

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
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Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22-287 / 000

**Drug Name:** Dexlansoprazole modified release Capsules (KAPIDEX<sup>®</sup>)

**Indication(s):** Healing of erosive esophagitis (EE); Maintenance of healed EE; Treatment of symptomatic gastroesophageal reflux disease (GERD)

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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

Dexlansoprazole MR 60 mg and 90 mg QD showed erosive esophagitis (EE) healing rates similar to lansoprazole 30mg; however, no additional clinical benefit over lansoprazole was indicated. For maintenance of healed EE, dexlansoprazole MR 30 mg and 60 mg showed clinical improvement in efficacy compared with placebo. There were no clinically or statistically meaningful treatment differences among the dexlansoprazole MR doses for either indication.

### 1.2 Brief Overview of Clinical Studies

TAP Pharmaceutical Products, Inc. submitted the NDA for KAPIDEX<sup>®</sup> (dexlansoprazole) modified release (MR) capsules (30, 60(b) (4) mg) for the following indications: (1) Healing (b) (4) of all grades of EE – 60(b) mg QD for up to 8 weeks; (2) Maintaining healing of EE(b) (4) – 30(b) mg QD; and (3) Treating(b) (4) heartburn (b) (4) associated with gastroesophageal reflux (b) (4) – 30 mg QD for 4 weeks.

A total of six phase 3, randomized, controlled studies were conducted to evaluate the efficacy and safety of dexlansoprazole MR, including two studies supporting the healing EE indication, two studies supporting the maintenance of healed EE indication, and two studies supporting the symptomatic GERD indication. The four studies for the healing EE and maintenance of healed EE indications are evaluated in this review. The two studies for the indication of symptomatic GERD are evaluated in a separate statistical review.

For the EE healing indication, Studies T-EE04-084 and T-EE04-085 were phase 3, randomized, double-blind, active-controlled, multicenter, 3-arm studies with treatment periods of up to eight weeks. The studies were designed to evaluate healing of EE, relief of GERD-related symptoms (including heartburn), and safety of dexlansoprazole MR 60 mg and 90 mg compared with delayed-release lansoprazole 30 mg. An endoscopy was performed at Week 4; if a subject's EE was healed, the subject was considered to have completed the study. For those subjects who were not healed and continued in the study, an additional endoscopy was performed at Week 8. Subjects whose EE had healed at Week 4 or Week 8 were eligible for enrollment in the 6-month maintenance of healed EE studies.

The maintenance of healed EE studies T-EE04-086 and T-EE05-135 were phase 3, randomized, double-blind, multicenter, placebo-controlled, 3-arm studies with treatment periods of up to six months. The studies were each designed to evaluate maintenance of healed EE, symptom relief, and safety of two doses of dexlansoprazole MR compared with placebo. Endoscopic assessments were performed at Month 1, 3, and 6, and subjects were terminated from the study if erosions recurred.

For symptomatic GERD, Studies T-GD04-082 and T-GD05-137 were phase 3, randomized, double-blind, multicenter, placebo-controlled, 3-arm studies with 4-week treatment periods. The studies were each designed to evaluate symptom relief and safety of two doses of dexlansoprazole MR compared with placebo. These studies are evaluated in a separate statistical review.

In all six phase 3 studies, the presence of heartburn, severity of heartburn, and use of rescue medication were analyzed from diary data that subjects recorded twice daily. Subjects also completed symptom severity and Quality of Life (QOL) questionnaires, the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) and the Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life Index (PAGI-QOL), respectively.

### 1.3 Statistical Issues and Findings

For the two phase 3 healing EE studies, non-inferiority of dexlansoprazole MR to lansoprazole was demonstrated with respect to healing rate at eight weeks. However, the sponsor's superiority claim for dexlansoprazole MR 90 mg QD over the active control of lansoprazole 30 mg QD is not valid due to an improper multiplicity adjustment approach. Moreover, the differences for two key secondary efficacy endpoints failed to show consistent statistical significance for either dose in both studies. Although the sponsor did not provide justification for their proposed non-inferiority margin of 10%, the lower confidence bound for the CI for the treatment differences was larger than -2%, and the point estimates for dexlansoprazole healing rates were consistently larger than those for the active control.

A wide range of subgroup analyses, integrated analyses, and supportive life-table analyses were done by the sponsor and reviewer in an effort to show consistency of benefit of dexlansoprazole MR compared with lansoprazole and to explore possible advantage of the higher 90 mg dose. While many of these analyses were not prespecified, they underscored the principal, non-inferiority results. The sponsor's data do not show that the higher (b) (4) dexlansoprazole dose of 90 mg has benefit over the lower (b) (4) dose of 60 mg.

