- Other upper gastrointestinal (GI) diseases including gastric ulcer, duodenal ulcer, or procedures.

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

- PPIs.
- H2RA.

#### 9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the pretreatment assessment immediately prior to the start of investigational drug) will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system;

(10) lymph nodes; (11) other. All subsequent physical examinations should assess clinically significant changes from the baseline examination.

#### 9.1.4 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and with shoes off. Body mass index (BMI) is calculated by sponsor or its designee using metric units with the formula provided below.

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

#### 9.1.5 Vital Sign Procedure

Vital sign measurements including body temperature (oral, tympanic, or infra-axillary in Centigrade), blood pressure (systolic and diastolic) and pulse (beats per minute) will be collected. Blood pressure and pulse will be measured while the subjects are in a sitting position after they have been seated for at least 5 minutes. Vital signs will be assessed at all time points specified in the 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 withdrawal.

#### 9.1.6 GERD Symptoms Investigator Assessment

Subjects will have a GERD symptom assessment performed by the investigator during the Screening Period (on Day -1) and at the Week 4/Final Visits of the Treatment Period. The maximum severity of the GERD symptoms of heartburn, acid regurgitation, dysphagia, belching and epigastric pain will be assessed by appropriate site personnel as either none, mild, moderate, severe, or very severe as defined below, during the 7 days prior to the subject's study visit and recorded on the appropriate eCRF. The definitions for the symptoms being assessed are:

- Heartburn: A burning feeling in the mid epigastric area and/or chest area.
- Acid regurgitation: Flow of sour or bitter fluid into the mouth.
- Dysphagia: Difficulty in swallowing.
- Belching: The voiding of gas from the stomach through the mouth, which may be associated with acid regurgitation.
- Epigastric pain: Central upper abdominal pain.
- None: No symptoms.
- Mild: Symptom does not last long and is easily tolerated.
- Moderate: Symptom causes discomfort and/or interrupts usual activities (including sleep).
- Severe: Symptom causes great interference with usual activities and may be incapacitating (including sleep).

- Very Severe: Symptom causes intense and constant discomfort and/or marked interference with usual activities (including sleep).

#### 9.1.7 Daily eDiary

Subjects will be given an eDiary on the first day of the Screening Period. Throughout the Screening Period and Treatment Period, subjects will document the presence and maximum severity of daytime and nighttime heartburn symptoms each day in their daily eDiary. Subjects will also record the use of rescue medication. If the subject experiences no heartburn on any given day, they should also provide this information. The daily eDiary should be completed every morning upon waking and every evening before bedtime. The last entry for the Treatment Period is in the morning prior to their Week 4/Final Visit site visit.

The electronic diaries will be reviewed at subsequent visits. Subjects must bring their electronic dairy device at every visit. The severity of heartburn will be graded by the subject according to the definitions outlined in [Appendix F](#). Should the electronic diaries be lost or destroyed, the subject should contact the site immediately to receive additional eDiary to insure continuity of symptom reporting.

#### 9.1.8 Documentation of Concomitant Medications

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

#### 9.1.9 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at screening/baseline examination. The condition (ie, diagnosis) should be described and assessed during subsequent site visits where physical examination is required.

#### 9.1.10 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood at any single visit is approximately 20 mL, and the approximate total volume of blood for the study is 140 mL. Details of these procedures and required safety monitoring will be given in the laboratory manual.



**Table 9.a Clinical Laboratory Tests**

Hematology	Serum Chemistry	Urinalysis
RBCs	ALT	Specific gravity
WBCs with Differential	AST	pH
Hemoglobin	Alkaline phosphatase (ALP)	Protein
Hematocrit	Albumin	Ketones
Platelets	Glucose (a)	Glucose
	Gastrin (a,b)	Bilirubin
	Total bilirubin	RBC
	Total protein	WBC
	Serum Creatinine	
	Blood urea nitrogen (BUN)	
	Creatine kinase	
	Bicarbonate(Total CO <sub>2</sub> )	
	γ-glutamyl transferase (GGT)	
	Lactate dehydrogenase (LDH)	
	Potassium	
	Sodium	
	Magnesium (c)	
	Calcium	
	Phosphorus	
	Chloride	
	Serum iron	
	Uric acid	
	Total cholesterol	
	Triglycerides (a)	
	Vitamin B12	

