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

SAP Approve Date: 14 February 2018

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

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

TAKEDA DEVELOPMENT CENTER

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-390MR_301

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

PHASE 3

Version**:** Final

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Prepared by:

PPD

1.1 APPROVAL SIGNATURES

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TDC Approvals:

PPD

01/DEC/2017
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PPD

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PPD

05 Dec 2017
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Date

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3.0 LIST OF ABBREVIATIONS

AE	adverse event
BMI	body mass index
CMH	Cochran-Mantel-Haenszel
ECG	electrocardiogram
EE	erosive esophagitis
FAS-H	Full Analysis Set – Healing Period
FAS-M	Full Analysis Set – Maintenance Period
GERD	gastroesophageal reflux disease
HLT	high level term
MedDRA	Medical Dictionary for Regulatory Activities
MAV	markedly abnormal values
PT	preferred term
QD	once daily
SI	System International
SOC	system organ class
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is to compare the efficacy of dexlansoprazole capsules (60 mg QD) and lansoprazole capsules (30 mg QD) in healing erosive esophagitis (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.

4.2 Secondary Objectives

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.

4.3 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 gastroesophageal reflux disease (GERD) related symptoms. Approximately 450 subjects will be enrolled at an estimated 25 sites across China. Further details can be found in the study protocol (Protocol Amendment 3, 20 February 2017).

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 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, electrocardiogram (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, 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 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 adverse events (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).

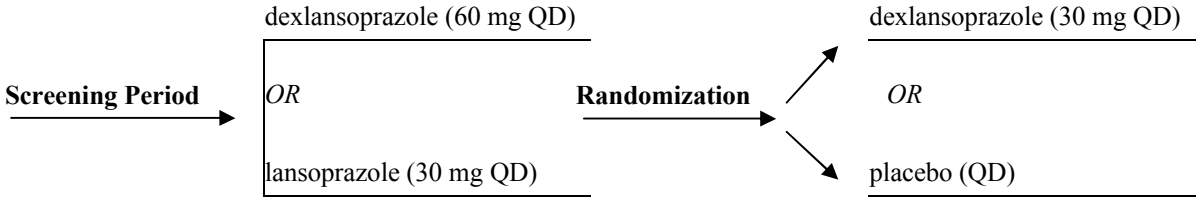
At the Month 3 Visit, the subject will undergo a physical examination including vital signs, laboratory evaluations and urine pregnancy test (all women of childbearing potential). An optional endoscopy may be performed based on investigator's discretion if the subject presents with GERD symptoms at any 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 4.a.

Figure 4.a Schematic of Study Design



Healing Period **Maintenance Period**

Day -1	Day 1	Week 4	Week 8/Final Visit	Day 1	Mo 1	Mo 3	Mo 6/Final Visit
Randomize	1st Dose		Healing Period	Randomize 1st Dose			Maintenance Period

Mo=month.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

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

5.2 Secondary Endpoints

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

5.3 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 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.

5.4 Safety Assessments

Safety will be assessed by AEs, clinical laboratory evaluations (including gastrin), vital signs, physical examination, and ECGs.

6.0 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.

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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Considerations

Statistical analysis will be performed using the SAS System, Version 9.2 or higher.

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

7.1.1 Definition of Study Days and Visit Window

Study day will be 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 will be 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 will be calculated as:

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

Baseline is defined as the last non-missing measurement prior to or on Study Day 1 (prior to first dose). The baseline values for the Maintenance Period will be the assessment performed at the Week 8 visit of the Healing Period.The visit windows for each post baseline visit are defined in Table 7.a. If a subject has more than 1 measurement in the same visit window, the measurement closest to the scheduled visit will be used. If 2 measurements in the same window are of equal distance to the scheduled visit, the measurement that occurs after the scheduled visit will be used. If 2 or more measurements occur on the same day, the last value obtained will be used.

