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

NCT Number: NCT02873689

SAP Approve Date: 07 Dec 2018

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

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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STATISTICAL REPORT AMENDMENT 01

Title of Study	*A Phase 3 Double Blind Study to Evaluate the Efficacy and Safety of Dexlansoprazole (30 mg QD) compared to Placebo on Heartburn Relief in Subjects With Symptomatic Nonerosive Gastroesophageal Reflux Disease (GERD)*
Protocol Number:	*Protocol Incorporating Amendment No. 03*
Name of Finished Product	*Dexlansoprazole capsule*
Name of Active Ingredient	*Dexlansoprazole*
Indication	*Symptomatic Nonerosive Gastroesophageal Reflux Disease*
Sponsor	*Takeda Development Center Asia, Pte. Ltd.*
First Patient First Visit Date	*27 December 2016*
Last Patient Last Visit Date	*19 April 2018*
Database Lock Date	*11 May 2018*
Investigators	*20 investigators in China*
Study center	*20 sites in China*
Biostatistician	Personally Protected Data
Clinical Science	Personally Protected Data
Author	Personally Protected Data
Original Report Date	*08 Nov 2018*
Amendment 01 Report Date	*07 Dec 2018*

GCP Statement

This study was performed in compliance with Good Clinical Practice

Confidentiality Statement

Statistical Analysis Report Amendment 01 Signature Page

	Name	Signature	Date
Prepared By:	Personally Protected Data		07 Dec 2018
Title:			
Company:			

PREVIOUS AMENDMENTS

There were no previous amendments to the statistical analysis report.

REASON FOR AMENDMENT

After the original statistical analysis report was approved, some errors in data presentation were identified. These errors have been corrected in this amendment. In addition, some other modifications have been made for consistency with presentation of information in the clinical study report.

DESCRIPTION OF CHANGES

All affected sections have been updated to reflect the correct data or consistent presentation of results. Changes are listed below, and a more detailed description of each change is provided in Section 12.7.

1. Correct the incidence of TEAEs that were mild in intensity and recovered/resolved (Synopsis).
2. Correct the cross-references for some data presented (Section 8.1) and correct the description of how many adverse events that led to premature discontinuation had recovered or resolved (Section 8.1).
3. Add the information about adverse events that led to study discontinuation as “other significant adverse events” (Section 8.1.2.3).
4. Clarify the type of markedly abnormal hematology values observed during the study (Section 8.2.1).
5. Correct the cross-references for some data presented and add the number of subjects at visit 4 (week 4) for gastrin results (Section 8.2.4).
6. Modify the language in the safety conclusion regarding the SAE or AE that led to premature discontinuation for consistency with the clinical study report (Section 8.6).
7. Replace the table of efficacy results with one that does not include the ad hoc analyses. Update references in text accordingly.

Synopsis

Name of Sponsor/Company: Takeda Development Center Asia, Pte. Ltd	(For National Authority Use Only)
Name of Finished Product: Dexlansoprazole capsule	
Name of Active Ingredient: Dexlansoprazole	

Title of Study:

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

Protocol No: Protocol Incorporating Amendment No. 03

Objectives:

- Primary Objective:

  To compare the efficacy of dexlansoprazole capsule (30 mg QD) and placebo in relief of daytime and nighttime heartburn over 4 weeks in Chinese subjects with symptomatic nonerosive GERD as assessed by daily electronic diary (eDiary).
- Secondary Objective:

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

Methodology:

This was a phase 3, randomized, double-blind, multicenter, placebo-controlled, 2-arm study with a 4-week treatment period. This study compared the efficacy of dexlansoprazole capsule (30 mg QD) with that of placebo when administered orally as a single daily dose in the morning, without regard to food. The study was designed to evaluate heartburn relief in subjects with symptomatic nonerosive GERD. Two hundred and seventeen subjects over 18 years of age were randomized in the study at 20 sites in China: 108 subjects in Group I (dexlansoprazole 30 mg QD) and 109 subjects in Group II (placebo QD).

The study consisted of 2 periods: a screening period, which lasted a maximum of 21 days, and a treatment period, which lasted 4 weeks.

Number of subjects (planned and analyzed):

Planned = 200; Analyzed = 217.

Endpoints:

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

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

Additional endpoints of this study were as follows:

- The severity of GERD symptoms at Weeks 2 and 4 as assessed by the investigator.
- The percentage of days without rescue medication over 4 weeks as assessed by daily eDiary.

Safety was assessed by adverse events (AEs), clinical laboratory evaluations (including gastrin), vital signs, physical examination, and electrocardiograms (ECGs).

Statistical methods:

Efficacy Analysis:

Name of Sponsor/Company: Takeda Development Center Asia, Pte. Ltd	(For National Authority Use Only)
Name of Finished Product: Dexlansoprazole capsule	
Name of Active Ingredient: Dexlansoprazole	

Primary Efficacy Endpoint:

The Full Analysis Set (FAS) was used for the summary of the efficacy endpoints. The percentage of days with neither daytime nor nighttime heartburn over the 4 weeks of treatment was summarized descriptively (mean, median, standard deviation, minimum, and maximum). Comparisons between dexlansoprazole capsules and placebo were made using a Wilcoxon rank-sum test with a two-sided p-value for the difference between dexlansoprazole capsules and placebo. Statistical significance was determined at the 0.05 level.

The above descriptive statistics and analysis were also performed on the primary endpoint to summarize the treatment effects by subgroup.

Secondary Efficacy Endpoint:

The statistical methods performed on the primary endpoint were likewise performed on the secondary endpoint.

Pharmacokinetic/Pharmacodynamic Analysis:

Not applicable.

Other Outcomes:

Not applicable.

Safety Analysis:

Adverse Events:

All AEs were coded by system organ class (SOC) and preferred term (PT) using the MedDRA Dictionary (Version 21.0). Treatment-emergent adverse events (TEAEs) with onset occurring within 30 days (onset date – last date of dose $\leq$30) after study drug administration were included in the summary tables. All AEs were presented in the listings.

Clinical Laboratory Evaluations, Vital Signs, and 12-Lead ECGs:

Summaries of descriptive statistics and individual listings were presented. Markedly abnormal value (MAV) tables and listings were also presented in the unit specified in the MAV criteria.

Other Observations Related to Safety:

Physical examination results were presented in data listings only.

Name of Sponsor/Company: Takeda Development Center Asia, Pte. Ltd	(For National Authority Use Only)
Name of Finished Product: Dexlansoprazole capsule	
Name of Active Ingredient: Dexlansoprazole	

Summary:

Disposition:

A total of 325 subjects were screened. Of the subjects screened, 108 (33.2%) were ineligible for entrance into the treatment period. The primary reasons for screen failure were subject did not meet entrance criteria (80.6%), withdrawal by subject (13.9%), and other reasons (5.6%).

Of the subjects screened, 217 (66.8%) entered the treatment period at 20 sites in China: 108 subjects were randomized to the dexlansoprazole capsules group and 109 subjects were randomized to the placebo group. Of note, one subject in each group never received any study drug.

A total of 10 subjects prematurely discontinued study drug, and 205 subjects completed all the study drug and planned study visits.

Efficacy Analysis:

Primary Efficacy Endpoint:

For the percentage of days with neither daytime nor nighttime heartburn over the 4 weeks, the median value of dexlansoprazole capsules group (51.72) was greater than placebo group (32.67). The difference between the dexlansoprazole and placebo groups was not statistically significant (P=0.057).

Secondary Efficacy Endpoint:

For the percentage of days without nighttime heartburn over 4 weeks, the median value of dexlansoprazole capsules group (67.86) was greater compared with placebo group (54.67) and the difference was not statistically significant (P=0.268).

Safety Analysis:

Adverse Events:

The incidence of TEAEs was similar between dexlansoprazole capsules group (36.4%) and placebo group (32.4%). Most of TEAEs were mild in intensity and recovered and resolved. The most frequently reported adverse event occurring in ≥5% of subjects were upper respiratory tract infection and nasopharyngitis, both of which were reported less frequently for dexlansoprazole capsules group than placebo group. The incidence of TEAEs leading to study drug discontinuation was low, occurring in 2 subjects (1.9%) in each treatment group. One SAE (animal scratch in a subject in the placebo group) was reported; the investigator assessed this event as not related to study drug. No deaths were reported.

Clinical Laboratory Evaluations, Vital Signs, and12-Lead ECGs:

The MAVs for a few of laboratory parameters were observed but weren't reported as TEAEs or SAEs. None of the clinical laboratory results were clinically concerning. No subjects had any clinically concerning ECG or vital signs results.

Conclusion:

In this 4-week study of dexlansoprazole 30 mg or placebo in Chinese subjects with symptomatic nonerosive GERD, dexlansoprazole was safe and well tolerated. Subjects taking dexlansoprazole had a greater percentage of days without daytime or nighttime heartburn (difference of 19 percentage points) and without nighttime heartburn alone (difference of 13 percentage points) than subjects taking placebo, but the differences between the treatment groups were not statistically significant. Statistically significant improvements were observed, however, in several investigator-assessed GERD symptoms after 4 weeks of treatment with dexlansoprazole (an additional endpoint). In addition, subjects taking dexlansoprazole used statistically significantly less rescue medication than

Name of Sponsor/Company: Takeda Development Center Asia, Pte. Ltd	(For National Authority Use Only)
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those taking placebo. ***Date of the report: 07 December 2018***	

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
ECG	electrocardiogram
FAS	full analysis set
GERD	gastroesophageal reflux disease
GGT	γ - glutamyl transferase
HLT	high level term
ICF	informed consent form
IWRS	interactive web response system
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MAV	markedly abnormal values
PT	preferred term
QD	once daily
RBC	RBC red blood cells
SAE	serious adverse event
SOC	system organ class
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
ULN	upper limit of normal
WBC	white blood cells
WHODrug	World Health Organization Drug Dictionary

1.0 STUDY OBJECTIVES

1.1 Primary Objective

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

1.2 Secondary Objectives

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

2.0 STUDY DESIGN

This was a phase 3, randomized, double-blind, multicenter, placebo-controlled, 2-arm study with a 4-week treatment period. This study compared the efficacy of dexlansoprazole capsule (30 mg QD) with that of placebo when administered orally as a single daily dose in the morning, without regard to food. The study was designed to evaluate heartburn relief in approximately 200 subjects with symptomatic nonerosive GERD. The study consisted of 2 periods: a Screening Period, which lasted a maximum of 21 days, and a Treatment Period, which lasted 4 weeks.

