



Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Dexlansoprazole (60 mg QD) and an Active Comparator, Lansoprazole (30 mg QD) on Healing of Erosive Esophagitis, and Maintenance of Healing in Subjects With Healed Erosive Esophagitis With Dexlansoprazole (30 mg QD) and Placebo

NCT Number: NCT02873702

Protocol Approve Date: 20 February 2017

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PROTOCOL AMENDMENT

A Phase 3 Study to Evaluate the Efficacy and Safety of Dexlansoprazole (60 mg QD) and an Active Comparator, Lansoprazole (30 mg QD) on Healing of Erosive Esophagitis, and Maintenance of Healing in Subjects With Healed Erosive Esophagitis With Dexlansoprazole (30 mg QD) and Placebo

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

Study Number: TAK-390MR_301

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

Compound: TAK-390MR Dexlansoprazole Capsules

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

Amendment History:

Date	Amendment Number	Amendment Type	Region
05 August 2011	Initial Protocol	Not applicable	China
16 December 2015	01	Substantial	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	PPD
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 are provided on the last page of this document.

PPD _____

Date

PPD _____

Date

PPD _____

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.

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 I](#).

Changes in Amendment 3

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

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Asia, Pte. Ltd.		Compound: Dexlansoprazole	
Title of Protocol: A Phase 3 Study to Evaluate the Efficacy and Safety of Dexlansoprazole (60 mg QD) and an Active Comparator, Lansoprazole (30 mg QD) on Healing of Erosive Esophagitis, and Maintenance of Healing in Subjects With Healed Erosive Esophagitis With Dexlansoprazole (30 mg QD) and Placebo		IND No.: Not applicable	EudraCT No.: Not applicable
Study Number: TAK-390MR_301		Phase: 3b	
Study Design: This is a phase 3, randomized, double-blind, multicenter, active-controlled, 2-arm study with an initial 8-week Healing Period, followed by a randomized, double-blind, placebo-controlled 6-month Maintenance Period. The study is designed to evaluate healing of erosive esophagitis (EE), maintenance of healed EE and the effect of therapy on relieving gastroesophageal reflux disease (GERD) related symptoms			
Primary Objectives: The primary objective is to determine the efficacy of dexlansoprazole capsules (60 mg once daily [QD]) compared with lansoprazole capsules (30 mg QD) in healing EE over 8 weeks of treatment in Chinese subjects with endoscopically-proven EE.			
Secondary Objectives: The secondary objective is to confirm the efficacy and safety of dexlansoprazole capsules (30 mg QD) compared with placebo in the maintenance of healing of EE over 6 months of treatment in Chinese subjects with healed EE.			
Subject Population: Subjects 18 years or older, inclusive, with EE.			
Number of Subjects: Estimated total: approximately 450 <u>EE Healing (8 Weeks):</u> <ul style="list-style-type: none"> Approximately 225 subjects/ dexlansoprazole 60 mg capsules. Approximately 225 subjects/ lansoprazole 30 mg capsules. <u>Maintenance (6 Months):</u> <ul style="list-style-type: none"> Approximately 150 subjects/dexlansoprazole 30 mg capsules. Approximately 150 subjects/placebo. 		Number of Sites: Estimated total: 25 sites in China	
Dose Level(s): <u>Healing Period:</u> Dexlansoprazole 60 mg capsules QD Lansoprazole 30 mg capsules QD <u>Maintenance Period:</u> Dexlansoprazole 30 mg capsules QD Placebo QD		Route of Administration: Oral	
Duration of Treatment: 32 Weeks		Period of Evaluation: 39 Weeks	

Main Criteria for Inclusion:

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) prior to the initiation of any study procedures. The subject is a man or woman and aged at least 18 years. Must have endoscopically-confirmed EE as defined by the Los Angeles (LA) Classification Grading System (A-D). All women of childbearing potential, or men subjects with women partners who are sexually active, agree to use adequate contraception from signing of 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 excluded 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_302) or 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, or antacid (eg, magnesium trisilicate or similar antacid). The subject has a history of malignancy or was treated for malignancy within 5 years before the start of the Screening Visit (the subject may be included in the study if he/she has cured cutaneous basal cell carcinoma). The subject has a known history or any suspicious Barrett's esophagus with dysplastic changes 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. The subject has any abnormal screening laboratory value 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 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 1 month 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 need 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 subjects who have complete healing of EE over 8 weeks as assessed by endoscopy.

Secondary endpoint: The percentage of subjects who maintain complete healing of EE over 6 months as assessed by endoscopy.

Additional endpoints:

- The percentage of days with neither daytime nor nighttime heartburn over the 8 weeks of the Healing Period as assessed by the daily paper diary.
- The percentage of days with neither daytime nor nighttime heartburn over the 6 months of the Maintenance Period as assessed by the daily diary among the subjects who were healed at Week 8.
- The percentage of days without rescue medication use over the 8 weeks of the Healing Period as assessed by the daily diary.
- The percentage of days without rescue medication use over the 6 months of the Maintenance Period as assessed by the daily diary among the subjects who were healed at Week 8.
- The severity of GERD symptoms at Weeks 4 and 8 as assessed by the investigator during the Healing Period.
- The severity of GERD symptoms at Months 1, 3, and 6 as assessed by the investigator during the Maintenance Period.

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

Statistical Considerations:

Efficacy Assessments

The primary efficacy variable will be the percentage of subjects who have complete healing of EE over 8 weeks as assessed by endoscopy. The treatment difference of healing rate between dexlansoprazole and lansoprazole will be calculated and the lower bound of 95% confidence interval will be compared with -10%. Noninferiority to lansoprazole will be declared if the lower bound is greater than -10%.

The secondary efficacy variable will be the percentage of subjects who maintained complete healing of EE over 6 months as assessed by endoscopy. A comparison between dexlansoprazole and placebo will be made using Cochran-Mantel-Haenszel (CMH) test using stratification factor of baseline grade.

Safety Assessments

Safety will be assessed by summarizing the incidence of AEs, clinical laboratory values, gastrin levels, physical exams, electrocardiograms (ECG) and vital signs.