Table 7.a Visit Windows for Healing Period

Visit	Scheduled Day	Safety Labs	Serum Gastrin	Vital Signs	ECG	Endoscopy	GERD Symptoms Investigator Assessment
Baseline	Day -1	≤1	≤1	≤1	≤1	≤1	≤1
Week 4	Day 28	2-42	NA	2-42	NA	NA	2-42
Week 8	Day 56	43-70	2-70	43-70	NA	2-70	43-70

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 will not be included in the analyses.

Additionally, for subjects with healed EE by Week 8 who are randomized and receive at least 1 dose of maintenance study drug, the window selection for the Week 8 Visit will include only measurements assessed on or before the date of the first dose of maintenance period study drug; for visits during the Maintenance of Healed EE Period, the window selection will only include measurements assessed after the date of the first dose of maintenance period study drug.

The summary of visits during the maintenance period will be relative to the start of maintenance treatment rather than relative to the start of the study. The table below summarizes the visit windows for each visit during the Maintenance of Healed EE Period.

For the purpose of the diary compliance calculation and derivation of diary-based endpoints, the last day of study drug in each period will not be included since the subject will not be expected to have completed the diary entries for that day by the Week 8 or month 6 Final Visit. Therefore, summaries for the healing period weeks of treatment will include Study Day 1 through Study Day 70 or the day before the last dose of healing period study drug, or the day before the first dose of maintenance study drug, whichever occurs first; summaries for the Maintenance period will include the day of the first dose of maintenance study drug through maintenance Study Day 180 or the day before the last dose of maintenance study drug, whichever occurs first.

Table 7.b Visit Windows for Maintenance Period

Visit	Scheduled Day	Safety Labs and Vital Signs	Serum Gastrin	ECG	Endoscopy	GERD Symptoms Investigator Assessment
Maintenance Baseline	-1M	≤1M	≤1M	≤1M	≤1M	≤1M
Month 1	30M	2M-60M	2M-60M	NA	2M-60M	2M-60M
Month 3	90M	61M-135M	61M-135M	NA	61M-135M	61M-135M
Month 6	180M	136M-210M	136M-210M	2M-210M	136M-210M	136M-210M

Note: Safety laboratory (including gastrin), vital signs, and ECG data obtained more than 7 days after the last day of study drug of Maintenance period and efficacy data obtained more than 7 days after the last day of study drug of Maintenance period will not be included in the analyses.
M=Maintenance Period.

7.2 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.

7.3 Disposition of Subjects

Subjects' study completion data, including reasons for premature termination, will be provided in listings and also summarized. Summaries of the reasons for premature termination will be presented separately for the healing period and for the maintenance of healed EE period.

A summary of screening failures and listings of inclusion/exclusion criteria responses will be provided.

Significant protocol deviations captured on the electronic Case Report Form will be summarized.

7.4 Demographic and Baseline Characteristics

Demographic variables will be summarized for the FAS-H and the FAS-M. For continuous variables (age, weight, height and body mass index [BMI]), summary statistics will be generated. The number and percentage of subjects in each category will be presented (eg, gender, race). BMI (in kg/m^2) will be calculated using the subject's baseline height and weight measurement and summarized.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using MedDRA. Medical history and concurrent medical conditions will be presented in a data listing.

7.6 Medication History and Concomitant Medications

All medication history and concomitant medications will be coded by therapeutic classification, subclassification, and medication using the World Health Organization Drug Dictionary (WHO Drug). A concomitant medication is defined as a medication that is 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. Medication history and concomitant medications will be presented in a data listing.

7.7 Study Drug Exposure and Compliance

Overall study drug compliance (%) will be determined as (total count of capsules taken) / total number of days on study drug × 100%, separately for the healing period and for the maintenance period.

For the healing period, the total number of days on study drug (exposure) will be calculated as date of last dose of study drug - date of first dose of study drug + 1, assuming there is no gap in the dosing. If the last dose date is missing, then the duration of the treatment period will be imputed as 70 days or the day before first dose date in maintenance period, whichever is earlier.

For the maintenance period, the total number of days on study drug (exposure) will be calculated as date of last dose of maintenance study drug - date of first dose of maintenance study drug + 1, assuming there is no gap in the dosing. Any gaps in dosing will be ignored when calculating the total. If the last dose date of the maintenance period is missing, then the duration of the maintenance period will be imputed as 189 days.