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

During the Screening Period, subjects underwent various procedures to determine eligibility for the Treatment Period. Screening evaluations included the following: demographics, medical and social history, physical examination including vital signs, height and weight, ECG, endoscopy, clinical laboratory evaluations including hepatitis panel, urine and serum pregnancy test (all women subjects of childbearing potential), and concomitant medication assessment. The screening clinical laboratory tests, hepatitis panel, and endoscopy were to be performed within 14 days prior to randomization. Subjects were given rescue medication and eDiary on the first day of the Screening Period. Throughout the Screening Period, subjects recorded their usage of rescue medication (which was supplied throughout the screening period) and documented the presence and maximum severity of daytime and nighttime heartburn symptoms each day in their eDiary. Endoscopy data were collected to exclude subjects with EE.

Subjects who satisfied the screening evaluation and selection criteria (as described in Protocol Section 7.1 and 7.2) were entered into the study.

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

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

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

Group I: dexlansoprazole capsules (30 mg QD)

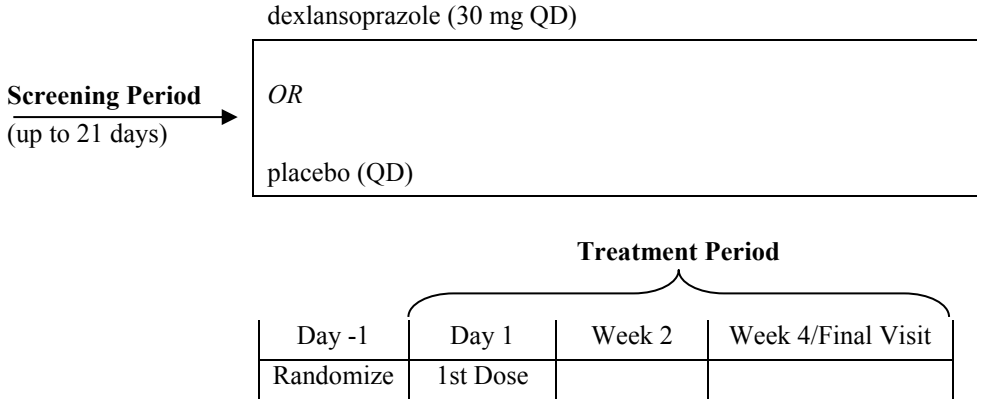
Group II: placebo (QD)

During this 4-week Treatment Period, study drug was self-administered, orally, once a day, in the morning, without regard to food. Subjects continued to document the presence and maximum

severity of daytime and nighttime heartburn symptoms and record usage of rescue medication using an eDiary. Subject visits were conducted at Weeks 2 and 4 of the Treatment Period to collect and/or dispense study drug, assess GERD symptoms, review concomitant medication use, assess adverse events, and perform a physical examination including vital signs. In addition, at the Week 4/ Final Visit, all subjects underwent laboratory evaluations, ECG, fasting serum gastrin and urine pregnancy test (all women of childbearing potential). Subjects who prematurely discontinued after randomization underwent Week 4/Final Visit procedures no later than 5 days after the last dose of study drug.

A schematic of the study design is included as Figure 2.a.

Figure 2.a Schematic of Study Design



3.0 ENDPOINTS

3.1 Primary Endpoint

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

3.2 Secondary Endpoints

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

3.3 Additional Endpoints

- The severity of GERD symptoms at Weeks 2 and 4 as assessed by the investigator.
- The percentage of days without rescue medication over 4 weeks as assessed by daily eDiary.

3.4 Safety Assessments

Safety was assessed by adverse events (AEs), clinical laboratory evaluations (including gastrin), vital signs, physical examination, and electrocardiograms (ECGs).

4.0 SAMPLE SIZE CALCULATIONS

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

5.0 STATISTICAL METHODS

5.1 Data Analysis Methods

5.1.1 General Considerations

Statistical analysis was performed using SAS software (SAS Institute, Inc., Cary, North Carolina) Version 9.2.

All study-related raw data for enrolled subjects, including derived data, were presented in data listings. Continuous data were summarized using number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical data were summarized using the number and percentage of subjects for each category where appropriate.

All tabulations of analysis results including summaries were displayed for the following treatment groups: dexlansoprazole 30 mg QD and placebo QD.

5.2 Data Handling Conventions

5.2.1 Premature Withdrawal

The investigator may have discontinued a subject's study participation at any time during the study when the subject met the study termination criteria. In addition, a subject may have discontinued his or her participation without giving a reason at any time during the study. Should a subject's participation have been discontinued, the primary criterion for termination was recorded. Discontinued or withdrawn subjects were not replaced after enrollment. All available data from subjects who were withdrawn from the study were listed and all available planned data were included in summary.

5.2.2 Handling of Missing Data

With the exception of missing or partial dates (Section 5.2.3), no imputed values were used for missing data.

5.2.3 Handling of Missing/Partial Date

Completely missing start or end dates remained missing, with no imputation applied.

Partial dates were imputed using the below conventions:

- If the partial date was a start date and:
  - If only missing day, then impute as the first day of the month.
  - If missing both month and day then, impute as the first day of the year.
- If the partial date was an end date and:
  - If only missing day, then impute as the last day of the month.
  - If missing both month and day, impute as the last day of the year.

- If the partial date was in the same month (only missing day) or same year (missing both month and day) as the study treatment, and the imputed start date of an adverse event (not pretreatment event) was prior to the start of study treatment, then the start date of study treatment was assumed to be the start date. The AE would then be considered as start on treatment (worst case scenario).
- If the imputed end date was after the subject's last visit date (or last contact date), then the last visit date (or last contact date), was considered as the end date.

The recorded partial date was displayed in the listings.

5.2.4 Definition of Baseline and Change from Baseline

Baseline was defined as the last non-missing measurement prior to or on the date of the first dose of study drug (Study Day 1).

The change from baseline was calculated by subtracting the baseline values from the individual post-baseline values. If either the baseline or post-baseline value was missing, the change from baseline was set to missing as well.

5.2.5 Definition of Study Days and Visit Window

Study day was calculated relative to the date of the first dose of study drug in the study. The study day prior to the first dose of study drug was calculated as:

Date of assessment/event – date of first dose of study drug

The study day on or after the first dose of study drug was calculated as:

Date of assessment/event – date of first dose of study drug + 1.

The visit windows for the post baseline visits were defined in Table 5.a. If a subject had more than 1 measurement in the same visit window, the measurement closest to the scheduled visit was used. If 2 measurements in the same window were of equal distance to the scheduled visit, the measurement that occurred after the scheduled visit was used. If 2 or more measurements occurred on the same day, the last value obtained was used.

Table 5.a Visit Window

Visit	Scheduled Day	Safety Labs & Serum Gastrin	Vital Signs	ECG	GERD Symptoms Investigator Assessment
Baseline	Day -1	≤1	≤1	≤1	≤1
Week 2	Day 14	2-21	2-21	NA	2-21
Week 4	Day 28	22-35	22-35	2-35	22-35

Note: Safety labs (including gastrin), vital signs, and ECG data obtained more than 7 days after the last day of study drug and efficacy data obtained more than 7 days after the last day of study drug weren't included in the analyses.

Diary entries were assigned to study days according to the beginning of the recall period. Specifically, entries completed in the evening (reporting heartburn during the day) were assigned

to the same day; entries completed in the morning (reporting heartburn during the night) were assigned to the previous day.

For the purpose of diary compliance calculation and derivation of diary-based endpoints, the last day of study drug wasn't included since the subject was not expected to have completed the diary entries for that day by the Week 4/Final Visit. Therefore, summaries for the 4 weeks of treatment included Study Day 1 through Study Day 35 or the day before the last dose of study drug, whichever occurred first.

For efficacy variables summarized by visit, the value closest to the last day of study drug was summarized for each subject, including those within 7 days of the last day of study drug. If 2 measurements were of equal distance to the last day of study drug, the later measurement was used.

AEs that started more than 30 days after the last dose of study drug were listed, but excluded from the summaries and analyses.

5.3 Analysis Sets

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

5.4 Disposition of Subjects

A subject disposition summary was provided. Subjects' study completion data, including reasons for premature termination, were provided in listings and also summarized.

A summary of screening failures was also provided.

5.5 Significant Protocol Deviations

A summary of the number and percentage of subjects with a significant protocol deviation by type of deviation was provided using the safety analysis set. Individual subject listings of significant protocol deviations were provided.

5.6 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics variables were summarized using the safety analysis set.

For continuous variables (age, weight, height, and body mass index [BMI]), summary statistics were generated.

For categorical variables, the number and percentage of subjects in each category was presented.

The following baseline characteristics were summarized.