Sample Size Justification:

A total of 450 subjects with EE documented during Screening are planned to be enrolled into this study. Approximately 300 subjects are expected to enter the Maintenance Period.

Assuming a 10% dropout rate during the Healing Period and an 85% healing rate at Week 8 for both lansoprazole and dexlansoprazole, 225 subjects per arm will provide at least 80% power at the 1-sided 0.025 level of significance to meet the noninferiority criteria between lansoprazole and dexlansoprazole. Noninferiority to lansoprazole will be declared if the lower bound of the confidence interval for the difference in healing rates is greater than -10%.

Assuming a 33% dropout rate during the Maintenance Period and that maintenance rates are 14% and 66% for placebo and dexlansoprazole 30 mg, respectively, 150 subjects per arm will have at least 99% power at the 2-sided 0.05 level of significance to detect a difference between the treatment groups.

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 _{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COX-2	cyclooxygenase-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
FAS - H	full analysis set for the Healing Period
FAS - M	full analysis set for the Maintenance Period
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GGT	γ -glutamyl transferase
(H ⁺ , K ⁺)-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>
HRQOL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification

IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
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	overencapsulated
PK	pharmacokinetic
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 medicines
TEAE	treatment-emergent adverse event
t_{\max}	time to reach C_{\max}
Total CO ₂	bicarbonate
TRAE	treatment-related adverse event
ULN	upper limit of normal
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 Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
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 one 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, males develop erosive esophagitis (EE) and Barrett's esophagus more often than females [1], and females develop nonerosive GERD more often than males [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. Erosive esophagitis is defined as the presence of superficial esophageal erosions in patients with or without typical GERD symptoms. EE is diagnosed during endoscopy in up to 50% of patients with GERD symptoms [7]. The severity of these symptoms is associated with the extent and duration of gastric acid exposure in the esophagus [8,9]. 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 the premalignant condition of Barrett's esophagus [4,5].

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, histamine₂-receptor antagonists (H₂RA), 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 [10].

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) [11] or ulcers, and other GERD-related conditions. This is reflected by the high number of prescriptions written for twice daily (BID) dosing of currently available PPIs [12]. 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 [13]. In addition, concomitant antacid use has been reported by 37% of patients receiving PPIs [14]. 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 [15].

The validated LA Classification System is used to grade the severity of EE based on the extent of visible mucosal breaks seen in the esophagus [11]. Patients with more severe disease (Grades C and D) constitute a more difficult to treat population, as evidenced by lower EE healing rates and higher incidence of relapse and complications [16,17]. Approximately 25% of patients with EE present with baseline Grades C or D [18-20], and use of once-daily PPI therapy in these patients results in lower healing rates than those with Grades A and B [18-20]. Therefore, improvement in acid suppression therapy may reduce the risk for development of serious complications and enhance quality of life in these patients.

Erosive esophagitis is among the gastric acid-related disorders in which gastric acid reflux to the esophagus leads to problems in affected individuals. In 1994, the concept of a “mucosal break,” defined as “an area of slough or an area of erythema with a discrete lined demarcation from the adjacent or normal looking mucosa,” was introduced in the LA classification for diagnosis and grading of erosive esophagitis. Erosive esophagitis is graded by severity into 4 grades (A-D) based on the extent of mucosal breaks. Acid reflux induces prolonged, unpleasant subjective symptoms, such as heartburn or gastric acid reflux, in symptomatic patients with erosive esophagitis, often aggravating their health-related quality of life (HRQoL).

The PPIs, such as lansoprazole, represent the drugs of first choice for erosive esophagitis, and are being widely used all over the world.

The PPIs inhibit the hydrogen, potassium adenosine triphosphatase ($[H^+, K^+]$ -ATPase) enzyme (proton pump) which represents the final step in acid secretion by the parietal cells in the gastric mucosa, and produce potent antisecretory efficacy for acid-related disorders.

Dexlansoprazole is the R-enantiomer of lansoprazole. 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, also known as TAK-390MR and 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 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 ≥ 52 weeks, 382 subjects were exposed to doses of either 60 or 90 mg for ≥ 48 weeks and 863 subjects to doses of 30, 60, or 90 mg for 6 months (≥ 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 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 [21]. 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 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, Canada, Europe, Russia, India, Australia, New Zealand, South Africa, and South America have demonstrated positive results using dexlansoprazole for healing of EE and maintenance of healed EE. This study will be the first to examine the effectiveness and safety of dexlansoprazole capsules in Chinese subjects with EE. Efficacy and safety of dexlansoprazole capsules has been demonstrated in the phase 3 clinical program for the indications of symptomatic nonerosive GERD, healing of EE and maintenance of healed EE. All tested dexlansoprazole doses were highly effective in controlling and preventing the return of heartburn and other GERD symptoms, healing EE, preventing relapse of erosive esophagitis 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 capsules (60 mg QD) and lansoprazole capsules (30 mg QD) in healing EE over 8 weeks of treatment in Chinese subjects with endoscopic evidence of EE; the primary comparison will be to determine whether dexlansoprazole is noninferior to lansoprazole.

5.1.2 Secondary Objective

The secondary objective is to compare the efficacy of dexlansoprazole capsules (30 mg QD) and placebo in the maintenance of healing in Chinese subjects with healed EE; the primary comparison will be to determine whether dexlansoprazole is superior to placebo.

5.1.3 Additional Objective

CCI



5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is the percentage of subjects who have complete healing of EE over 8 weeks as assessed by endoscopy.

5.2.2 Secondary Endpoint

The secondary endpoint is the percentage of subjects who maintain complete healing of EE over 6 months as assessed by endoscopy.

5.2.3 Additional Endpoints

Additional endpoints include:

- The percentage of days with neither daytime nor nighttime heartburn over the 8 weeks of the Healing Period as assessed by the daily paper diary.
- The percentage of days with neither daytime nor nighttime heartburn over the 6 months of the Maintenance Period as assessed by the daily diary among the subjects who were healed at Week 8.
- The percentage of days without rescue medication use over the 8 weeks of the Healing Period as assessed by the daily diary.