Subjects with unreturned study drug will be 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% will be set to 100% in the analysis.

In addition, diary compliance will be determined as the percentage of days during treatment with 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%

Exposure and compliance data will be presented in a data listing.

7.8 Efficacy Analysis

The efficacy endpoints will be summarized using the FAS-H for the healing period and using the FAS-M for the maintenance period.

7.8.1 Primary Efficacy Endpoint

The primary efficacy variable will be the percentage of subjects who have complete healing of EE over 8 weeks as assessed by endoscopy Subjects who do not have endoscopically documented healing and who prematurely discontinue will be considered as not healed. The primary endpoint will be presented in a data listing and summarized for the Healing period for the FAS-H.

7.8.2 Secondary Efficacy Endpoints

The secondary efficacy variable will be the percentage of subjects who maintained complete healing of EE over 6 months as assessed by endoscopy. Subjects who do not have endoscopically documented maintenance of healing and who prematurely discontinue will be considered to have relapsed. The secondary endpoint will be presented in a data listing and summarized for the Maintenance period for the FAS-M.

If a subject's final endoscopy was performed prior to the Month 6 Visit and indicated recurrence of EE, the subject will be considered to have recurrence of EE at the Month 6 Visit.

7.8.3 Additional Efficacy Endpoints

All additional efficacy variables will only be presented in data listings, no summary tables will be produced. The following are the additional efficacy variables to be listed:

The severity of GERD symptoms at Weeks 4 and 8 as assessed by the investigator during the Healing Period.

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.

- The severity of daytime and nighttime heartburn over the 8 weeks of the Healing Period and over the 6 months of the Maintenance Period as assessed by daily Diary.
- The severity of nighttime heartburn over the 8 weeks of the Healing Period and over the 6 months of the Maintenance Period as assessed by daily Diary.
- The severity of daytime heartburn over the 8 weeks of the Healing Period and over the 6 months of the Maintenance Period as assessed by daily Diary.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Not Applicable.

7.11 Safety Analysis

All safety analyses will be performed using the Safety Analysis Set-H for the Healing Period, and using the Safety Analysis Set-M for the maintenance period. Results will be summarized by treatment group.

7.11.1 Adverse Events

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

A Treatment Emergent Adverse Event (TEAE) will be defined as an AE that starts or worsens on or after Study Day 1, and no more than 30 days after the last dose of study drug. All TEAEs will be listed by subject number and MedDRA coding. A listing of all unique coded terms will also be provided.

The following summaries of TEAEs will be presented separately:

- TEAEs for subjects who enter into the Healing Period, occurring during the 8 week healing period (ie, TEAE starts or worsens on or after the first dose of healing phase study drug and no more than 30 days after the last dose if a subject does not receive any maintenance study drug or before the first dose of maintenance study drug) will be summarized by treatment group using the Safety Analysis Set-H.
- TEAEs for subjects who enter into Maintenance period, occurring during the 6 months maintenance treatment period (ie, TEAE starts or worsens on or after the first dose of maintenance study drug and before 30 days after last dose of maintenance) will be summarized by treatment group using the Safety Analysis Set-M.

The number and percentage of subjects with TEAEs will be summarized in several different tables:

- All AEs by system organ class (SOC), high level term (HLT), and preferred term (PT).
- Treatment-related AEs (TRAEs) by SOC, HLT, and PT.
- Most frequent AEs by SOC and PT (sorted by frequency of PT occurring in ≥5% of subjects).
- Most frequent TRAEs by SOC and PT (sorted by frequency of PT occurring in ≥2% of 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 will be 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 AEs, deaths and TEAEs resulting in premature discontinuation from study drug will be listed and summarized by SOC and PT. The most frequent treatment-emergent non-serious AEs will also be summarized by SOC and PT.

A pre-treatment event will be defined as an AE that starts before Study Day 1. A list of pre-treatment AEs by subject number and MedDRA coding will be presented separately. Pre-treatment AEs will be summarized by SOC, HLT and PT.