- Number of days with daytime or nighttime heartburn between Study Days -8 and -2, inclusive.
- Number of days with nighttime heartburn between Study Days -8 and -2, inclusive.
- Number of days with daytime heartburn between Study Days -8 and -2, inclusive.
- Mean severity of daytime and nighttime heartburn between Study Days -8 and -2, inclusive.
- Mean severity of nighttime heartburn between Study Days -8 and -2, inclusive.
- Mean severity of daytime heartburn between Study Days -8 and -2, inclusive.
- Baseline severity of GERD symptoms as assessed by the investigator.
- Baseline number of days with daytime/nighttime rescue medication use.

5.7 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions were presented in a data listing and were summarized, count and percent, using the safety analysis set.

5.8 Medication History and Concomitant Medications

All medication history and concomitant medications were coded by therapeutic classification, sub classification, and medication using the World Health Organization Drug Dictionary (WHO Drug). A concomitant medication was defined as a medication that was ongoing as of Study Day 1, ends on or after Study Day 1, or starts on or after Study Day 1 and no more than 1 day after the last dose of study drug.

The number and percentage of subjects taking each concomitant medication was summarized for the safety analysis set. A subject with 1 or more concomitant medications within the same level of the WHODrug classification was counted only once in that level. WHODrug preferred term and therapeutic classification was used for summary:

- Medication history that the study subjects stopped taking within 90 days prior to the screening visit.
- Concomitant medications that started and stopped prior to baseline.
- Concomitant medications that started prior to and were ongoing at baseline.
- Concomitant medications that started after baseline.
- Concomitant medications that were ongoing at baseline and those that started after baseline.

5.9 Study Drug Exposure and Overdose

Overall study drug compliance (%) was determined as (total count of capsules taken / total number of days on study drug) ×100%. The total number of days on study drug (exposure) was

calculated as date of last dose of study drug - date of first dose of study drug + 1, assuming no gaps in the dosing interval. Any gaps in dosing interval was ignored in the calculation of the total. If last dose date was missing, then 35 days were imputed as treatment period. Summary statistics for the total number of days on study drug and overall compliance were generated for the safety analysis set.

The number and percentage of subjects with overall study drug compliance of <80%, 80-<90%, and ≥90% was also summarized for the safety analysis set. Subjects with unreturned study drug were assumed to have taken 1 capsule of study drug for each day of exposure for the calculation of overall compliance. Subjects with overall compliance ≥100% were set to 100% in the analysis.

In addition, diary compliance was determined as the percentage of days during treatment with two diary entries:

> Diary Compliance =
> (Number of days with two diary entries collected during treatment period)/(Number of days with two diary entries expected during treatment period) × 100%

5.10 Efficacy Analysis

The FAS was used for the summary of the efficacy endpoints.

5.10.1 Primary Efficacy Endpoint

The percentage of days with neither daytime nor nighttime heartburn over the 4 weeks of treatment was summarized descriptively. Comparisons between dexlansoprazole capsules and placebo was made using a Wilcoxon rank-sum test. The two-sided p-value was presented for the difference between dexlansoprazole capsules and placebo; the difference was considered statistically significant if the p-value was less than 0.05.

The percentage of days with neither daytime nor nighttime heartburn was calculated for each subject who has at least 1 daytime or nighttime heartburn result (presence or absence of heartburn) during the 4 weeks of treatment (up to last dose day or Day 35 whichever is first) by calculating:

> Percentage of days with neither daytime nor nighttime heartburn = (the days that were heartburn-free during Treatment Period)/ (Total number of days for which either a daytime or nighttime result was marked during Treatment Period) × 100%;

all entries on a day must be heartburn-free in order for the day to be counted as a day with neither daytime nor nighttime heartburn.

The days with missing diary results for both daytime and nighttime were excluded from the numerator and denominator. If a subject prematurely terminated, the Treatment Period was defined as from first dose date to last dose date + 1 day. If last dose date was missing, then 35 days was imputed as treatment period.

Subgroup Analyses:

Similar descriptive statistics and Wilcoxon rank-sum tests were repeated on the primary endpoint to evaluate the treatment effect within the different baseline subpopulation levels as follows:

- Age (<45, ≥45 to <65, ≥65 years).
- Gender (male, female).
- BMI (<25, 25-<30, ≥30 kg/m^2).
- *H pylori* status (positive, negative).
- Overall study drug compliance (<80%, 80-<90%, ≥90%).

Ad Hoc Sensitivity Analysis

Similar descriptive statistics and two sample T-test were repeated on the primary endpoint to evaluate the treatment effect.

5.10.2 Secondary Efficacy Endpoints

Descriptive statistics (mean, median, standard deviation, minimum and maximum) were presented similarly to the primary endpoint. Comparisons between dexlansoprazole capsules and placebo was made using a Wilcoxon rank-sum test. The p-value was presented for the difference between dexlansoprazole capsules and placebo; the difference was considered significant if the two-sided p-value was less than 0.05. The ad hoc sensitivity analysis described for the primary endpoint was also performed on the secondary endpoint.

5.10.3 Additional Efficacy Endpoints

The severity of GERD symptoms at Weeks 2 and 4 was analyzed using a Cochran-Mantel-Haenszel (CMH) test for ordered responses with baseline severity as the stratum. The p value was presented for the difference between dexlansoprazole capsules and placebo; the difference was considered significant if the p-value was less than 0.05.

The percentage of days without rescue medication over 4 weeks as assessed by daily eDiary was analyzed using the Wilcoxon rank-sum test.

In addition, descriptive statistics were presented for the endpoints below:

- The percentage of days without daytime heartburn over the 4 weeks of treatment as assessed by daily eDiary.
- The severity of daytime and nighttime heartburn hurt over the 4 weeks of treatment as assessed by daily eDiary.
- The severity of nighttime heartburn hurt over the 4 weeks of treatment as assessed by daily eDiary.
- The severity of daytime heartburn hurt over the 4 weeks of treatment as assessed by daily eDiary.

5.11 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

5.12 Other Outcomes

Not applicable.

5.13 Safety Analysis

All safety analyses were performed using the safety analysis set.

5.13.1 Adverse Events

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent adverse event (TEAE) was defined as an AE that started or worsened on or after Study Day 1 (defined as day first dosed), and no more than 30 days after the last dose of study drug. All TEAEs were listed by subject number and MedDRA coding. A listing of all unique coded terms was also provided.

The number and percentage of subjects with treatment-emergent AEs was summarized in several different tables:

- All AEs by system organ class (SOC), high level term (HLT), and preferred term (PT).
- Treatment-related AEs by SOC, HLT, and PT.
- Most frequent AEs by SOC and PT (sorted by total frequency of PT occurring in ≥5% of subjects in any treatment group).
- Most frequent treatment-related AEs (TRAEs) by HLT and PT (sorted by total frequency of HLT occurring in ≥2% of subjects in any treatment group). If no events met the 2% criteria, the most frequent TRAEs were defined as those events occurring in 2 or more subjects.
- Severity of all AEs by SOC and PT (mild, moderate, or severe).
- Severity of TRAEs by SOC and PT (mild, moderate, or severe).
- Relationship to study drug for all AEs by SOC and PT (not related, related).

A subject with 2 or more AEs within the same level of the MedDRA term was counted only once in that level using the most extreme incident (most severe for the severity tables and related for the relationship to study drug tables).

Additionally, treatment-emergent serious adverse events, deaths, and TEAEs resulting in premature discontinuation from study drug were listed and summarized by SOC, HLT and PT. The most frequent treatment-emergent non-serious AEs were also summarized by SOC, HLT and PT.

A pretreatment event was defined as an AE that ends prior to Study Day 1 (defined as day first dosed), or ends but not worsens on or after Study Day 1 (defined as day first dosed). A list of

pretreatment AEs by subject number and MedDRA coding was presented separately. Pretreatment AEs were summarized by SOC and PT.

5.13.2 Clinical Laboratory Evaluations

Clinical laboratory variables (including serum fasting gastrin) were summarized using descriptive statistics for baseline, post baseline, and change from baseline to post baseline values.

Individual results for clinical hematology and chemistry laboratory tests that were within the predefined laboratory markedly abnormal value (MAV) criteria (Appendix A) were summarized in tables. All clinical laboratory data were presented in data listings.

The percentages of subjects with elevated gastrin values ≥200 pg/mL and ≥400 pg/mL were summarized.

The number and percentages of patients with the following elevations in hepatic laboratory tests were summarized:

- ALT or AST >8×ULN.
- ALT or AST >5×ULN.
- ALT or AST >3×ULN in conjunction with elevated total bilirubin >2×ULN.

Summaries and listings of laboratory data were presented. MAV tables and listings were presented in the unit specified in the MAV criteria.

5.13.3 Vital Signs

Vital signs were summarized using descriptive statistics for Baseline, post baseline, and change from Baseline to post baseline values.

All individual vital signs that met predefined criteria for MAVs (Appendix B) were summarized in tables. All vital sign data were presented in data listings.

5.13.4 12-Lead ECGs

ECG results were interpreted using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Week 4 ECG assessments were cross-tabulated against the baseline assessment.

All individual quantitative ECG values that met predefined criteria for MAVs (Appendix C) were listed. All ECG data were presented in a data listing.

5.13.5 Other Observations Related to Safety

Physical examination results were presented in a data listing and weren't summarized.

5.14 Interim Analysis

Not applicable.

5.15 Changes in the Statistical Analysis Plan

After the unblinded results for the primary and secondary endpoints were available an ad hoc sensitivity analysis was performed. This was done since the placebo response was higher than expected and since the p-value for the primary analysis of the primary endpoint was greater than the level of significance by a small amount. The sensitivity analysis doesn't replace the primary analysis but to see if the conclusion was replicated with a different testing method. Additionally, the most frequent AEs were displayed by SOC and PT instead of HLT and PT.