For the two phase 3 maintenance of healed EE studies, the superiority claims of all three doses of dexlansoprazole MR over placebo were clearly established for both primary and secondary efficacy endpoints. However, there was no clear evidence of any dose-response effect, and the efficacy difference in the 30 mg and 60 mg dose groups was minimal to none. Additional subgroup and supportive analyses showed results that were consistent with the primary efficacy analyses.

## 2. INTRODUCTION

### 2.1 Overview

Gastroesophageal reflux disease (GERD) is a common recurring medical problem in the United States (U.S.) adult population. Prevalence of GERD-related symptoms ranges from at least once a month in approximately 40%, once a week in 20%, to daily in 14% of patients. GERD affects men and women in nearly equal proportions; however, fewer men than women (40% versus 60%) have nonerosive GERD, while more men than women (59% versus 41%) have EE. A number of risk factors, such as advancing age, obesity, smoking, and alcohol and caffeine consumption have been associated with the development of GERD.

Erosive esophagitis (EE) is diagnosed during endoscopy in up to 50% of patients with GERD symptoms, the severity of which is associated with the extent and duration of exposure of the esophagus to gastric acid. Patients with GERD who do not receive treatment, or in whom acid reflux is not effectively controlled, are at risk of developing significant complications, such as bleeding, strictures, and the premalignant condition of Barrett's esophagus. Maintenance of healed EE also requires continued adequate acid suppression therapy, as over 90% of healed patients will relapse within 6 to 12 months if treatment is discontinued.

Using the Los Angeles (LA) Classification System, Grade A and Grade B are generally considered to be mild esophagitis, while Grade C and Grade D represent moderate to severe esophagitis. The overall distribution of baseline esophagitis grades, based on published literature, suggests approximately 75% of subjects present with Grades A or B, and 25% with Grade C or D. Furthermore, the baseline rate of Grades C and D is approximately 18% and 6%, respectively, in clinical trials with proton pump inhibitors (PPIs).

The sponsor claims that acid suppression therapy with PPIs is the most effective pharmacologic treatment for relieving GERD symptoms, healing the injured mucosa, maintaining a healed mucosa, and preventing the development of complications. The sponsor further claims that PPIs are widely used and have well-established safety profiles. Marketed for over 12 years, Prevacid® (lansoprazole) is among the five PPIs presently marketed in the U.S. Initially approved for marketing in France on December 11, 1990 and in the U.S. on May 10, 1995, lansoprazole has been approved in 97 countries worldwide (as of June 2007). The estimated global patient exposure to lansoprazole is over 432 million. Lansoprazole is approved to treat a variety of acid-related gastrointestinal disorders, including EE healing, maintenance of healed EE, and symptomatic GERD.

Dexlansoprazole is the R-enantiomer of lansoprazole. The sponsor claims that dexlansoprazole exhibits a greater in vivo pharmacological response compared with an equivalent dose of the S-enantiomer of lansoprazole (S-lansoprazole), due to the rapid clearance of S-lansoprazole compared with dexlansoprazole. After oral administration of lansoprazole, dexlansoprazole is the predominant circulation enantiomer, representing approximately 85% of the area under the plasma concentration-time curve (AUC). Racemic conversion of dexlansoprazole to S-

lansoprazole does not occur in humans, as no S-lansoprazole is detectable following oral administration of dexlansoprazole. The sponsor hence concluded that the majority of the treatment effect following dosing of lansoprazole is attributable to the R-enantiomer and selected dexlansoprazole as the enantiomer for clinical development.

To enhance the potential for dexlansoprazole to demonstrate clinical benefit, the sponsor developed a dual pH-dependent delayed release formulation, referred to as dexlansoprazole MR. This novel formulation consists of two types of enteric-coated granules contained within a single capsule. Each type of granule releases at a different pH. One type of granule is designed to release the drug substance at  $\text{pH} \geq 5.5$  after the granules reach the proximal small intestine, and the other type is designed to release the drug substance at  $\text{pH} \geq 6.75$  after reaching the distal small intestine. Approximately 25% of the drug is released within the first hour of administration, followed by a second release for the remaining 75% of the dose within four to five hours. The sponsor claims that the advantage of this formulation is to extend the duration of drug exposure and maintain pharmacologically active levels of drug over a longer time period. As a result, the pharmacokinetic profile of dexlansoprazole following the administration of dexlansoprazole MR is characterized by a concentration-time profile with two distinct peaks.