- The percentage of days without rescue medication use over the 6 months of the Maintenance Period as assessed by the daily diary among the subjects who were healed at Week 8.
- The severity of GERD symptoms at Weeks 4 and 8 as assessed by the investigator during the Healing Period.
- The severity of GERD symptoms at Months 1, 3, and 6 as assessed by the investigator during the Maintenance Period.

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

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 3, randomized, double-blind, multicenter, active-controlled, 2-arm study with an initial 8-week healing period with noninferiority design, followed by a randomized, placebo-controlled 6-month maintenance period. The study is designed to evaluate healing, maintenance of healed EE and the effect of therapy on relieving GERD-related symptoms. Approximately 450 subjects will be enrolled at an estimated 25 sites across China.

The study consists of 3 periods; a Screening Period (maximum 21 days), a Healing Period, which will last 8 weeks, and a Maintenance Period of up to 6 months. After signing an informed consent form (ICF) subjects will undergo a screening evaluation within 21 days prior to the first dose of study drug (Study Day 1). Subjects will be instructed that lifestyle or behavior modifications designed to treat their symptoms of GERD should not be altered throughout the study. Subjects will be given a diary on the first day of the Screening Period. Throughout the Screening Period, subjects will record the presence and maximum severity of daytime and nighttime heartburn symptoms each day in their diary.

During the Screening Period, subjects will undergo various procedures to determine eligibility for the Healing 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 tests for serum and urine pregnancy (all women of childbearing potential) and hepatitis panel, and concomitant medication assessment. The screening clinical laboratory tests, hepatitis panel, and endoscopy must be performed within 14 days prior to randomization. Endoscopy data will be collected to identify subjects with EE, and only those subjects with endoscopically-confirmed EE Grades A-D as defined by the LA Classification Grading System ([Appendix E](#)), will be eligible for this study. Endoscopic pictures will be taken by the study site and kept in the site's source document files according to the site's practice.

Subjects who satisfy the screening evaluation and selection criteria, and have EE confirmed by endoscopy, may be entered into the study. Subjects having an esophageal stricture will be excluded from the study. The endoscope must pass freely into the stomach during the endoscopy.

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 of childbearing potential), physical examination, and vital signs measurements to assure continued eligibility. Subjects will be dispensed study drug on Study Day -1 according to an interactive web response system (IWRS) and will begin taking study drug on the following day (Study Day 1). In addition, subjects will be assessed for GERD symptoms such as heartburn, acid regurgitation, dysphagia, belching, and epigastric pain by the investigator.

- Subjects will be assigned in a 1:1 ratio to one of the following 2 treatment groups during the 8-week Healing Period; the randomization will be stratified by baseline endoscopic findings (grades A/B or C/D).
 - Group I: dexlansoprazole capsules (60 mg QD)
 - Group II: lansoprazole capsules (30 mg QD)

During the 8-week Healing Period, study drug will be self-administered orally QD before breakfast in the morning. Subjects will document the presence and maximum severity of daytime and nighttime heartburn symptoms using a diary. Subjects will also record the use of rescue medication. Subject visits will be conducted at Weeks 4 and 8 of the Healing Period to collect and/or dispense study drug, assess GERD symptoms, review concomitant medication use, and assess AEs.

At the Week 4 Visit, the subject will undergo a physical examination including vital signs, laboratory evaluations, and urine pregnancy test (all women of childbearing potential).

At the Week 8 Visit, all subjects will undergo a physical examination including vital signs, laboratory evaluations, fasting serum gastrin, serum and urine pregnancy test (all women of childbearing potential), ECG and an endoscopy. In addition, study drug will be collected, a review of concomitant medication use will be performed, and an assessment of AEs will be conducted. If the subject's EE has healed completely as determined by endoscopy, the subject will have completed the Healing Period of the study, and will continue in the Maintenance Period. If the subject's EE has not completely healed after 8 weeks of treatment, all Final Visit procedures will be performed and the subject will not be eligible to continue into the Maintenance Period.

For subjects who prematurely discontinue during the Healing Period, efforts should be made to perform all procedures scheduled for the Week 8 / Early Termination Visit no later than 5 days after the last dose of study drug.

At the start of the 6-Month Maintenance Period, subjects with healed EE will be randomized in a 1:1 ratio to one of the following 2 groups; the randomization will be stratified by baseline endoscopic findings (grades A/B or C/D).

- Group I: dexlansoprazole capsules (30 mg QD)
- Group II: placebo (QD)

During the 6-month Maintenance Period, study drug will be self-administered orally, QD in the morning before breakfast. Subjects will continue to document the presence and maximum severity of daytime and nighttime heartburn symptoms using a diary. Subjects will also record the use of rescue medication. Subject visits will be conducted at Months 1, 3 and 6, of the Maintenance Period to collect and/or dispense study drug, assess GERD symptoms, review concomitant medication use, and assess AEs. Endoscopies will be performed at Months 1 and 6/Final Visit to evaluate maintenance of healed EE. Subjects with endoscopic evidence of relapsed EE will be discontinued from the study.

At the Month 1 Visit, the subject will undergo a physical examination including vital signs, laboratory evaluations, endoscopy, and urine pregnancy test (all women of childbearing potential).