6.0 STUDY RESULTS

6.1 Disposition of Subjects

A total of 325 subjects were screened. Of the subjects screened, 108 (33.2%) were ineligible for entrance into the treatment period. The primary reasons for screen failure were subject did not meet entrance criteria (80.6%), withdrawal by subject (13.9%), and other reasons (5.6%).

Of the subjects screened, 217 (66.8%) entered the treatment period at 20 sites in China: 108 subjects were randomized to the dexlansoprazole capsules group and 109 subjects were randomized to the placebo group. Of note, one subject in each group never received any study drug.

A total of 10 subjects prematurely discontinued study drug, and 205 subjects completed all the study drug and planned study visits.

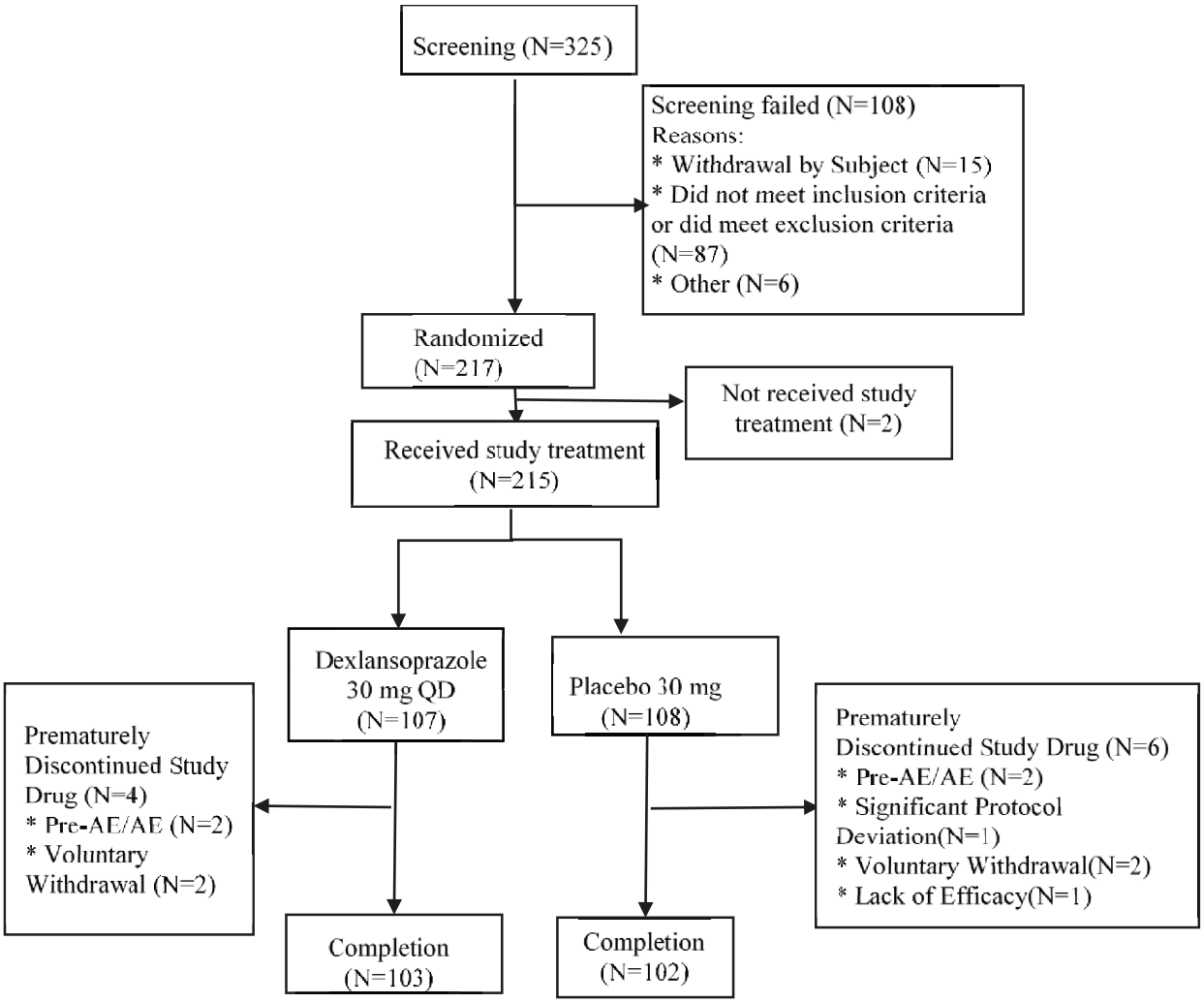
Overall subject disposition is presented in Table 6.a, and a flow chart is presented Figure 6.a. By-subject listings of screen failures and subject disposition are provided in Appendix 16.2.1.2 and 16.2.1.3.

Table 6.a Overall Disposition of Subjects

	Placebo QD N (%)	Dexlansoprazole 30 mg QD N (%)	Total N (%)
Subject Screened			325
Subjects Eligible for Entrance Into Treatment Period (a)			217 (66.8)
Randomized But Not Treated (b)	1 (<1)	1 (<1)	2 (<1)
Completed Study Drug (b)	102 (93.6)	103 (95.4)	205 (94.5)
Prematurely Discontinued Study Drug (b)	6 (5.5)	4 (3.7)	10 (4.6)
Completed All Planned Study Visits (b)	102 (93.6)	103 (95.4)	205 (94.5)
Did Not Complete All Planned Study Visits (b)	7 (6.4)	5 (4.6)	12 (5.5)
Subjects Not Eligible for Entrance Into Treatment Period (a)			108 (33.2)
Primary Reason Subject not Eligible for Treatment Period (c)			
Adverse Event			0
Significant Protocol Deviation			0
Lost to Follow-up			0
Withdrawal by Subject			15 (13.9)
Study Termination by Sponsor			0
Pregnancy			0
Did not Meet Inclusion Criteria or Did Meet Exclusion Criteria			87 (80.6)
Other			6 (5.6)

Source: Table 15.1.3 and Table 15.1.5.
(a) Denominator of the percentage is the number of subjects screened.
(b) Denominator of the percentage is the total number of subjects who are eligible for entrance into treatment period.
(c) Denominator of the percentage is the total number of subjects who aren't eligible for entrance into treatment period.

Figure 6.a Flow Chart of Subject Disposition



6.2 Significant Protocol Deviation

A total of 23 subjects had at least one significant protocol deviation, including 9 (8.3%) subjects in placebo group and 14 (13.1%) subjects in dexlansoprazole group. Overall, the categories of deviations based on the information available in the clinical database were entry criteria (3.7%), procedure not performed per protocol (2.8%), study medication (2.8%), and concomitant medication (2.3%).

Two protocol deviations were discovered after database lock, and are not reflected in above summary. These are described as follows, with additional details provided in TAK 390MR_302_File_Note.zip.

1. *One subject (20016-001) had technical difficulties with the eDiary during screening, so the data for that subject were captured on paper for 2 days and are not included in the database. This was not expected to affect the analysis since the subject met the screening heartburn criteria.*
2. *After the database was locked, site quality control revealed that one subject (20015-007) had heartburn symptoms for fewer than 4 days during the 7 days prior to Day -1. The subject did not meet the inclusion criterion for number of days with heartburn symptoms, but was enrolled in error and completed dosing with placebo for the entire study.*

None of the reported deviations were considered to have affected subject safety or the overall conclusions of the study.

6.3 Analysis Sets

A total of 217 subjects were randomized and included in the randomized set: 109 subjects in placebo group and 108 subjects in the dexlansoprazole capsules group. Two subjects were excluded from the safety analysis set and full analysis set because they did not receive study drug (Table 15.1.7).The remaining 215 subjects were included in the safety analysis set and full analysis set: 108 subjects in placebo group and 107 subjects in dexlansoprazole capsules group.

6.4 Demographics and Other Baseline Characteristics

The mean age of the subjects was 44.3 years. More than half of subjects were female. For the number of days with heartburn at baseline, the mean values were similar between treatment groups. And for the mean severity of heartburn at baseline, the mean values were also similar between treatment groups. Detailed demographic and baseline characteristics data are summarized in Table 15.1.8.

6.5 Medical History and Concurrent Medical Conditions

Similar percentages of subjects reported a medical history item across the treatment groups. The most common were Caesarean section (2.3%), hysterectomy (2.3%) and chronic gastritis (2.3%). The incidence for all other medical history items was low (<2%). Details of medical history information are provided in Table 15.1.9 and Appendix 16.2.4.2.

The incidence of concurrent medical conditions was also similar across the treatment groups. The most common concurrent medical condition was chronic gastritis (48.4%) and *Helicobacter* test positive (16.3%). The details of the concurrent medial conditions information are listed in Table 15.1.10 and Appendix 16.2.4.3.

6.6 Medication History and Concomitant Medications

6.6.1 Medication History

The incidence of medication history was similar across the treatment groups. The most common of these medications were propofol (48.8%) and dyclonine hydrochloride (34.9%). The details of medication history information are listed in Table 15.1.11 and Appendix 16.2.4.4.

6.6.2 Concomitant Medications

Concomitant medications included any medication taken which was ongoing as of Study Day 1, ended on or after Study Day 1 or started on or after Study Day 1 and no more than 1 day after the last dose of study drug.

For the concomitant medications that started and stopped prior to baseline, the incidence was similar across the treatment groups, and the most common concomitant medications were propofol: dexlansoprazole capsules group (54.2%) and placebo group (54.6%); dyclonine hydrochloride: dexlansoprazole capsules group (43.0%) and placebo group (34.3%); and hydrotalcite: dexlansoprazole capsules group (29.0%) and placebo group (38.0%).