**Other:** *H. pylori* serology screening visit only

Serum	Urine
hCG (if child-bearing potential)	Urine Pregnancy test (if child-bearing potential)
FSH (if menopausal)	
Hepatitis panel including: HBsAg, HCV-antibody (d)	

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

- (a) To be measured under fasting conditions except the Screening Visit (Days -21 to -2).
- (b) Gastrin levels to be measured under fasting conditions. Gastrin levels will be blinded to both investigators and the medical monitor during the study period.
- (c) If, at any time after enrollment into the study, a subject's serum magnesium is less than or equal to 1.1 mEq/L ( $\leq 0.55$  mmol/L), a 24 hour urine for magnesium will be collected to verify the serum chemistry result.
- (d) Hepatitis panel including HBsAg and HCV-antibody can be measured either at the central laboratory or the local laboratory, depending on the site capability.

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

The investigator is responsible for transcribing laboratory results which were conducted locally to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

If subjects experience ALT or AST  $>3 \times \text{ULN}$ , follow-up laboratory tests (at a minimum, serum alkaline phosphatase, ALT, AST, total bilirubin, GGT, and INR) should be performed within a maximum of 7 days and preferably within 48 to 72 hours after the abnormality was found. (Please refer to Section 7.5 for discontinuation criteria, and Section 10.2.3 for the appropriate guidance on reporting of abnormal liver function tests in relation to ALT or AST  $>3 \times \text{ULN}$  in conjunction with total bilirubin  $>2 \times \text{ULN}$ .)

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

Given the possibility that the use of dexlansoprazole may be associated with increases in serum gastrin, the subjects will be examined for gastrin to investigate the magnitude of these increases during the Treatment Phase. Gastrin levels will be blinded to both investigators and the medical monitor during the study period.

The screening clinical laboratory, including hepatitis panel, must be performed within 14 days prior to randomization.

#### **9.1.11 Contraception and Pregnancy Avoidance Procedure**

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

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

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

\*\*Sterilized 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) where applicable\*:**

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

**Intrauterine devices (IUDs):**

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

**Hormonal contraceptives:**

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

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

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

During the course of the study, regular hCG pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures ([Appendix A](#)). In addition to a negative serum and urine hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test at Day -1.

### 9.1.12 Pregnancy

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

If the pregnancy occurs during administration of active study medication, eg, after Visit 2 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](#).

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the woman subject and/or woman partner of a man who is a subject agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject/woman partner of 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.

#### **9.1.13 ECG**

A standard 12-lead ECG will be recorded. The investigator (or a qualified observer at the investigational site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

The time that the ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG tracing: heart rate, RR interval, PR interval, QT interval, and QRS interval.

As ECG tracings on thermal paper fade over time, any such tracings should be completely photocopied and both the original tracing and the counter-signed copy should be filed in the subject's medical record.

#### **9.1.14 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.

The IWRS should be contacted as a notification of screen failure.

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

- Pretreatment event/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other.

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

#### **9.1.15 Documentation of Study Randomization**

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the Treatment Phase.

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

All screening procedures and test must be reviewed prior to randomization. Subjects who meet all the inclusion and none of the exclusion criteria will be randomized via IWRS.

Instructions on accessing and using the IWRS will be provided in a separate manual. Blinded details of subject treatment allocation (medication ID numbers) provided via the IWRS should be documented in the subject's medical record and/or eCRF.

#### **9.1.16 Endoscopy**

During Screening Visit an endoscopy will be performed on all subjects to document the presence/absence of EE. Endoscopy should be performed while subjects are fasted and according to the usual practice of the institution (ie, with regard to premedications or concomitant therapies, as long as they are not prohibited in Section 1 of this protocol). Subjects with macroscopic normal esophagus will be eligible for the study.

The screening endoscopy must be performed within 14 days prior to randomization. Any reliable, documented results available from an endoscopy performed in a routine clinical setting (before signing of informed consent) in the same institution will be accepted, given the invasive nature of the procedure.

Any subjects with suspicious Barrett's esophagus seen during screening endoscopy will be excluded from the study. These Endoscopy assessments will be recorded on the eCRF and a copy of the results should be kept with the subject's notes. Digital images of the endoscopy should be captured and stored at the investigational site; images may be accessed by Takeda as necessary for quality assurance purpose.