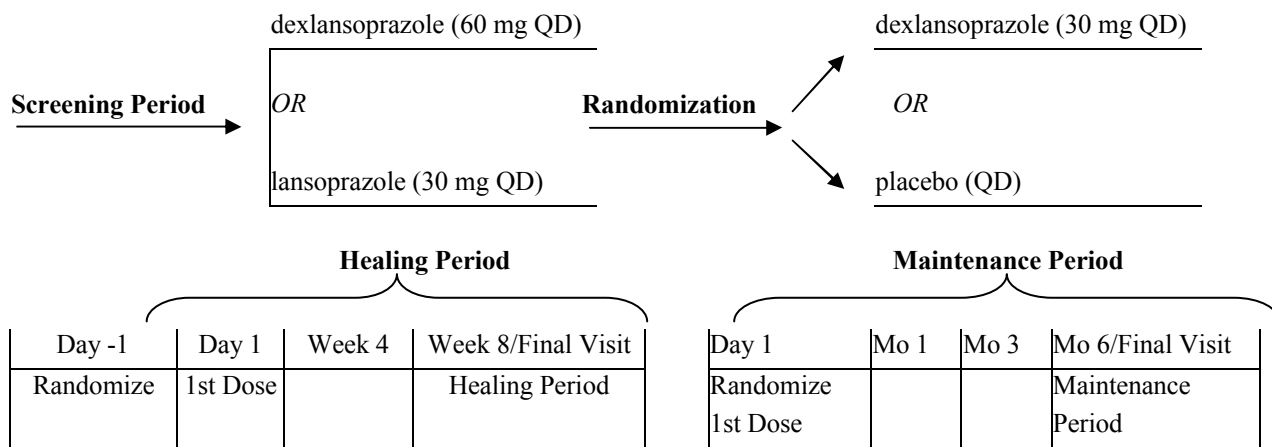
At the Month 3 Visit, the subject will undergo a physical examination including vital signs, laboratory evaluations and urine pregnancy test (all women of childbearing potential). An optional endoscopy may be performed based on investigator’s discretion if the subject presents with GERD symptoms at any time point during the Maintenance Period.

At the Month 6 Visit, all subjects will undergo a physical examination including vital signs, laboratory evaluations, fasting serum gastrin, serum and urine pregnancy test (all women of childbearing potential), endoscopy, and ECG. In addition, study drug will be collected, a review of concomitant medication use will be performed, and an assessment of AEs will be conducted.

For subjects who prematurely discontinue during the Maintenance Period, efforts should be made to perform all procedures (including endoscopy) scheduled for the Month 6 / Early Termination Visit 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



Mo=month.

6.2 Justification for Study Design, Dose, and Endpoints

This EE Healing Period of the study will compare dexlansoprazole 60 mg capsules QD with lansoprazole 30 mg capsules QD during the Healing Period.

Dexlansoprazole 60 mg capsules are approved in over 30 countries and lansoprazole 30 mg capsules are approved in China for healing of EE over an 8-week treatment period. Subjects with endoscopically-proven healing of EE after 8 weeks of treatment will continue into the Maintenance Period of the study. During this period all subjects with healed EE will receive either dexlansoprazole 30 mg capsules QD or placebo QD for 6 months. The study design, endpoints and dose of dexlansoprazole capsules for healing of EE (60 mg QD) and maintenance of healed EE

(30 mg QD) have been selected based on completed, multicenter, controlled phase 3 registration studies.

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 benefit:risk 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 prior to the initiation of any study procedures.
3. The subject is a man or woman and aged at least 18 years.
4. The subject must have endoscopically confirmed EE as defined by the LA Classification Grading System (A-D).
5. All women of childbearing 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.
6. All male subjects who are nonsterilized* and sexually active with women 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 excluded medication section (Section 7.3).
3. The subject has received any investigational drug or participated in another clinical study (other than study TAK-390MR_302) 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 had 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 or any suspicious Barrett's esophagus with dysplastic changes 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. The subject has any abnormal screening or Day-1, laboratory value 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.
11. The subject is known to have the 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).
12. The subject has current Zollinger-Ellison syndrome (gastric acid hypersecretion) or a history of gastric acid hypersecretion.
13. The subject is scheduled for surgery that requires hospitalization or requires surgical treatment during his/her participation in the study.
14. 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.
15. 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.

16. 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.
17. 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.
18. 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.
19. 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

Excluded medications and periods of exclusion are listed in [Table 7.a](#). 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

Excluded Medications	Period of Exclusion
Prescription or nonprescription H2RA	During Screening and throughout the study.
Antacids (except the rescue medication or similar antacid)	During Screening and throughout the study.
PPIs (except study-supplied dexlansoprazole or lansoprazole)	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 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.
- 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 diary upon rising in the morning on a daily basis. The subject should also record the use of rescue medication since the start of the Screening Period as well as his/her 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 Healing Period and the Maintenance Period, 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 woman 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 9.1.13.

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 post-randomization 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. Relapse of EE during the Maintenance Period.
- 4. 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.
- 5. 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).
- 6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
- 7. 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.
- 8. 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.
- 9. 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 the IWRS, which will assign a unique study drug identification number. The subject will be randomized into the Healing Period in a 1:1 ratio into 1 of 2 treatment groups:

- Dexlansoprazole 60 mg capsules.
- Lansoprazole 30 mg capsules.

At Week 8 of the Treatment Period, if the subject is healed per the endoscopy, the subject will be randomized into the Maintenance Period in a 1:1 ratio to 1 of 2 treatment groups:

- Dexlansoprazole 30 mg capsules.
- Placebo capsules.

Randomization will be stratified by baseline endoscopic findings (grades A/B or C/D) for both the Healing and Maintenance Periods.

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.

During the 8-week Healing Period and for the 6-month Maintenance Period, blinded study drug will be provided according to [Table 8.a](#).

Table 8.a Study Drugs

Study Drugs	Dosage Strength/Dosage Form	Manufacturer
Dexlansoprazole	30 and 60 mg capsules	Takeda Pharmaceutical Company Ltd.
Lansoprazole	30 mg capsules	Tianjin Takeda Pharmaceuticals Company Ltd.
Placebo	capsules (dose is not applicable)	Fisher Clinical Services

The study sites will be supplied with study medication that is blinded via overencapsulation (OE) of dexlansoprazole 60 mg capsules and lansoprazole 30 mg capsules for subjects in the 8-week Healing Period. Sites enrolling subjects in the Maintenance Period will also be supplied with OE dexlansoprazole 30 mg and placebo. The study drugs will be foil/foil blistered and packaged in 7-day child resistant blister cards containing 7 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 Fisher Clinical Services. 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 as follows: dexlansoprazole capsules (30 and 60 mg) are manufactured by Takeda Pharmaceutical Company Limited, Osaka, Japan; lansoprazole (30 mg) is manufactured by Tianjin Takeda Pharmaceuticals Co., Ltd., Tianjin, China; the placebo is manufactured by Fisher Clinical Services. 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 60 mg capsules.
- OE lansoprazole 30 mg capsules.
- OE dexlansoprazole 30 mg capsules.
- 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 diary.