For the concomitant medications that started prior to and were ongoing at baseline, the incidence in dexlansoprazole capsules group (15.9%) was less than that in placebo group (27.8%), and the most common concomitant medications was hydrotalcite: dexlansoprazole capsules group (3.7%) and placebo group (8.3%).

For the concomitant medications that started after baseline, the incidence in dexlansoprazole capsules group (34.6%) was less than that in placebo group (45.4%), and the most common concomitant medications was hydrotalcite: dexlansoprazole capsules group (15.9%) and placebo group (23.1%).

For the concomitant medications that were ongoing at baseline and those that started after baseline, the incidence in dexlansoprazole capsules group (39.3%) was less than that in placebo group (53.7%), and the most common concomitant medications was hydrotalcite: dexlansoprazole capsules group (16.8%) and placebo group (25.9%).

The details of the concomitant medications information are summarized in Table 15.1.12.1, 15.1.12.2, 15.1.12.3, and 15.1.12.4, and by-subject listing are presented in Appendix 16.2.4.5. The glossary of medication history and concurrent medications by preferred medication name is provided in Table 15.1.13.

6.7 Study Drug Exposure and Overdose

The mean duration of study drug exposure was the same in each treatment group (26.8 days). Mean study drug compliance was high in both groups, with values over 99%. Diary compliance was high in both treatment groups, with 95.74% compliance in the placebo group and 93.84% in the dexlansoprazole group.

The details of study drug exposure and compliance information are summarized in Table 15.1.14 and listed in Appendix 16.2.5.1 and 16.2.5.2.

7.0 EFFICACY EVALUATION

The FAS was used for the summary of the efficacy endpoints. All the efficacy data are presented in Appendix 16.2.6.2 and 16.2.6.3.

7.1 Primary and Secondary Efficacy Endpoint

The median percentage of days with neither daytime nor nighttime heartburn for subjects in the dexlansoprazole capsules group (51.72%) was greater than for subjects in the placebo group (32.67%) with the difference of 19.05%. The difference between treatment groups was not statistically significant (P=0.057) (Table 7.a.).

Subgroup analyses were performed on the primary endpoint, and these results are presented in Table 7.b. For subjects with positive *H pylori* results, the median percentage of days with neither daytime nor nighttime heartburn for subjects in the dexlansoprazole capsules group (68.62%) was greater than for those in the placebo group (34.62%), and the difference (34.00%) was statistically significant with p-value = 0.032. For subjects with the highest overall study drug compliance (≥90%), the median in the dexlansoprazole capsules group (51.72%) was also greater than for those in the placebo group (30.29%), and the difference (21.43%) was statistically significant with p-value = 0.037.

For the secondary endpoint of percentage of days without nighttime heartburn over 4 weeks, the median value of dexlansoprazole capsules group (67.86%) was greater compared with placebo group (54.67%). The difference (13.19%) between treatment groups was not statistically significant (P=0.268) (Table 7.a).

For the percentage of days without daytime heartburn over 4 weeks, the median value of dexlansoprazole capsules group (62.96%) was greater compared with placebo group (46.55%) (Table 7.a).

An ad hoc sensitivity analysis was performed on the primary and secondary efficacy endpoints.. For primary efficacy endpoint, the difference between treatment groups was statistically significant (P=0.029) (Table 15.2.6). For the secondary efficacy endpoint, the difference between the treatment groups was not statistically significant (P=0.365) (Table 15.2.7).

Table 7.a Percentage of Days Without Heartburn During Treatment (Full Analysis Set)

	Placebo QD N = 108	Dexlansoprazole 30 mg QD N = 107
Primary endpoint: percentage of days with neither daytime nor nighttime heartburn during treatment [a]		
N	108	107
Mean (SD)	36.98 (31.999)	47.21 (35.995)
Median	32.67	51.72
P-value [b]		0.057
Secondary endpoint: percentage of days without nighttime heartburn during treatment		
N	108	107
Mean (SD)	50.38 (34.309)	54.83 (37.449)
Median	54.67	67.86
P-value [b]		0.268
Additional endpoint: percentage of days without daytime heartburn during treatment		
N	108	107
Median	46.55	62.96

Source: Table 15.2.1.
QD: once daily.
[a] Percentage of days with neither daytime nor nighttime heartburn = (the days that are heartburn-free during treatment period) / (total number of days for which either a daytime or nighttime result is marked during treatment period) × 100%.
[b] The 2-sided p-value was obtained using the Wilcoxon rank-sum test.

Table 7.b Subgroup Analyses of Percentage of Days With Neither Daytime Nor Nighttime Heartburn Over 4 Weeks (Full Analysis Set)

	Placebo QD N=108	Dexlansoprazole 30 mg QD N=107
Age (<45 years)		
N	46	50
Mean (SD)	39.40 (34.297)	53.09 (34.458)
P-value		0.068
Age (≥45 to 65 years)		
N	57	53
Mean (SD)	35.02 (29.633)	41.79 (36.018)
P-value		0.472
Age (≥65 years)		
N	5	4
Mean (SD)	37.17 (41.722)	45.37 (52.932)
P-value		0.898
Gender (Male)		
N	43	47
Mean (SD)	34.40 (33.307)	49.51 (37.033)
P-value		0.063
Gender (Female)		
N	65	60
Mean (SD)	38.70 (31.248)	45.40 (35.370)
P-value		0.381
BMI (<25 kg/m^2)		
N	69	72
Mean (SD)	37.94 (31.249)	45.50 (36.638)
p-value		0.298
BMI (≥25 to 30 kg/m^2)		
N	34	28
Mean (SD)	34.93 (33.229)	51.55 (36.338)
p-value		0.104
BMI (≥30 kg/m^2)		
N	5	7
Mean (SD)	37.78 (40.352)	47.39 (30.665)
p-value		0.744

	Placebo QD N=108	Dexlansoprazole 30 mg QD N=107
H pylori status (positive)		
N	41	40
Mean (SD)	39.87 (30.941)	55.95 (35.893)
p-value		**0.032**
H pylori status (negative)		
N	67	67
Mean (SD)	35.22 (32.733)	41.99 (35.294)
p-value		0.403
Overall study drug compliance (<80%)		
N	0	1
Mean (SD)		0.00 (NA)
p-value		NA
Overall study drug compliance (80-<90%)		
N	1	3
Mean (SD)	83.33 (NA)	64.74 (37.701)
p-value		>0.999
Overall study drug compliance (≥90%)		
N	106	103
Mean (SD)	35.95 (31.370)	47.15 (35.884)
p-value		**0.037**

Source: Table 15.2.2.
Note 1: Percentage of days with neither daytime nor nighttime heartburn = (the days that are heartburn-free during Treatment Period)/(Total number of days for which either a daytime or nighttime result is marked during Treatment Period) * 100%.
Note 2: The p-value was obtained using the Wilcoxon rank-sum test.

7.2 Additional Efficacy Endpoints

7.2.1 Symptom Severity

7.2.1.1 Investigator-Assessed Symptom Severity

Investigator assessment of GERD symptoms included heartburn, acid regurgitation, dysphagia, belching, and epigastric pain. For each symptom, the investigator gave an assessment of none, mild, moderate, severe, and very severe, which were numerically scored as 0,1,2,3,4, respectively. Assessments were performed at baseline and at weeks 2 and 4, results are presented in Table 15.2.3. For each symptom the severity scores decreased from baseline at weeks 2 and 4 for both placebo and dexlansoprazole groups. Reductions in severity for heartburn were significantly greater in the dexlansoprazole group than placebo for both Week 2 (p=0.009) and Week 4 (p=0.005). Reductions in severity for acid regurgitation and belching were statistically

significantly greater in the dexlansoprazole group than placebo at Week 4 (p=0.008 and p=0.042). There were no significant difference for dysphagia or epigastric pain.

Some data issues about investigator-assessed GERD symptoms were discovered after database lock, therefore are not reflected in the above description: There were 3 subjects whose heartburn assessment at Week 4/Final Visit was entered into the database as "None," but should have been "Mild." The related subjects were 20002-003 (dexlansoprazole group), 20002-004 (dexlansoprazole group), and 20002-001 (placebo group). Subject 20002-001 (placebo group) also had acid regurgitation assessment at Week 4/Final Visit that was entered into the database as "Mild," but should have been "None." This was not expected to affect the analysis. More detailed information is listed in TAK 390MR_302_File_Note.zip.

7.2.1.2 Subject-Reported Heartburn Severity

For all the endpoints listed below, the mean value of dexlansoprazole capsules group was less than placebo group but the difference wasn't statistically significant (Table 15.2.5).

- The severity of daytime and nighttime heartburn over the 4 weeks of treatment as assessed by daily eDiary.
- The severity of nighttime heartburn over the 4 weeks of treatment as assessed by daily eDiary.
- The severity of daytime heartburn over the 4 weeks of treatment as assessed by daily eDiary.

7.2.2 Rescue Medication Use

For the percentage of days without rescue medication over 4 weeks, the mean value of dexlansoprazole capsules group (97.81%) was greater compared with placebo group (94.40%) and for the value reached 100%, the number of subjects in dexlansoprazole capsules group (84) was greater compared with placebo group (69). The distribution of the percentage of days without rescue medication use was statistically significant (P=0.009) (Table 15.2.4) different for the dexlansoprazole 30 mg QD and placebo.

7.3 Efficacy Conclusions

In this 4-week study comparing treatment with dexlansoprazole 30 mg QD or placebo in Chinese subjects with symptomatic nonerosive GERD, subjects treated with dexlansoprazole had a greater percentage of days with neither daytime nor nighttime heartburn and without nighttime heartburn than subjects taking placebo, but these differences were not statistically significant according to the pre-planned analysis.