As of July 20, 2007, 6475 subjects have participated in phase 1 and phase 3 studies. Out of those, 4794 subjects have received dexlansoprazole MR at doses ranging from 30 mg to 300 mg.

A total of 16 phase 1 studies have been conducted to provide PK, PD, and safety data for dexlansoprazole MR. Based on the PK/PD data from phase 1 studies, TAP added a 30 mg dose to the dexlansoprazole MR phase 3 development plan. This revision enabled combined analyses for Study T-GD04-082 with T-GD04-083 (nonerosive, symptomatic GERD; 60 mg, 90 mg, placebo) and Study T-EE04-086 with T-EE04-087 (maintenance of healed EE; 60 mg, 90 mg, placebo). The combined results for these studies were named according to the first study in each pairing, i.e., Study T-GD04-082 or Study T-EE04-086, respectively.

Six phase 3, randomized, controlled studies have been conducted to evaluate the efficacy and safety of dexlansoprazole MR, including two studies (T-GD04-082 and T-GD05-137) supporting the symptomatic GERD indication, two studies (T-EE04-084 and T-EE04-085) supporting the healing EE indication, and two studies (T-EE04-086 and T-EE05-135) supporting the maintenance of healed EE indication. In the GERD studies, dexlansoprazole MR doses of 30 mg, 60 mg, or 90 mg QD were administered for four weeks. In the EE healing studies, dexlansoprazole MR doses of 60 mg or 90 mg QD were administered for up to eight weeks. In the maintenance of healed EE studies, dexlansoprazole MR doses of 30 mg, 60 mg, or 90 mg QD were administered for up to six months. This review will focus on the four phase 3 studies for the healing EE and maintenance of healed EE indications. Refer to a separate statistical review of the two phase 3 studies for the GERD indication.

In addition to these studies, an open-label, long-term extension safety study (T-GI04-088) enrolled subjects who had completed one of the randomized, double-blind symptomatic GERD studies and had a diagnosis of GERD or EE. Dexlansoprazole MR doses of 60 mg or 90 mg QD were administered for up to 12 months. This study was still ongoing at the time of this

submission; however, the results of an interim analysis were submitted with this application. See the clinical team's review regarding safety issues.

## **2.2 Data Sources**

Materials reviewed include study reports (T-EE04-084, T-EE04-085, T-EE04-086, and T-EE05-135) and integrated study reports for the indications of healing EE and maintenance of healed EE. This application was submitted in electronic Common Technical Document (eCTD) format, with SAS datasets provided as CDISC files in accordance with eCTD guidances, to EDR at \\Cdsesub1\evsprod\NDA022287\0000.

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### 3. STATISTICAL EVALUATION

An overview of the six studies conducted to support the establishment of the efficacy of dexlansoprazole MR is provided in the following table.

**Table 3.1. Dexlansoprazole MR Efficacy Studies**

Study	Treatment Groups	Design	N <sup>a</sup>	Duration of Treatment	Study Population	Primary Efficacy Endpoint
<b>Phase 3 Pivotal Studies</b>						
<b>Healing of Erosive Esophagitis</b>						
T-EE04-084	Dexlansoprazole MR 60 mg QD 90 mg QD  Lansoprazole delayed release 30 mg QD	Randomized, double-blind, active-controlled	2038	4 or 8 weeks	Males and females ≥18 years of age with endoscopically confirmed EE.	The percentage of subjects who have complete healing of EE over 8 weeks as assessed by endoscopy.
T-EE04-085	Dexlansoprazole MR 60 mg QD 90 mg QD  Lansoprazole delayed release 30 mg QD	Randomized, double-blind, active-controlled	2054	4 or 8 weeks	Males and females ≥18 years of age with endoscopically confirmed EE.	The percentage of subjects who have complete healing of EE over 8 weeks as assessed by endoscopy.
<b>Maintenance of Healed of Erosive Esophagitis</b>						
T-EE05-135	Placebo QD  Dexlansoprazole MR 30 mg QD 60 mg QD	Randomized, double-blind, placebo-controlled	445	6 months	Males and females ≥18 years of age who successfully completed T-EE04-084 or T-EE04-085 with endoscopically proven healed EE requiring maintenance therapy.	The percentage of subjects who maintained healed EE over 6 months as assessed by endoscopy.
T-EE04-086	Placebo QD  Dexlansoprazole MR 60 mg QD 90 mg QD	Randomized, double-blind, placebo-controlled	451	6 months	Males and females ≥18 years of age who successfully completed T-EE04-084 or T-EE04-085 with endoscopically proven healed EE requiring maintenance therapy.	The percentage of subjects who maintained healed EE over 6 months as assessed by endoscopy.
<b>Symptomatic GERD</b>						
T-GD05-137	Placebo QD  Dexlansoprazole MR 30 mg QD 60 mg QD	Randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm	947	4 weeks	Males and females ≥18 years of age who identified heartburn as their primary symptom, had a history of heartburn episodes for ≥6 months, experienced heartburn on ≥4 of the 7 days preceding Study Day -1, and showed macroscopically normal esophageal mucosa at the screening endoscopy.	Percentage of days that subjects had neither daytime nor nighttime heartburn during treatment as assessed by daily electronic diary.
T-GD04-082	Placebo QD  Dexlansoprazole MR 60 mg QD 90 mg QD	Randomized, double-blind, multicenter, placebo-controlled, parallel-group, 3-arm	908	4 weeks	Males and females ≥18 years of age who identified heartburn as their primary symptom, had a history of heartburn episodes for ≥6 months, experienced heartburn on ≥4 of the 7 days preceding Study Day -1, and showed macroscopically normal esophageal mucosa at the screening endoscopy.	Percentage of days that subjects had neither daytime nor nighttime heartburn during treatment as assessed by daily electronic diary.