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	Manufacturer
Talcid chewable tablets (hydrotalcite)	500 mg	Bayer China Ltd.
Gaviscon Tablets	aluminum hydroxide 0.05g magnesium trisilicate 0.0125g alginate 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 (dexlansoprazole, lansoprazole, 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 60 mg capsules.
- OE lansoprazole 30 mg capsules.
- OE dexlansoprazole 30 mg capsules.
- 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

All subjects with EE confirmed by endoscopy at Screening will be assigned to 60 mg dexlansoprazole or 30 mg lansoprazole capsules QD for 8 weeks of treatment. At the Week 8 Visit, all EE subjects will have an endoscopy. EE subjects who have healed will be randomized to dexlansoprazole 30 mg capsules or placebo for 6 months to assess maintenance of healed EE.

The number of cards subjects will receive at each visit is outlined in [Table 8.c](#).

Table 8.c Study Medication Dispensed at Each Visit

Study Visits	Number of 7-Day Cards Dispensed at #Each Visit
Day -1/Visit 2	5 cards of Dexlansoprazole 60 mg or Lansoprazole 30 mg capsules
Week 4/Visit 3	5 cards of Dexlansoprazole 60 mg or Lansoprazole 30 mg capsules
Week 8/Visit 4	5 cards of Dexlansoprazole 30 mg capsules or Placebo capsules
Month 1/Visit 5	9 cards of Dexlansoprazole 30 mg capsules or Placebo capsules
Month 3/Visit 6	13 cards of Dexlansoprazole 30 mg capsules or Placebo capsules

All subjects will self-administer 1 capsule of blinded study medication QD at approximately the same time each morning. The last dose of study medication is taken with a sip of water on the morning of their visit (Visits 3, 4, 5, 6 and 7).

Table 8.d Study Medication Supplies

Investigational Product	Formulation	Dosage	Mode of Administration	Manufacturer and Location
Dexlansoprazole	30 mg capsule	30 mg QD AM	Oral	Takeda Pharmaceutical Company Ltd
Dexlansoprazole	60 mg capsule	60 mg QD AM	Oral	Takeda Pharmaceutical Company Ltd
Lansoprazole	30 mg capsule	30 mg QD AM	Oral	Tianjin Takeda Pharmaceuticals Company Ltd
Placebo	0 mg capsule	0 mg QD AM	Oral	Fisher Clinical Services

8.1.3.1 Missed Doses

Subjects should be instructed that all doses of study medication (dexlansoprazole or lansoprazole) 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 both the Healing and Maintenance Periods.

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 schedules for both the Healing Period and for the Maintenance Period 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 Healing Period. The study drug kit number will encode the subject's randomization to 1 of the 2 arms (dexlansoprazole 60 mg QD or lansoprazole 30 mg QD) at a ratio of 1:1, according to the randomization schedules generated prior to study start.

Subjects with healed EE at the end of the Healing Period will be randomized again via the IWRS for the subsequent Maintenance Period. A study drug kit number will be assigned by IWRS and 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.

Randomization will be stratified by baseline endoscopic findings (grades A/B or C/D) for both the Healing and Maintenance Periods.

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 also be recorded on the eCRF.

If any site personnel are unblinded during the Healing or Maintenance Periods, 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 60 mg, lansoprazole 30 mg, dexlansoprazole 30 mg, 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 and 60 mg, lansoprazole 30 mg, 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:

- EE.
- Other upper gastrointestinal (GI) diseases including gastric ulcer, duodenal ulcer, nonerosive GERD, 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), Weeks 4, and 8/Final Visit of the Healing Period and Months 1, 3, and 6/Final Visit of the Maintenance 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 Diary

Subjects will be given paper diaries on the first day of the Screening Period. Throughout the Screening Period, Healing Period, and Maintenance Period, subjects will document the presence and maximum severity of daytime and nighttime heartburn symptoms each day in their daily diary. 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 diary should be completed every morning upon waking and every evening before bedtime. The last entry for the Healing Period is in the morning prior to their Week 8/Final Visit site visit. The last entry for the Maintenance Period is in the morning prior to the subject's Month 6/Final Visit site visit.

The paper diaries will be collected and reviewed at subsequent visits. Subjects must return their daily dairies at every visit. The severity of heartburn will be graded by the subject according to the definitions outlined in [Appendix G](#). Should paper diaries be lost or destroyed, the subject should contact the site immediately to receive additional diary pages 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
	Creatinine	
	Blood urea nitrogen (BUN)	
	Creatine kinase	
	γ -glutamyl transferase (GGT)	
	Lactate dehydrogenase (LDH)	
	Potassium	
	Sodium	
	Bicarbonate	
	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 (Day -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 (≤ 0.55 mmol/L), a 24-hour urine sample for magnesium will be collected to verify the serum chemistry result.
- (d) To 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 or lansoprazole 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.

Screening laboratory results from the TAK-390MR_302 study performed in the same institution can be accepted as screening laboratory results in TAK-390MR_301 study, on a case-by-case basis, given the burden of frequent blood draws in a short period of time. The investigator must contact the medical monitor for a discussion of the relevant subject details before subject's 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** male 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 of childbearing potential* who are sexually active with nonsterilized men** 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 serum and 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, 60 mg, lansoprazole 30 mg, and matching placebo) should be discontinued immediately. In addition, any pregnancies in the partner of a male 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. 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 Procedure

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 Healing Period.

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 into the Healing Period via IWRS.

Subject with healed EE at the end of the Healing Period will be randomized again via the IWRS for the subsequent Maintenance Period.

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

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 7.3 of this protocol).

The investigator (or designee) will record the results of endoscopy (including results of the LA classification and other gradings) performed promptly in the subject's medical record.