Subjects in the dexlansoprazole treatment group with positive *H pylori* results or who were ≥90% compliant with study drug did have a statistically significantly greater percentage of days without daytime and nighttime heartburn than those in the placebo group. Subjects in the dexlansoprazole treatment group also had statistically significantly greater reduction in severity of heartburn, acid regurgitation, and belching according to investigator assessment of symptoms after 4 weeks of treatment. In addition, subjects taking dexlansoprazole had a statistically

significantly greater percentage of days without rescue medication use over 4 weeks of treatment.

8.0 SAFETY EVALUATION

All the safety data were summarized in the safety analysis set.

8.1 Adverse Events

Similar percentages of subjects experienced at least 1 TEAE in the placebo and dexlansoprazole groups (32.4% and 36.4%, respectively) (Table 8.a). The majority of TEAEs in both groups were mild in severity and were not related to study drug.

No subjects died during the study (Appendix 16.2.7.4). One subject in the dexlansoprazole group experienced an SAE; the event was not related to study drug and did not lead to premature discontinuation (Appendix 16.2.7.3). Two subjects in each treatment group prematurely discontinued the study due to adverse events, the majority of which recovered and resolved (Appendix 16.2.7.2).

Table 8.a Overview of Treatment-Emergent AEs (Safety Analysis Set)

	Placebo QD N=108		Dexlansoprazole 30 mg QD N=107	
Category	**Events**	**Subjects n (%)**	**Events**	**Subjects n (%)**
Treatment-Emergent adverse event (TEAE)	70	35 (32.4)	63	39 (36.4)
Mild	61	27 (25.0)	47	26 (24.3)
Moderate	7	6 (5.6)	13	10 (9.3)
Severe	2	2 (1.9)	3	3 (2.8)
Related	21	13 (12.0)	24	15 (14.0)
Not Related	49	22 (20.4)	39	24 (22.4)
Leading to Study Drug Discontinuation	3	2 (1.9)	5	2 (1.9)
Serious adverse event (SAE)	0	0	1	1 (<1)
Related	0	0	0	0
Not Related	0	0	1	1 (<1)
Leading to Study Drug Discontinuation	0	0	0	0
Deaths	0	0	0	0

Source: Table 15.3.1.1.

8.1.1 Display of Adverse Events

All TEAEs are listed by subject in Appendix 16.2.7.1. Overall, the most frequently reported TEAEs occurring in ≥5% of subjects in either treatment group (by MedDRA PT) were upper respiratory tract infection and nasopharyngitis (Table 8.b). All of these were non-serious adverse events that were not considered by the investigator to be related to study drug, and none led to study drug discontinuation.

Table 8.b Most Frequent Treatment-Emergent Adverse Events by Preferred Term - PT Occurring in ≥5% of Subjects in Either Treatment Group (Safety Analysis Set)

	No. of Subjects (%)	
PT	**Placebo QD N=108**	**Dexlansoprazole 30 mg QD N=107**
Subjects with any TEAEs	35 (32.4)	39 (36.4)
Upper respiratory tract infection	8 (7.4)	5 (4.7)
Nasopharyngitis	7 (6.5)	4 (3.7)

Source: Table 15.3.1.7.1.

8.1.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

8.1.2.1 Deaths

No death was reported.

8.1.2.2 Other Serious Adverse Events

One subject experienced a single serious adverse event during the study. This subject was in the dexlansoprazole group and experienced an event of "cat claw scratch" on Day 1. The event resolved on Day 50. It was not considered related to study drug and did not lead to discontinuation of study drug (Appendix 16.2.7.3).

8.1.2.3 Other Significant Adverse Events

A total of 4 subjects (2 from each group) experienced 8 TEAEs leading to study drug discontinuation (Appendix 16.2.7.2). All of these TEAEs were considered by the investigator to be related to study drug. In the placebo group, one subject discontinued from study drug due to dizziness (mild) and hypertension (moderate); the other subject discontinued from study drug due to sleep disorder (severe). In the dexlansoprazole group, one subject discontinued from study drug due to fall (mild), joint injury (mild), dizziness (mild), and syncope (moderate); the other subject discontinued from study drug due to dyspepsia (moderate).

8.2 Clinical Laboratory Evaluation

8.2.1 Hematology

By-subject hematology parameters result are presented in Appendix 16.2.8.1.1 and the out-of-normal-range results are presented in Appendix 16.2.8.1.5.

Descriptive statistics for baseline, post baseline, and change from baseline to post baseline values for relevant hematology parameters are summarized in Table 15.3.4.1.3. Mean changes from baseline in hematology parameters in both groups were small and were not clinically concerning.

Some shifts from baseline to week 4 in hematology values were observed in both treatment groups and are summarized in Table 15.3.4.1.5. These shifts occurred in few subjects overall, and none were clinically concerning.

Hematology MAVs are summarized in Table 15.3.4.1.7.1 and listed in Appendix 16.2.8.1.8. No subjects in the dexlansoprazole group had hematology MAVs during treatment. Two subjects in the placebo group had hematology MAVs at week 4. One subject had markedly abnormally low hemoglobin (<88g/L). The second subject had markedly abnormally low platelets (<75× $10^3/\mu L$). The hematology MAVs were not reported as AEs.

No subject had abnormalities in hematology parameters that were classified as SAEs.

8.2.2 Serum Chemistry

By-subject serum chemistry parameters results are presented in Appendix 16.2.8.1.2 and the out-of-normal-range result was presented in Appendix 16.2.8.1.6.

Descriptive statistics for baseline, post baseline, and change from baseline to post baseline values for relevant serum chemistry parameters are summarized in Table 15.3.4.1.4. Mean changes from baseline in chemistry parameters in both groups were small and were not clinically concerning.

Some shifts from baseline to week 4 in chemistry values were observed in both treatment groups and are summarized in Table 15.3.4.1.6. These shifts occurred in few subjects overall, and none were clinically concerning.

Chemistry MAVs are summarized in Table 15.3.4.1.7.1 and listed in Appendix 16.2.8.1.8. Two subjects (1 in each group) had a chemistry MAV during treatment. None of the MAVs were reported as an AE and none were clinically concerning.

8.2.3 Urinalysis

By-subject urinalysis results are presented in Appendix 16.2.8.1.3 and the out-of-normal range results are presented in Appendix 16.2.8.1.7. None of the urinalysis results were clinically concerning.

8.2.4 Serum Gastrin

The percentages of subjects with elevated gastrin values ≥200 pg/mL and ≥400 pg/mL are presented in Table 8.c. The number and the percentage of subjects with elevated gastrin values was greater in the dexlansoprazole capsules group than in the placebo group at week 4.

Descriptive statistics for baseline, post baseline, and change from baseline to post baseline values for gastrin are summarized in Table 15.3.4.1.10. The mean change value in the dexlansoprazole capsules group (73.9 pg/mL) were greater than those in the placebo group (-3.8 pg/mL) at week 4.

Table 8.c Summary of Gastrin Results (Safety Analysis Set)

	No. of Subjects (%)	
Elevated Gastrin Values	**Placebo QD N=108**	**Dexlansoprazole 30 mg QD N=107**
No. of Subjects at Visit 4 (Week 4)	102	103
≥200 pg/mL	6 (5.9)	15 (14.6)
≥400 pg/mL	3 (2.9)	4 (3.9)

Source: Table 15.3.4.1.8.

8.3 Vital Signs

By-subject vital signs data are presented in Appendix 16.2.8.2.1. Details of vital signs MAVs are summarized in Table 15.3.4.2.3.2 and listed in Appendix 16.2.8.2.2.

The descriptive statistics for baseline, post baseline, and change from baseline to post baseline values for vital signs are summarized in Table 15.3.4.2.2. The mean changes from baseline to week 4 in each group were small and not clinically concerning.

None of the vital signs MAVs were reported as an AE and none were clinically concerning.

8.4 12-Lead ECGs

By-subject ECG results are presented in Appendix 16.2.8.3.1. The descriptive statistics for baseline, post baseline, and change from baseline to post baseline ECG results are summarized in Table 15.3.4.3.2.

ECG MAVs are summarized in Table 15.3.4.3.3 and are listed by subject in Appendix 16.2.8.3.2. None of the ECG MAVs were reported as an AE and none were clinically concerning.

Shifts in ECG interpretation results are summarized in Table 15.3.4.3.4 and none were clinically concerning.

8.5 Other Observations Related to Safety

Physical examination results are presented in Appendix 16.2.8.4.

8.6 Safety Conclusions

In this 4-week study in Chinese subjects with symptomatic non-erosive GERD, treatment with dexlansoprazole 30 mg QD was generally well tolerated. The incidence of TEAEs was similar between subjects taking placebo or dexlansoprazole; most events were mild in intensity and were considered unrelated to treatment. The most frequently reported TEAEs were consistent with the known safety profile of dexlansoprazole. Few subjects experienced an AE that led to premature discontinuation. No study drug-related SAE was reported. There were no remarkable findings in the safety clinical laboratory, vital signs, or ECG data. Overall, no safety concerns were identified in this study.

9.0 DISCUSSION AND OVERALL CONCLUSIONS

9.1 Discussion

Phase 3 studies performed in the United States have demonstrated positive results using dexlansoprazole capsules for heartburn relief in subjects with symptomatic nonerosive GERD. This study was the first to examine the efficacy and safety of dexlansoprazole capsules in Chinese subjects with symptomatic nonerosive GERD.

The main objective of this phase 3, double-blind, randomized study was to compare the efficacy of dexlansoprazole capsule (30 mg QD) and placebo in relief of daytime and nighttime heartburn over 4 weeks in Chinese subjects with symptomatic nonerosive GERD as assessed by daily electronic diary (eDiary).