### **9.2 Monitoring Subject Treatment Compliance**

Subjects will be required to bring study medication containers and unused medications to each dispensing site visit and final visit. Investigators or designee should perform subject treatment compliance checks by reviewing the subject's eDiary and returned medications.

If a subject is persistently noncompliant with the study medication [dexlansoprazole 30 mg capsules or placebo] (eg, at more than 2 consecutive compliance checks to have taken less than 80% or more than 120% of the study medication), the subject should be withdrawn from the study. At each applicable study visit it should be documented in the subject's medical record that study medication was dispensed or collected, and/or checked for compliance. All subjects should be

reinstuctured about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

When rescue medication has been taken for more than 7 consecutive days during the study Treatment Period, the investigator should discuss with CRO/sponsor and decide whether to withdraw the subject.

### 9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in [Appendix A](#).

#### 9.3.1 Screening

Subjects will be screened within 21 days prior to randomization. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Sections 9.1.14 for procedures for screening failures.

The clinical laboratory tests, hepatitis panel and endoscopy must be performed within 14 days prior to randomization.

Any reliable, documented results available from an endoscopy performed in a routine clinical setting (before signing of informed consent) in the same institution will be accepted, given the invasive nature of the procedure.

#### Procedures to be Completed During the Screening Period (Days -21 to Day -2) include:

- Informed consent.
- Demographics, medical and social history.
- Medication history.
- Physical examination.
- Vital signs.
- Weight and height.
- Concomitant medication(s).
- Concurrent medical condition(s).
- Pretreatment events assessment.
- Prescribe rescue medication and give the medical instruction, as necessary.
- Screening clinical laboratory tests and hematology (to be performed within 14 days prior to randomization).
- Urinalysis.
- Serum and urine hCG (women of child-bearing potential only).
- FSH (only performed if menopause is suspected).

- Guidance on the avoidance of pregnancy.
- Instructions on how to make entries in the subject eDiary, provision of the eDiary, and commencement of eDiary entry.
- ECG.
- Hepatitis panel including: HBsAg and HCV-antibody (to be performed within 14 days prior to randomization).
- Endoscopy (to be performed within 14 days prior to randomization)

### 9.3.2 Study Randomization

If the subject has satisfied all of the inclusion criteria and none of the exclusion criteria for randomization, the subject should be randomized using the IWRS system, as described in Section 8.2. Subjects will be instructed when to take the first dose of investigational drug as described in Section 6.1. The procedure for documenting Screening failures is provided in Section 9.1.14.

#### 9.3.2.1 Day -1

- Physical exam.
- Vitals signs.
- Weight.
- Clinical laboratory tests (subjects should be fasting for a minimum of 8 hours prior to all labs) to include:
  - Urine and serum pregnancy test (baseline serum pregnancy test will not be needed if the screening pregnancy test is within 14 days of randomization).
  - Fasting gastrin.
- GERD symptoms investigator assessment.
- Daily eDiary review including compliance check.
- Concomitant medication(s).
- Pretreatment events assessment.
- IWRS randomization.
- Dispense study medication via IWRS.
- Rescue medication compliance and accountability.
- Dispense rescue medication as needed.

### 9.3.3 Treatment Period

#### 9.3.3.1 Day 1

- Begin study medication.
- Complete daily eDiary.

#### 9.3.3.2 Week 2 Visit ( $\pm 3$ Days)

Procedures to be completed at Week 2 Visit include:

- Physical examination.
- GERD symptoms investigator assessment.
- Vital signs.
- Weight.
- AE assessment.
- Concomitant medication(s).
- Daily eDiary review and compliance check.
- Study drug compliance and accountability.
- Rescue medication compliance and accountability.
- Dispense study medication via IWRS.

#### 9.3.4 Final Visit or Early Termination ( $\pm 3$ Days)

Procedures to be completed at Week 4/Final Visit include:

- Physical examination.
- GERD symptoms investigator assessment.
- Vital signs.
- Weight.
- AE assessment.
- Concomitant medication(s).
- Clinical laboratory tests (subjects should be fasting for a minimum of 8 hours prior to all labs) to include:
  - Chemistry panel and hematology.
  - Serum and urine hCG.
  - Urinalysis.