To ensure the accuracy of the EE evaluation according to LA grading, a 2nd review process of the endoscopic images will be established at each site. The 1st reviewer, ie, the endoscopist should take sufficient images or videotape the process at each endoscopic examination. The 2nd reviewer will evaluate the EE LA grading according to the endoscopic images.

- Preferably, the principal investigator performs as the 2nd reviewer and conducts the 2nd review in a timely manner after the endoscopy is performed by the 1st reviewer who is a subinvestigator in this study.
- In cases where the principal investigator is the 1st reviewer, a subinvestigator at the same site can be delegated as the 2nd reviewer and conducts the 2nd review in a timely manner.
- Only investigators (either principal investigators or subinvestigators) can be delegated as the 2nd reviewer.

If the LA grading by the 2 reviewers are consistent, this result becomes the final report. If not, the 2 reviewers will discuss their findings and reach a consensus which will then become the final report.

During Screening and at Week 8/Final Visit of the Healing Period, an endoscopy will be performed on all subjects to document the presence/absence of EE. Erosive esophagitis will be graded according to the LA Classification of Esophagitis Grading System ([Appendix E](#)).

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) within 14 days prior to randomization in the same institution will be accepted instead, given the invasive nature of the procedure.

Any Barrett's esophagus seen during screening endoscopy will exclude the subject from study. These endoscopic assessments will be recorded on the eCRF and a copy of the results should be kept with the subject's notes.

If a subject has endoscopically confirmed healing of EE at Week 8, they will be randomized into the Maintenance Period. During the Maintenance Period, endoscopies will be performed at Months 1 and 6/Final Visit to evaluate maintenance of healed EE. Subjects with endoscopic evidence of relapsed EE will be discontinued from the study.

Subjects who prematurely discontinue the study during the Maintenance Period should undergo Month 6 / Early Termination procedures no later than 5 days after the last dose of study drug, including the endoscopy.

Digital images of the current esophageal erosions 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 diary and returned medications.

If a subject is persistently noncompliant with the study medication [dexlansoprazole 30, 60 mg, lansoprazole 30 mg, 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 reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the subject source records.

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 Section 9.1.14 for procedures for documenting screening failures.

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.

Screening laboratory results from the TAK-390MR_302 study performed in the same institution can be accepted as a screening laboratory results in TAK-390MR_301 study, on a case-by-case basis, given the burden of frequent blood draws in a short period of time. The investigator must contact the medical monitor for a discussion of the relevant subject details before subject's randomization.

Procedures to be Completed During the Screening Period (Days -21 to -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 childbearing potential only).
- FSH (only performed if menopause is suspected).
- Guidance on the avoidance of pregnancy.
- Instructions on how to make entries in the subject diary, provision of the diary, and commencement of diary 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

Study randomization will take place on Day -1. The following procedures will be performed and documented during study randomization:

- 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 hCG (baseline serum pregnancy test will not be needed if the screening pregnancy test is within 14 days of baseline).
 - Fasting gastrin.
- GERD symptoms investigator assessment.
- Daily diary review/dispense new diary pages.
- Concomitant medication(s).
- Pretreatment events assessment.
- IWRS randomization.
- Dispense study medication via IWRS.

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 on 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.

9.3.3 Healing Period

9.3.3.1 Day 1

- Begin study medication.
- Complete daily diary.

9.3.3.2 *Week 4 Visit (± 3 Days)*

Procedures to be completed at Week 4 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.
 - Urine hCG.
 - Urinalysis.
- Daily diary review/dispense new diary pages.
- Dispense study medication via IWRS.
- Return of study medication.
- Study drug compliance and accountability.

9.3.3.3 *Week 8/Final Visit (± 3 Days)*

Procedures to be completed at Week 8/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.
- Daily diary review.
- Return of all study medication for healing period and instruct the subject NOT to take them anymore if the medication is not returned for any special reason(s).
- Study drug compliance and accountability.
- ECG.
- Endoscopy.

9.3.4 Maintenance Period

Subjects at Week 8 of the Healing Period who have endoscopically confirmed healing of EE will be randomized into the Maintenance Period. Week 8 Visit procedures will be considered Day -1 assessments for the Maintenance Period.

9.3.4.1 Day -1

- IWRS randomization.
- Dispense study medication via IWRS.
- Dispense daily diary.

9.3.4.2 Day 1

- Begin study medication for Maintenance Period.
- Complete daily diary.

9.3.4.3 Month 1 (± 7 Days)

Procedures to be completed at Month 1 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.

- Urine hCG.
- Urinalysis.
- Daily diary review/dispense.
- Dispense study medication via IWRS.
- Return of study medication.
- Study drug compliance and accountability.
- Endoscopy.

9.3.4.4 Month 3 (± 7 Days)

Procedures to be completed at Month 3 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.
 - Urine hCG.
 - Urinalysis.
- Daily diary review/dispense new diary pages.
- Dispense study medication via IWRS.
- Return of study medication.
- Study drug compliance and accountability.
- An optional endoscopy may be performed based on investigator discretion if subject presents with GERD symptoms.

9.3.5 Final Visit or Early Termination

The Final Visit will be performed at the 6 Month Visit. The following procedures will be performed and documented:

- 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.
- Daily diary review.
- Return of study medication.
- Study drug compliance and accountability.
- Endoscopy.

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

9.3.6 Unscheduled Visit

An unscheduled visit may occur when the subject returns to the clinic at any time during the Healing or Maintenance 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.
- Concomitant medication(s).
- Fasting gastrin.
- Endoscopy.

9.3.7 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.

9.3.8 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 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 retest 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) 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 diary 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. eCRFs 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

The full analysis set (FAS) will be defined separately for the Healing and Maintenance Periods. The full analysis set for the Healing Period (FAS – H) will include all randomized subjects who have documented EE at screening and receive at least 1 dose of study drug during the first 8 weeks of treatment. The full analysis set for the Maintenance Period (FAS – M) will include all subjects with healed EE by week 8 who are randomized and receive at least 1 dose of study drug during 6 months of maintenance treatment.