No major differences in subject disposition were observed across treatment groups. Subject discontinuation rates in dexlansoprazole capsules groups (3.7%) were generally lower than placebo group (5.5%). Treatment compliance was high in all groups, with ≥97% of the total 215 subjects maintaining greater than 90% compliance with the dosing schedule. Similarly, no major differences were observed across treatment groups in subject demographics. More females (58.1%) were enrolled in the study (consistent across treatment groups); however, this gender difference did not have an impact on the analysis of efficacy results. Approximately 51% of subjects were aged from 45 to 65 years. A small proportion of subjects were aged 65 years or older (4.2%); therefore, any interpretation of efficacy results in these subjects is limited.

The results of Study TAK-390MR_302 showed that, although subjects in the dexlansoprazole group had a greater percentage of days with neither daytime nor nighttime heartburn than those taking placebo, the results of the primary endpoint (percentage of days and nights without heartburn) did not reach statistical significance based on the original planned analysis (p=0.057). Statistical significance was missed by a small margin. As an indication of how close the results were to reaching significance, when analyzed in subjects with the highest treatment compliance (≥90%), the difference was statistically significant; these results indicate that dexlansoprazole treatment was more effective than placebo for treating Chinese subjects with symptomatic nonerosive GERD when the medication was taken consistently. Subjects who took dexlansoprazole also had a greater percentage of nights without heartburn than those who took placebo, but the difference was not statistically significant. Subjects in the dexlansoprazole group had statistically significantly greater reductions in investigator-assessed symptoms of heartburn, acid regurgitation, and belching after 4 weeks of treatment, and also used statistically significantly less rescue medication than subjects in the placebo group.

After the unblinded results for the primary and secondary endpoints were available, an *ad hoc* sensitivity analysis (two sample t-test) was performed to explore the influence of the higher than expected placebo response in light of the fact that the p-value for the primary analysis of the primary endpoint was insignificant by only a small amount. The sensitivity analysis results in a statistically significant difference between the group means for the primary endpoint (percentage of days with neither daytime nor nighttime heartburn, p=0.029). The difference between groups

for the secondary endpoint (percentage of days without nighttime heartburn) was not statistically significant based on the sensitivity analysis (p=0.365).

The results of Study TAK-390MR_302 were similar to Study T-GD05-137 (on which the assumptions for study power were based) for measuring the dexlansoprazole treatment effect, but were not consistent for measuring the placebo effect. Because this was a well-controlled clinical trial, a few of the reasons that might explain this outcome are discussed herein.

One possible reason for the outcome of this study is random chance. With a type 1 error rate of 5%, this study had a 1 in 20 chance of showing non-significant results when a true treatment difference existed. It is interesting to recall that in the dexlansoprazole pivotal trials, a stronger level of significance (α=0.0025) was used and satisfied.

Another possible reason for the outcome may be that the placebo effect is higher among the population sampled in this study than the population sampled in previous dexlansoprazole studies. In this case, the situation is not that the active treatment is disproven as effective, but is that the study wasn't adequately powered to measure the treatment differences. The assumptions for which this study was powered (ie, sample size determination) were based on Study T-GD05-137, in which the mean percentage of days without daytime or nighttime heartburn for subjects taking placebo was 25%; this placebo response rate was similar in the other dexlansoprazole studies that included a placebo arm (Studies T-GD04-082 and T-GD07-170). High placebo response rates have been observed in other studies of symptomatic GERD [1-3]. Chinese subjects who took placebo in Study TAK-390MR_302, however, had a higher placebo response rate (mean percentage of days without daytime or nighttime heartburn was 37%).

A final reason for the outcome of Study TAK-390MR_302 may be that the disease burden of those sampled was not exactly comparable to that of the patients who participated in the US pivotal and supportive studies, which resulted in the higher than expected placebo response.

For at least two of the three possible reasons described here, the lack of statistical significance shown for the primary endpoint in Study TAK-390MR_302 is not because of a lack of treatment effect, but because the study was not adequately powered to detect the treatment differences. The result of the *ad hoc* sensitivity analysis supports this conclusion. The t-test used in the sensitivity analyses is a more statistically powerful test than the Wilcoxon rank sum test, when certain assumptions are met. In the case of a large sample size (eg. 200 subjects), the t-test is robust.

Although the placebo response rate observed in this study of Chinese subjects was unexpected based on previous dexlansoprazole data, it is not inconsistent with the results of a similar study in another Asian population. Specifically, Hongo, et al, studied the efficacy of famotidine (an H2RA) in Japanese patients with nonerosive reflux disease in a double-blind, placebo-controlled, parallel-group, multicenter study [4]. The percentage of days without heartburn over 8 weeks for subjects on active treatment in this study ranged between 59% and 62% depending on dose, while subjects who took placebo had a response rate of 55%. The authors who reported the results of this study concluded that "the efficacy of placebo is considerably higher in Japanese nonerosive GERD patients than in Western nonerosive GERD patients."

There may be several physiological reasons for the higher-than-expected placebo response rate observed in Chinese patients with symptomatic nonerosive GERD in Study TAK-390MR_302. Asian patients have lower gastric acid output than white patients [5], as well as lower rates of TLESR [6]; thus, Asian patients may experience fewer acid-related GERD symptoms than their western counterparts. It has also been suggested that factors other than acid may be important in the pathophysiology of nonerosive GERD in Chinese patients, such as esophageal hypersensitivity, weakly acid or weakly alkaline reflux, or psychosocial factors [7]. This hypothesis was based on the results of an esomeprazole study in Chinese patients with symptomatic nonerosive GERD, in which esomeprazole was effective in relieving symptoms, but a lower complete symptom response rate was observed than in studies of PPIs in Western patients with nonerosive GERD. It is important to keep in mind, however, that it is not possible to draw definitive conclusions about placebo response rates in Asian patients compared to their western counterparts based only on data from 2 relatively small studies in Chinese patients.

For the additional analyses, a statistically significant improvement in the days without rescue medication over 4 weeks was observed for dexlansoprazole capsules compared with placebo. For each GERD symptom, the mean severity scores decreased from baseline at weeks 2 and 4 for both placebo and dexlansoprazole groups. Reductions in severity for heartburn were significantly greater in the dexlansoprazole group than placebo for both Week 2 (p=0.009) and Week 4 (p=0.005). Reductions in severity for acid regurgitation and belching were significantly greater in the dexlansoprazole group than placebo at Week 4 (p=0.008 and p=0.042). There were no significant difference for dysphagia or epigastric pain.

The proportion of subjects with any TEAE was similar in the placebo and dexlansoprazole groups (32.4% and 36.4%, respectively).The proportion of subjects with a TEAE that led to study discontinuation was low, supporting that dexlansoprazole capsules were well tolerated by Chinese subjects. Only one SAE was observed, but it was not considered to be related to study drug. No deaths were reported during this study. There were no abnormalities that were classified as SAEs with respect to vital signs, ECG results, or laboratory parameters.

9.2 Conclusion

In this 4-week study of dexlansoprazole 30 mg or placebo in Chinese subjects with symptomatic nonerosive GERD, dexlansoprazole was safe and well tolerated. Subjects taking dexlansoprazole had a greater percentage of days without daytime or nighttime heartburn (difference of 19 percentage points) and without nighttime heartburn alone (difference of 13 percentage points) than subjects taking placebo, but the differences between the treatment groups were not statistically significant. Statistically significant improvements were observed, however, in several investigator-assessed GERD symptoms after 4 weeks of treatment with dexlansoprazole (an additional endpoint). In addition, subjects taking dexlansoprazole used statistically significantly less rescue medication than those taking placebo.

10.0 REFERENCES

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4. Hongo M, Kinoshita Y, Haruma K. A randomized, double-blind, placebo-controlled clinical study of the histamine H2-receptor antagonist famotidine in Japanese patients with nonerosive reflux disease. J Gastroenterol 2008;43(6):448-56.
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Appendix A Criteria for Identification of Markedly Abnormal Laboratory Values

Hematology—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
Hemoglobin	<0.8 × LLN,	>1.2 × ULN
Hematocrit	<0.8 × LLN,	>1.2 × ULN
RBC count	<0.8 × LLN,	>1.2 × ULN
WBC count	<0.5 × LLN	>1.5 × ULN
Platelet count	<75 x 10^3/μL	>600 x 10^3/μL

RBC=red blood cell, WBC=white blood cell. LLN=lower limit of normal, ULN=upper limit of normal

Chemistry—Criteria for Markedly Abnormal Values

Parameter	Low Abnormal	High Abnormal
ALT	--	≥3x ULN
AST	--	≥3x ULN
GGT	--	≥3x ULN
Alkaline phosphatase	--	≥3x ULN
Total bilirubin	--	>2.0 mg/dL
Albumin	<2.5 g/dL	--
Total protein	<0.8x LLN	>1.2x ULN
Creatinine	--	>2.0 mg/dL
Blood Urea Nitrogen	--	>30 mg/dl
Sodium	<130 mEq/L	>150 mEq/L
Potassium	<3.0 mEq/L	>6.0 mEq/L
CPK	--	≥5 x ULN

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, CPK=creatine phosphokinase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix B Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Pulse	bpm	<50	>120
Systolic blood pressure	mm Hg	<85	>180
Diastolic blood pressure	mm Hg	<50	>110
Body temperature	ºC	<35.6	>37.7

Appendix C Criteria for Markedly Abnormal Values for Electrocardiograms

Parameter	Unit	Lower Criteria	Upper Criteria
Heart Rate	bpm	<50	>120
QT Interval	msec	≤50	≥460
QTcB Interval	msec	≤50	≥500 OR ≥30 change from baseline and ≥450
QTcF Interval	msec	≤50	≥500 OR ≥30 change from baseline and ≥450

11.0 DATA ISSUE NARRATIVES

There are some data issues after site quality control, but they didn't make a difference to the overall conclusion. For the data issues about protocol deviations and GERD symptoms, they were noted in section 6.2 and 7.2, respectively. For the other data issues, they were all listed in TAK 390MR_302_File_Note.zip.