- Fasting gastrin.
- ECG.
- Daily eDiary review.
- Return of study medication.
- Study drug compliance and accountability.
- Rescue medication compliance and accountability.

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

### **9.3.5 Unscheduled Visit**

An unscheduled visit may occur when the subject returns to the clinic at any time during the Treatment Period of the study for the evaluation of symptoms or side effects.

At minimum, the following procedures are to be completed with additional procedures at the investigator's discretion:

- Physical examination.
- GERD symptoms investigator assessment.
- Vital signs.
- Weight.
- AE assessment.
- Fasting gastrin.
- Concomitant medication(s).

### **9.3.6 Follow-up**

The study center staff will follow up with a phone call 5 to 10 days post-treatment and any new AEs will be recorded in the eCRFs and subject's source documents. Follow-up will begin the first day after the Final Visit/Early Termination and will continue until 10 days post treatment.

### **9.3.7 Post Study Care**

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

## 10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

### 10.1 Definitions

#### 10.1.1 Pretreatment Events

A pretreatment event (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/PTEs:

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

Preplanned surgeries or procedures:

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

Elective surgeries or procedures:

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

Insufficient clinical response (lack of efficacy):

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

Overdose:

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

#### 10.1.4 SAEs

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

1. Results in DEATH.
2. Is LIFE THREATENING.
  - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Is 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 seizures	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 can be argued, 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 study medication was temporarily interrupted (discontinued) (including voluntary drug interruption by the subject) due to the particular AE, and resumed at a later date.

#### **10.1.12 Outcome**

- Recovered/resolved – Subject returned to first assessment status with respect to the AEs/PTE.
- Recovering/resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AEs/PTE with the condition remaining “recovering/resolving.”
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the

subject died from another cause with the particular AEs/PTE state remaining “Not recovered/not resolved.”

- Resolved with sequelae – the subject recovered from an acute AEs/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 AEs/PTE cannot be followed up due to hospital change or residence change at the end of the subject’s participation in the study.

## 10.2 Procedures

### 10.2.1 Collection and Reporting of AEs

#### 10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study medication 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. Routine collection of AEs will continue until the Final Visit or Early Termination. A follow-up phone call will be made to each subject 5 to 10 days following the last dose of study drug to collect any AEs that may have occurred.

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

#### 10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as “How have you been feeling since your last visit?” may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a 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 to be followed-up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study medication or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes observed. All 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. 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:

- Event term.
- Start and stop date and time.
- Severity.
- Investigator's opinion of the causal relationship between the event and administration of study medication(s) (related or not related) (not completed for PTEs).
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
- Action concerning study medication (not applicable for PTEs).
- Outcome of event.
- Seriousness.

Subject eDiary and questionnaire will not be used as a primary means to collect AEs. However, should the investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

### 10.2.2 Collection and Reporting of SAEs

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

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

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

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

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



Also, investigators should report any SAE in appropriate format (ie, locally required form) to related authorities, IRB/IECs in accordance with local GCP and/or local regulations.

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

### 10.2.3 Reporting of Abnormal Liver Function Tests

If a subject is noted to have ALT or AST elevated  $>3 \times \text{ULN}$  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 during the treatment or follow up period 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. Follow-up laboratory tests as described in Section 9.1.10 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

### 10.3 Follow-up of SAEs

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

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

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

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

## **11.0 STUDY-SPECIFIC COMMITTEES**

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

## 12.0 DATA HANDLING AND RECORDKEEPING

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

### 12.1 eCRF

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. eCRF must be completed in English. Data are entered directly onto eCRFs.

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

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

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

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

### 12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Conference on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is

discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

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

## **13.0 STATISTICAL METHODS**

### **13.1 Statistical and Analytical Plans**

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

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

#### **13.1.1 Analysis Sets**

All efficacy analyses will be performed on the full analysis set (FAS), which will be defined as all randomized subjects who receive at least 1 dose of study drug and have post-baseline (post Day-1) data for the appropriate efficacy variable. The safety analysis set will include all randomized subjects who receive at least one dose of study drug.

#### **13.1.2 Analysis of Demographics and Other Baseline Characteristics**

Demographic and baseline variables will be summarized using the safety analysis set and analyzed to assess the comparability of the treatment groups provided by randomization. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (eg, age and weight). The numbers and percentages of subjects will be presented for categorical variables (eg, gender, race).