The safety analysis set will be defined separately for the healing period and for the Maintenance Period. The safety analysis set for the Healing Period (Safety Set – H) will include all subjects who receive at least 1 dose of study drug during Healing Period. The safety analysis set for the Maintenance Period (Safety Set – M) will include all subjects with healed EE by Week 8 who are randomized and receive at least 1 dose of study drug during 6 months of maintenance treatment.

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 subjects who have complete healing of EE over 8 weeks as assessed by endoscopy. The treatment difference of healing rate between dexlansoprazole and lansoprazole will be calculated and the lower bound of 95% confidence interval will be compared with -10%. Noninferiority to lansoprazole will be declared if the lower bound is greater than -10%. Subjects who do not have endoscopically documented healing and who prematurely discontinue will be considered as not healed.

The secondary efficacy variable will be the percentage of subjects who maintained complete healing of EE over 6 months as assessed by endoscopy. A comparison between dexlansoprazole capsules and placebo will be made using Cochran-Mantel-Haenszel (CMH) test using

stratification factor of baseline grade. Subjects who do not have endoscopically documented maintenance of healing and who prematurely discontinue will be considered to have relapsed.

An additional efficacy variable will be the severity of GERD symptoms at Weeks 4 and 8 as assessed by the investigator during the Healing Period. The severity of GERD will be compared between dexlansoprazole and lansoprazole capsules using a CMH test for ordered responses with baseline severity as the stratum. The number of subjects at each severity level for each GERD symptom at Months 1, 3, 6 will be also summarized by treatment group and baseline severity. At each visit, the severity will be compared between treatment groups using a CMH test for ordered responses (row mean score statistic with table scores of 0, 1, 2, 3, and 4) with baseline severity as the strata.

The percentage of days with neither daytime nor nighttime heartburn and the percentage of days without rescue medication use over the 8 weeks of the Healing Period and over the 6 months of the Maintenance Period as assessed by the daily diary will be summarized by treatment groups. Comparisons between treatment groups will be made using Wilcoxon rank-sum tests.

13.1.4 Safety Analysis

Safety will be assessed by summarizing the incidence of AEs, clinical laboratory values, gastrin levels, ECG, and vital signs.

Summary of AEs, ECG results, clinical laboratory values, gastrin levels, and vital signs will be provided separately for the Healing Period and for the Maintenance Period. For the Healing Period, baseline values will be the last available assessment before the first dose of study drug. The baseline values for the Maintenance Period will be the assessment performed at the Week 8 visit of the Healing Period.

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. AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

Other safety assessments (ECG results, clinical laboratory values, gastrin levels, and vital signs) will be summarized by double-blind 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 Determination of Sample Size

A total of 450 subjects with EE documented during Screening are planned to be enrolled into this study. Approximately 300 subjects are expected to enter the Maintenance treatment period.

Assuming a 10% dropout rate during the Healing Period and an 85% healing rate at Week 8 for both lansoprazole and dexlansoprazole, 225 subjects per arm will provide at least 80% power at the 1-sided 0.025 level of significance to meet the noninferiority criteria between lansoprazole and

dexlansoprazole. Noninferiority to lansoprazole will be declared if the lower bound of the confidence interval for the difference in healing rates is greater than -10%.

The fixed noninferiority margin of -10% is based on a double-blind, parallel-group, comparative study that evaluated EE healing rates after an 8-week treatment period with lansoprazole 30 mg QD or placebo. In this study, the difference in response rate between the lansoprazole 30 mg dose group and the placebo group was 40.4%; the lower limit of the 2-sided 95% confidence interval was 25.9%. Hence, even with a conservative assumption of this lower bound as the treatment effect of lansoprazole 30 mg, a -10% noninferiority margin would assure that dexlansoprazole 30 mg retains more than 60% of the treatment effect of lansoprazole 30 mg [22].

Assuming a 33% dropout rate during the Maintenance Period and that maintenance rates are 14% and 66% for placebo and dexlansoprazole 30 mg, respectively, 150 subjects per arm will have at least 99% power at the 2-sided 0.05 level of significance to detect a difference between the treatment groups.

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.

16.0 REFERENCES

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Appendix A Schedule of Study Procedures

	Screening Period		Healing Period			Maintenance Period			Unscheduled Visit	Follow-up Phone Call (c)
	Screening	Study Day -1 Baseline	Study Day 1	Week 4 (a)	Week 8 (a)/ Final Visit	Study Month 1	Study Month 3	Month 6 (b) Final Visit		
Study Day/Week/Month:	Day -21 to -2	Day -1	Day 1	Week 4	Week 8	Month 1	Month 3	Month 6		Last dose +5 to 10 days
Visit Windows (Days):				±3	±3	±7	±7	±7		
Visit Number:	1	2		3	4	5	6	7		8
Informed consent	X									
Demographics/medical/social history	X									
Medication history	X									
Physical examination	X	X		X	X	X	X	X	X	
Concurrent medical conditions	X									
Vital signs, body weight and height	X(d)	X		X	X	X	X	X	X	
ECG	X				X			X	X	
Endoscopy	X (e)				X	X (n)	X(o)	X (n)	X(o)	
<i>H. Pylori</i> serology	X									
Clinical laboratory tests (j)	X (e)			X (f)	X (f)	X (f)	X (f)	X (f)		
Hepatitis panel (j)	X (e)									
Fasting serum gastrin (f)		X			X			X	X	
Urine pregnancy test (k)	X	X		X	X	X	X	X		
Serum hCG (k)	X	X			X			X		
Serum FSH	X(g)									
Guidance on avoidance of pregnancy and ova and sperm donation	X	X		X	X	X	X	X		
IWRS randomization		X			X (m)					

Footnotes are on last table page.