12.0 APPENDIX

12.1 Source Database, Analytic Database and Corresponding Variable Specification Document

The content was stored in the ZIP file "TAK-390MR_302-Statistical-Analysis-Report-Appendix.zip" as the appendix of the document.

12.2 Flow Chart of Subject Disposition

Please refer to Figure 6.a Disposition of Subjects.

12.3 Randomization Scheme

The content was stored in the ZIP file "TAK-390MR_302-Statistical-Analysis-Report-Appendix.zip" as the appendix of the document.

12.4 Blind Review Resolutions

The content was stored in the ZIP file "TAK-390MR_302-Statistical-Analysis-Report-Appendix.zip" as the appendix of the document.

12.5 Statistical Figures and Tables Supplementary to the Main Text

The content was stored in the ZIP file " TAK-390MR_302-Statistical-Analysis-Report-Appendix.zip" as the appendix of the document.

12.6 Data Issue File Note

The content was stored in the ZIP file " TAK-390MR_302-Statistical-Analysis-Report-Appendix.zip" as the appendix of the document.

12.7 Detailed Description of Amendments to Text

Change 1: Correct the incidence of TEAEs that were mild in intensity and recovered/resolved.

The change occurs in Synopsis:

Initial wording: All TEAEs were mild in intensity and all recovered and resolved.

Amended wording: ~~All~~ **Most** TEAEs were mild in intensity and all recovered and resolved.

Rationale for Change: Correct wording.

Change 2: Correct the cross-references for some data presented and correct the description of how many adverse events that led to premature discontinuation had recovered or resolved**.**

The change occurs in Section 8.1 Adverse Events:

Initial wording**:** No subjects died during the study (Appendix16.2.7.3). One subject in the dexlansoprazole group experienced an SAE; the event was not related to study drug and did not lead to premature discontinuation (Appendix 16.2.7.4). Two subjects in each treatment group prematurely discontinued the study due to adverse events that all recovered and resolved (Appendix16.2.7.2).

Amended wording: No subjects died during the study (Appendix 16.2.7.~~3~~**4**). One subject in the dexlansoprazole group experienced an SAE; the event was not related to study drug and did not lead to premature discontinuation (Appendix 16.2.7.4**3**). Two subjects in each treatment group prematurely discontinued the study due to adverse events ~~that all~~**, the majority of which** recovered and resolved (Appendix 16.2.7.2).

Rationale for Change: Correct wording and source data.

Change 3: Add the information about adverse events that led to study discontinuation as "other significant adverse events."

The change occurs in Section 8.1.2.3 Other Significant Adverse Events:

Initial wording: No other significant adverse event was reported.

Amended wording: ~~No other significant adverse event was reported.~~ **A total of 4 subjects (2 from each group) experienced 8 TEAEs leading to study drug discontinuation (Appendix 16.2.7.2). All of these TEAEs were considered by the investigator to be related to study drug. In the placebo group, one subject discontinued from study drug due to dizziness (mild) and hypertension (moderate); the other subject discontinued from study drug due to sleep disorder (severe). In the dexlansoprazole group, one subject discontinued from study drug due to fall (mild), joint injury (mild), dizziness (mild), and syncope (moderate); the other subject discontinued from study drug due to dyspepsia (moderate).**

Rationale for Change: Add the information that was inadvertently left out of the original SAR.

Change 4: Clarify the type of markedly abnormal hematology values observed during the study.

The change occurs in Section 8.2.1 Hematology :

Initial wording: Hematology MAVs are summarized in Table 15.3.4.1.7.1 and listed in Appendix 16.2.8.1.8. No subjects in the dexlansoprazole group had hematology MAVs during treatment. Two subjects in the placebo group had hematology MAVs at week 4. One subject had decreased hemoglobin (<88g/L). The second subject had decreased platelets (<75× 10^3/μL). The hematology MAVs were not reported as AEs.

Amended wording: Hematology MAVs are summarized in Table 15.3.4.1.7.1 and listed in Appendix 16.2.8.1.8. No subjects in the dexlansoprazole group had hematology MAVs during treatment. Two subjects in the placebo group had hematology MAVs at week 4. One subject had ~~decreased~~ **markedly abnormally low** hemoglobin (<88g/L). The second subject had ~~decreased~~

markedly abnormally low platelets (<75× 10^3/µL). The hematology MAVs were not reported as AEs.

Rationale for Change: Clarify wording.

Change 5: Correct the cross-references for some data presented and add the number of observed records of visit 4 (week 4) and clarity the format of table for the summary of gastrin results.

The change occurs in Section 8.2.4 Serum Gastrin:

Initial text and table: Descriptive statistics for baseline, post baseline, and change from baseline to post baseline values for gastrin are summarized in Table 15.3.4.1.8.a. The mean change value in the dexlansoprazole capsules group (73.9 pg/mL) were greater than those in the placebo group (-3.8 pg/mL) at week 4.

Table 8.c Summary of Gastrin Results (Safety Analysis Set)

	No. of Subjects (%)	
Elevated Gastrin Values	**Placebo QD N=108**	**Dexlansoprazole 30 mg QD N=107**
During Treatment (a)		
≥200 pg/mL	6 (5.7)	15 (14.3)
≥400 pg/mL	3 (2.8)	4 (3.8)
By Visit		
Visit 4 (Week 4)		
≥200 pg/mL	6 (5.9)	15 (14.6)
≥400 pg/mL	3 (2.9)	4 (3.9)

Note: (a) At least one markedly abnormal result During treatment.
Source: Table 15.3.4.1.8.

Amended text and table: Descriptive statistics for baseline, post baseline, and change from baseline to post baseline values for gastrin are summarized in Table 15.3.4.1.~~8.a~~**10**. The mean change value in the dexlansoprazole capsules group (73.9 pg/mL) were greater than those in the placebo group (-3.8 pg/mL) at week 4.

Table 8.c Summary of Gastrin Results (Safety Analysis Set)

	No. of Subjects (%)	
Elevated Gastrin Values	**Placebo QD N=108**	**Dexlansoprazole 30 mg QD N=107**
~~During Treatment (a)~~		
~~≥200 pg/mL~~	~~6 (5.7)~~	~~15 (14.3)~~
~~≥400 pg/mL~~	~~3 (2.8)~~	~~4 (3.8)~~
~~By Visit~~		
No. of Subjects at Visit 4 (Week 4)	**102**	**103**
≥200 pg/mL	6 (5.9)	15 (14.6)
≥400 pg/mL	3 (2.9)	4 (3.9)

~~Note: (a) At least one markedly abnormal result During treatment.~~
Source: Table 15.3.4.1.8.

Rationale for Change: Add the information that was inadvertently left out of the original SAR.

Change 6: Modify the language in the safety conclusion regarding the SAE or AE that led to premature discontinuation for consistency with the clinical study report (Section 8.6).

The change occurs in Section 8.6 Safety Conclusions:

Initial wording: In this 4-week study in Chinese subjects with symptomatic non-erosive GERD, treatment with dexlansoprazole 30 mg QD was generally well tolerated. The incidence of TEAEs was similar between subjects taking placebo or dexlansoprazole; most events were mild in intensity and were considered unrelated to treatment. The most frequently reported TEAEs were consistent with the known safety profile of dexlansoprazole. Few subjects experienced an SAE or an AE that led to premature discontinuation. There were no remarkable findings in the safety clinical laboratory, vital signs, or ECG data. Overall, no safety concerns were identified in this study.

Amended wording: In this 4-week study in Chinese subjects with symptomatic non-erosive GERD, treatment with dexlansoprazole 30 mg QD was generally well tolerated. The incidence of TEAEs was similar between subjects taking placebo or dexlansoprazole; most events were mild in intensity and were considered unrelated to treatment. The most frequently reported TEAEs were consistent with the known safety profile of dexlansoprazole. Few subjects experienced ~~an SAE or~~ an AE that led to premature discontinuation. **No study drug-related SAE was reported.** There were no remarkable findings in the safety clinical laboratory, vital signs, or ECG data. Overall, no safety concerns were identified in this study.

Rationale for Change: Clarify wording and for consistency with clinical study report.

Change 7: Replace the table of efficacy results with one that does not include the ad hoc analyses. Update references in text accordingly.

The change occurs in Section 7.1 Primary and Secondary Efficacy Endpoint:

Initial wording: An ad hoc sensitivity analysis was performed on the primary and secondary efficacy endpoints, and these results are also presented in Table 7.a. For primary efficacy endpoint, the difference between treatment groups was statistically significant (P=0.029). For the secondary efficacy endpoint, the difference between the treatment groups was not statistically significant (P=0.365).

[Table 7.a including ad hoc analyses]

Amended wording: An ad hoc sensitivity analysis was performed on the primary and secondary efficacy endpoints~~, and these results are also presented in Table 7.a~~. For primary efficacy endpoint, the difference between treatment groups was statistically significant (P=0.029) **(Table 15.2.6)**. For the secondary efficacy endpoint, the difference between the treatment groups was not statistically significant (P=0.365) **(Table 15.2.7)**.

[Table 7.a without ad hoc analyses and matching clinical study report]

Rationale for Change: Consistency with clinical study report, in which ad hoc analyses are not included in the in-text efficacy table in order to clarify which analysis was pre-planned.