#### **13.1.3 Efficacy Analysis**

The primary efficacy variable will be the percentage of days without daytime or night time heartburn over 4 weeks as assessed by daily eDiary. Comparisons between dexlansoprazole capsules and placebo will be made using a Wilcoxon rank-sum test.

The secondary efficacy variable will be the percentage of days without nighttime heartburn over 4 weeks as assessed by daily eDiary. Comparisons between dexlansoprazole capsules and placebo will be made using a Wilcoxon rank-sum test.

An additional efficacy variable will be the severity of GERD symptoms at Weeks 2 and 4 as assessed by the investigator. The severity of GERD symptoms at Weeks 2 and 4 will be analyzed using a Cochran-Mantel-Haenszel (CMH) test for ordered responses with baseline severity as the stratum. The percentage of days without rescue medication over 4 weeks as assessed by daily eDiary will be analyzed using Wilcoxon rank-sum test.

#### **13.1.4 Safety Analysis**

Safety will be assessed by summarizing the incidence of AEs, clinical laboratory tests, gastrin levels, ECG and vital signs using the safety analysis set.

All AEs will be coded using MedDRA. Treatment-emergent adverse events (TEAE) will be summarized using preferred term and primary system organ class overall, by severity, and by relationship to study drug for each treatment group. Separate summaries will also be generated for treatment-related adverse events (TRAEs) overall and by severity. Adverse events that were reported more than once by a subject during the treatment period will be counted only once for that subject at the maximum severity.

Other safety assessments (ECG results, clinical laboratory values, gastrin levels, physical exams and vital signs) will be summarized by treatment group at all visits assessed using descriptive statistics. Values outside the reference ranges and markedly abnormal laboratory values will be flagged and tabulated.

### **13.2 Interim Analysis and Criteria for Early Termination**

No interim analysis is planned.

### **13.3 Determination of Sample Size**

A total of 200 subjects are planned to be enrolled into this study to ensure 160 subjects with symptomatic nonerosive GERD will complete the study (assuming a 20% dropout rate). The sample size of 80 subjects per treatment group will provide at least 95% power at the 0.05 two-sided significance level to detect a difference of 25% in the mean percentage of days without daytime or nighttime heartburn over 4 weeks between dexlansoprazole capsules (50%) and placebo (25%). The dexlansoprazole and placebo rates were estimated from prior dexlansoprazole study T-GD05-137. The common standard deviation was assumed to be 35%.

## **14.0 QUALITY CONTROL AND QUALITY ASSURANCE**

### **14.1 Study-Site Monitoring Visits**

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

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

### **14.2 Protocol Deviations**

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the medical monitor (and IRB or IEC, 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 site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. The Significant Protocol Deviation eCRF is to be completed for deviations that are identified as significant by the sponsor.

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

## 15.0 ETHICAL ASPECTS OF THE STUDY

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

### 15.1 IRB and/or IEC Approval

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

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

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

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



## 15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

### **15.3 Subject Confidentiality**

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

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

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

### **15.4 Publication, Disclosure, and Clinical Trial Registration Policy**

#### **15.4.1 Publication and Disclosure**

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During 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 law, regulation and guidance, Takeda will, at a minimum register all clinical trials conducted in patients that it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before trial initiation. Takeda contact information, along with investigator's city, state (for US investigators), country, and recruiting status will be registered and available for public viewing.

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

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

#### **15.4.3 Clinical Trial Results Disclosure**

Takeda will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov or other publicly accessible websites, as required by applicable laws and/or regulations.