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Appendix A Schedule of Study Procedures (continued)

	Screening Period		Healing Period			Maintenance Period			Unscheduled Visit	Follow-up Phone Call (c)
	Screening	Study Day -1 Baseline	Study Day 1	Week 4 (a)	Week 8 (a)/ Final Visit	Study Month 1	Study Month 3	Month 6 (b) Final Visit		
Study Day/Week/Month:	Day -21 to -2	Day -1	Day 1	Week 4	Week 8	Month 1	Month 3	Month 6		Last dose +5 to 10 days
Visit Windows (Days):				±3	±3	±7	±7	±7		
Visit Number:	1	2		3	4	5	6	7		8
First day of study drug			X (l)		X (m)					
Concomitant medications	X	X		X	X	X	X	X	X	
AEs assessment	X	X		X	X	X	X	X	X	X
GERD symptoms assessment (p)		X		X	X	X	X	X	X	
Daily diary review/dispense (h)	---X---	X---	X---	X---	X---	X---	X---	X---		▶
Dispense study drug via IWRS		X (i)		X	X (m)	X(q)	X(q)			
Drug return/accountability				X	X	X	X	X		

Footnotes are on last table page.

- (a) Subjects who prematurely discontinue from the Healing Period should undergo Week 8 / Final Visit procedures no later than 5 days after the last dose of study drug.
- (b) Subjects who prematurely discontinue from the Maintenance Period should undergo Month 6 / Final Visit procedures no later than 5 days after the last dose of study drug.
- (c) Follow-up phone call will occur for all subjects from 5 to 10 days after their last dose of study medication.
- (d) Height is measured only at Screening.
- (e) 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.
- (f) 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.
- (g) Only if menopause is suspected.
- (h) Subjects should complete the diary every morning (for nighttime symptoms) and every evening (for daytime symptoms). The diary will be dispensed at Screening and reviewed/dispensed at corresponding subsequent visits.
- (i) 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 8 weeks (Healing Period) and then 6 months (Maintenance Period).
- (j) Clinical laboratory tests include chemistry, hematology, and urinalysis. Hepatitis panel including HBsAg and HCV-antibody can be done either at the central laboratory or the local laboratory, depending on the site capability.
- (k) Women of childbearing potential only. Baseline serum pregnancy test will not be needed if the screening pregnancy test is within 14 days of baseline.
- (l) Healing therapy (blinded dexlansoprazole 60 mg capsules QD or lansoprazole 30 mg capsules QD).
- (m) Perform only if endoscopy confirms successful EE healing. Randomize to maintenance therapy, and dispense (blinded dexlansoprazole 30 mg capsules QD or matching placebo) accordingly. The first dose of maintenance therapy should be taken approximately 24 hours after last dose of healing therapy (ie, in the morning).
- (n) If subject has endoscopically-proven EE, they should be terminated from the study and undergo Final Visit (Month 6) Procedures.
- (o) Unscheduled Visit and Month 3 Visit endoscopies are optional, and may be warranted if subject presents with symptoms during EE Maintenance Period based on investigator's discretion. If subject has endoscopically-proven EE, the subject should be terminated from the study and undergo Final Visit (Month 6) /Early Termination Visit Procedures.
- (p) GERD symptoms should be assessed by an Investigator. If possible the same Investigator should perform these assessments for an individual subject throughout the study.
- (q) Dispense study drug if subject has not had endoscopically-proven relapse of EE.

Appendix B Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

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

12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

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

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

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

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

25. Women of childbearing potential (eg, nonsterilized, premenopausal women) who are sexually active must use adequate contraception (as defined in the informed consent) from Screening and throughout the duration of the study. Regular pregnancy tests will be performed throughout the study for all women of childbearing potential. If a subject is found to be pregnant during study, study medication will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Men 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.

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 LA Classification of Esophagitis Grading System

LA Classification of Esophagitis Grading System	
Grade	Definition
O	No mucosal breaks
A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of 2 mucosal folds.
B	One (or more) mucosal break more than 5 mm long, that does not extend between the tops of 2 mucosal folds.
C	One (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds, but which involves less than 75% of the circumference.
D	One (or more) mucosal break, which involves at least 75 % of the esophageal circumference.

Appendix F GERD Symptoms Investigator Assessments

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).

Appendix G Definition of Heartburn Severity (Daytime/Nighttime)

Definitions of Daytime Heartburn Severity (Daytime=Awake Time)

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 H Diary

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 I Detailed Description of Amendments to Text

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

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

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

Description of change: Changed the contact for SAE, pregnancy, and special interest adverse event reporting from Mingfang Zhu to Jie Pan. The methods of contact were updated accordingly.

Rationale for Change: The contact was updated to reflect a change in responsibilities at the CRO.

Change 2: Change the appropriate contact for confirming available brands of rescue medication.

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

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.

Amended or new wording: If the listed rescue medications are not available, the subject should contact the ~~contract research organization (CRO) or Takeda Medical Advisor~~ **subject's responsible investigator** for confirmation of available brand. During the rescue medication administration, the following should be noted:

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.

Change 3: Gastrin levels will be blinded to both investigators and medical monitors during the study period.

The change occurs in Section 9.1.10 Procedures for Clinical Laboratory Samples, Table 9.a, footnote b:

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.**

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

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

Change 4: Clarify acceptable windows for screening labs and endoscopy.

The primary change occurs in Section 9.3.1 Screening.

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

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

Rationale for Change: The window for screening laboratory tests (including hepatitis panel) 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.

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 Study Randomization.
 - Appendix A Schedule of Study Procedures.
-

Change 5: Update one of the definitions of an SAE.

The change occurs in Section 10.1.4 SAEs:


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

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

Rationale for Change: Updated to be the correct definition.

Amendment 3 to A Phase 3 Study to Evaluate the Efficacy and Safety of Dexlansoprazole (60 mg QD) and an Active Comparator, Lansoprazole (30 mg QD) on Healing of Erosive Esophagitis, and Maintenance of Healing in Subjects With Healed Erosive Esophagitis With Dexlansoprazole (30mg QD)

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD 	Biostatistics Approval	22-Feb-2017 16:31 UTC
	Clinical Science Approval	22-Feb-2017 17:50 UTC
	Clinical Science Approval	23-Feb-2017 00:59 UTC