7.11.2 Clinical Laboratory Evaluations

Clinical laboratory variables (including serum gastrin) will be summarized using descriptive statistics for Baseline, postbaseline, and change from Baseline to postbaseline values using the safety analysis set-H for the healing period to summarize changes from Baseline and using the safety analysis set-M for the maintenance period to summarize changes from Week 8.

Individual results for serum fasting gastrin, clinical hematology and chemistry laboratory tests that are within the predefined “markedly abnormal laboratory value (MAV) criteria” will be summarized in tables. All clinical laboratory data will be presented in data listings.

The percentage of subjects with elevated gastrin values ≥200 pg/mL and ≥400 pg/mL will be summarized.

Elevated hepatic parameters will be summarized.

Summaries and listings of laboratory data will be presented in Systeme Internationale (SI) and conventional units. MAV tables and listings will be presented in the unit specified in the MAV criteria in Appendix A.

7.11.3 Vital Signs

Vital signs will be summarized using descriptive statistics for Baseline, postbaseline, and change from Baseline to postbaseline values using the Safety Analysis Set-H for the Healing Period to summarize changes from Baseline, using the Safety Analysis Set-M for the Maintenance period to summarize changes from Week 8.

All individual vital signs that meet predefined criteria for MAV (Appendix B) will be summarized in tables. All vital sign data will be presented in data listings.

7.11.4 12-Lead ECGs

ECG results will be interpreted using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Week 8 Visit ECG assessments will be cross-tabulated against the baseline assessment using the Safety Analysis Set-H. Month 6 ECG assessments will be cross-tabulated against the Week 8 assessment using the Safety Analysis Set-H.

All individual quantitative ECG values that meet predefined criteria for MAV (Appendix C) will be listed.

All ECG data will be presented in a data listing.

7.11.5 Other Observations Related to Safety

Physical examination results will be presented in a data listing and will not be summarized.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

None

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 $10^3/\mu L$	>600 x $10^3/\mu L$

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 Identification of Markedly Abnormal Vital Sign Values

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	^{o}C	<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

Appendix D Data Handling for Subject Daily Diary

Subjects will document the presence of daytime and nighttime heartburn(yes/no) and maximum severity (1=Mild, 2=Moderate, 3=Severe, or 4=Very Severe) and record their usage of rescue medication (yes/no) in their diary two times per day, once in the morning for nighttime heartburn and once in the evening for daytime heartburn. If a subject indicated that no heartburn was present during a diary entry, a heartburn severity of '0=None' will be assumed in the database.

For analysis purposes, diary entries will be assigned to a study day based on the day the collection interval started for that entry. For example, the Study Day 1 diary entries will include the evening diary completed on Study Day 1 (the collection interval started when the subject awoke on Study Day 1) and the morning entry completed on Study Day 2 (the collection interval started when the subject went to bed on Study Day 1).

For each subject, the percentage of days with neither daytime nor nighttime heartburn during treatment will be calculated using all days with at least 1 morning or evening diary entry during the Healing Period and during the Maintenance Period. For example, if a subject completed at least 1 diary entry on 52 of 56 days during the Healing Period, but missed both entries on 4 days, 52 days will be used as the denominator in the analysis. All entries on that day will need to be heartburn-free (when only one entry collected, that entry will need to be heartburn-free) in order for the day to be counted as a day with neither daytime nor nighttime heartburn.

A similar approach will be used to determine the percentage of days without rescue medication during treatment (the denominator would be total number of days with either a daytime or night time result marked during the Healing or Maintenance period).

The mean severity of daytime and nighttime heartburn during the Healing and Maintenance Periods for each subject will be calculated by taking the mean of the average severity on all days with at least one morning or evening diary entry. For each day, the average severity for the day will be determined by taking the mean of the morning and evening diary entries on that day. If one entry is missing, the average for the day will be the non-missing diary entry. These daily averages will then be averaged for all days with non-missing data to obtain the endpoint value for each subject.