#### **15.5 Insurance and Compensation for Injury**

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

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- (a) Subjects who prematurely discontinue from the Treatment Period should undergo Final Visit procedures no later than 5 days after the last dose of study drug.
- (b) Height is measured only at Screening.
- (c) The screening clinical laboratory tests, hepatitis panel and endoscopy must be performed within 14 days prior to randomization. Any reliable, documented results available from an endoscopy performed in a routine clinical setting (before signing of informed consent) in the same institution will be accepted instead, given the invasive nature of the procedure.
- (d) Except for Visit 1 (Screening Days -21 to -2), subjects should be fasting for a minimum of 8 hours prior to the specimen collection. During the study drug treatment period, subjects should be instructed to take their dose of study medication on the morning of their visit with a sip of water before specimen collection occurs. Breakfast should be eaten only after specimen collection.
- (e) Only if menopause is suspected.
- (f) Subjects should complete the eDiary every morning (for nighttime symptoms) and every evening (for daytime symptoms). The eDiary will be dispensed at Screening and reviewed at corresponding visit. eDiary needs to be checked carefully on Day -1 visit to assure the compliance and reeducate subjects accordingly if it's necessary.
- (g) Study drug dispensed on Study Day -1 of the Screening Period Visit after the subject has completed all of the Screening Period procedures and subject has met all admission criteria for the study. Study drug will be self-administered on a daily basis for 4 weeks.
- (h) Study drug will be returned at the Week 2 Visit for compliance verification.
- (i) Rescue medication will be dispensed at Screening and may be dispensed at Study day -1 and Week 2 if needed.
- (j) Rescue medication will be returned at Study day -1, Week 2 and Week 4 for accountability.
- (k) Women of childbearing potential only. Baseline serum pregnancy test will not be needed if the screening pregnancy test is within 14 days of randomization.
- (l) Hepatitis panel including HBsAg and HCV-antibody can be done either at the central laboratory or the local laboratory, depending on the site capability
- (m) Follow-up phone call will occur for all subjects from 5 to 10 days after their last dose of study medication.

## Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including 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 is experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.
19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue

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

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

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

### Definitions of GERD Symptoms Assessed by Investigator

Symptom	Definition
Heartburn	A burning feeling in the mid-epigastric area and/or chest area.
Acid Regurgitation	Flow of sour or bitter fluid into the mouth.
Dysphagia	Difficulty in swallowing.
Belching	The voiding of gas from the stomach through the mouth, which may have been associated with acid regurgitation.
Epigastric Pain	Central upper abdominal pain.

### Definitions of GERD Symptoms Severity by Investigator

Severity	Definition
None	No symptoms.
Mild	Symptom did not last long and was easily tolerated.
Moderate	Symptom caused discomfort and/or interrupted usual activities (including sleep).
Severe	Symptom caused great interference with usual activities and may have been incapacitating (including sleep).
Very Severe	Symptom caused intense and constant discomfort and/or marked interference with usual activities (including sleep).

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**Appendix F Definition of Heartburn Severity (Daytime/Nighttime)**

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**Definitions of Daytime Heartburn Severity (Daytime=Awake Time)**

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None	No heartburn.
Mild	Occasional heartburn, can be ignored, does not influence daily routine.
Moderate	Heartburn cannot be ignored and/or occasionally influences daily routine.
Severe	Heartburn present most of day and/or regularly influences daily routine.
Very Severe	Constant heartburn and/or markedly influences daily routine.

---

**Definitions of Nighttime Heartburn Severity (Nighttime=Sleep Time)**

---

None	No heartburn.
Mild	Occasional heartburn, can be ignored, does not influence sleep.
Moderate	Heartburn cannot be ignored and/or occasionally influences sleep.
Severe	Heartburn present most of night and/or regularly influences sleep.
Very Severe	Constant heartburn and/or markedly influences sleep.

---

## Appendix G eDiary

The following diary questions will be asked in the morning:

1. Did you have heartburn last night? Yes  No

If yes, what was the maximum severity? Choose 1.

- Mild
- Moderate
- Severe
- Very Severe

2. Did you take any rescue medication last night? (such as Talcid chewable tablets, Gaviscon tablets and/or other antacids) Yes  No

The following diary questions will be asked in the evening:

1. Did you have heartburn today? Yes  No

If yes, what was the maximum severity? Choose 1.

- Mild
- Moderate
- Severe
- Very Severe

2. Did you take any rescue medication today? (such as Talcid chewable tablets, Gaviscon tablets and/or other antacids) Yes  No



## Appendix H Detailed Description of Amendments to Text

This appendix describes content changes in reference to Protocol Incorporating Amendment No. 03, dated 20 February 2017.

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### Change 1: Update contract research organization (CRO) contact information.

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The change occurs in Section 1.1 [Contacts](#):

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Description of change:	Changed the contact for SAE, pregnancy, and special interest adverse event reporting from <b>Personally Protected Data</b> to <b>Personally Protected Data</b> . The methods of contact were updated accordingly.
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**Rationale for Change:** The contact was updated to reflect a change in responsibilities at the CRO.

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### Change 2: Remove the requirement that the Screening Period be a minimum of 7 days.

---

The primary change occurs in 6.1 [Study Design](#):

---

Initial wording:	The study consists of 2 periods: a Screening Period, which will last a minimum of 7 days and a maximum of 21 days, and a Treatment Period, which will last 4 weeks.
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Amended or new wording:	The study consists of 2 periods: a Screening Period, which will last a <del>minimum of 7 days and a</del> maximum of 21 days, and a Treatment Period, which will last 4 weeks.
-------------------------	--

---

This change also appears in Section 6.1 [Study Design](#), including [Figure 6.a](#).

---

**Rationale for Change:** This change was made to correct an error in the protocol. If a subject has heartburn on at least 4 days and has eligible based on all other protocol-required screening procedures, it is possible that the Screening Period may be fewer than 7 days.

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### Change 3: Change the appropriate contact for confirming available brands of rescue medication.

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The change occurs in Section 8.1.1.2 [Rescue Medication](#):

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Initial wording:	If the listed rescue medications are not available, the subject should contact the contract research organization (CRO) or Takeda Medical Advisor for confirmation of available brand.
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Amended or new wording:	If the listed rescue medications are not available, the subject should contact the <del>contract research organization (CRO) or Takeda Medical Advisor</del> <b>subject's responsible investigator</b> for confirmation of available brand. During the rescue medication administration, the following should be noted:
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**Rationale for Change:** The subject does not need to contact the CRO or Takeda Medical Advisor, but can discuss available rescue medications with the investigator directly.

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**Change 4:** Gastrin levels will be blinded to both investigators and medical monitors during the study period.

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The change occurs in Section 9.1.10, Procedures for Clinical Laboratory Samples, footnote b:

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Initial wording: (b) Gastrin levels to be measured under fasting conditions. Gastrin levels above the upper limit of normal will be evaluated by the medical monitor and principal investigator on a case-by-case basis.

---

Amended or new wording: (b) Gastrin levels to be measured under fasting conditions. ~~Gastrin levels above the upper limit of normal will be evaluated by the medical monitor and principal investigator on a case-by-case basis.~~ **Gastrin levels will be blinded to both investigators and the medical monitor during the study period.**

---

**Rationale for Change:** Because PPI treatment will be associated with increases in gastrin levels, reviewing these data during the study may reveal the subject's treatment assignment.

---

This change also appears in a later paragraph within the text of Section 9.1.10 Procedures for Clinical Laboratory Samples.

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**Change 5:** Clarify acceptable windows for screening labs and endoscopy.

---

The primary change occurs in Section 9.3.1 Screening.

---

Initial wording: The clinical laboratory tests, hepatitis panel and endoscopy must be performed within 7 days prior to randomization.

---

Amended or new wording: The clinical laboratory tests, hepatitis panel and endoscopy must be performed within ~~7~~ **14** days prior to randomization.

---

**Rationale for Change:** The window for screening labs and endoscopy was extended to 14 days prior to randomization in order to allow greater flexibility for scheduling procedures for subjects who may be eligible for study entry, but without compromising their safety.

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The following sections also contain this change:

- Section 6.1 Study Design.
  - Section 9.1.10 Procedures for Clinical Laboratory Samples.
  - Section 9.1.16 Endoscopy.
  - Section 9.3.2.1 Day -1.
  - Appendix A Schedule of Study Procedures.
-

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**Change 6:** Update one of the definitions of an SAE.

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The change occurs in Section 10.1.4 SAEs:

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Initial wording: 5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.

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Amended or new wording: 5. ~~Leads to~~ **Is** a CONGENITAL ANOMALY/BIRTH DEFECT.

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**Rationale for Change:** Updated to be the correct definition.

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Amendment 3 – A Phase 3 Double Blind Study to Evaluate the Efficacy and Safety of Dexlansoprazole (30 mg QD) compared to Placebo on Heartburn Relief in Subjects With Symptomatic Nonerosive Gastroesophageal Reflux Disease (GERD)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personally Protected Data	Biostatistics Approval	24-Feb-2017 21:46 UTC
	Clinical Science Approval	24-Feb-2017 22:46 UTC
	Clinical Science Approval	27-Feb-2017 00:56 UTC