<sup>a</sup> Indicates the number of subjects who received at least 1 dose of study drug.  
Source: Modules 2.5 – Clinical Overview, Table 2.5.b

This review will evaluate the studies supporting KAPIDEX<sup>®</sup> (dexlansoprazole) modified release capsules (30, 60 **(b) (4)** mg) for the following indications:

- Healing (b) (4) of all grades of erosive esophagitis (EE) – 60 (b) mg QD for up to 8 weeks
- Maintaining healing of EE (b) (4) – 30 (b) mg QD

The sponsor conducted two phase 3 studies supporting each indication. One of the studies supporting the maintenance of healed EE indication, Study T-EE04-086, is the combined study of T-EE04-086 and T-EE04-087 (60 mg, 90 mg, placebo) to add a study (T-EE05-135) evaluating 30 mg dose of dexlansoprazole MR (30 mg, 60 mg, placebo).

### 3.1 Overview of Efficacy

#### Healing EE (Section 3.3)

Two identical, multicenter, randomized, double-blind, active-controlled, 3-arm studies were conducted to assess the efficacy and safety of dexlansoprazole MR 60 mg and 90 mg compared with lansoprazole 30 mg. The primary efficacy endpoint, healing of EE by Week 8, was allegedly assessed using a closed testing procedure by first assessing non-inferiority of the dexlansoprazole MR doses to lansoprazole. If a dexlansoprazole MR dose was shown to be non-inferior to lansoprazole, then it would be tested for superiority. The secondary efficacy endpoints were: healing of EE by Week 4 and healing of EE with LA Grades C and D by Week 8. The crude rate method was used as the primary analyses and time-to-event (life-table) approach as supportive analyses.

The sponsor claimed that in both studies, the majority of subjects were healed by Week 4. The sponsor further claimed that dexlansoprazole MR 60 mg and 90 mg demonstrated non-inferiority to lansoprazole 30 mg and both were highly effective in healing by Week 8. The sponsor also claimed that dexlansoprazole MR 90 mg was statistically superior to lansoprazole 30 mg for healing EE after eight weeks of treatment in both studies. An integrated analysis of these two studies were performed by the sponsor after the study completion and the sponsor claimed that both the 60 mg and 90 mg doses of dexlansoprazole MR were statistically significantly superior to lansoprazole 30 mg over eight weeks of treatment. However, integrated analysis can only be supportive rather than confirmatory.

The dexlansoprazole MR studies enrolled approximately 30% of subjects with moderate to severe EE (LA Grades C and D), including 6% severe (Grade D). The sponsor claimed that each study demonstrated a higher healing rate in these moderate to severe subjects for the dexlansoprazole 90 mg dose compared with lansoprazole 30 mg, with therapeutic gains of (b) and 9 percentage points. Based on the integrated analysis, the sponsor further claimed that both dexlansoprazole dose groups had numerically higher healing rates than lansoprazole 30 mg at Week 4 and Week 8. The sponsor also used the results from the maintenance of healed EE studies to try to strengthen the conclusion of benefit of 90 mg dexlansoprazole MR by arguing that the subjects healed EE with 90 mg dexlansoprazole MR achieved higher maintenance rates than those subjects healed with dexlansoprazole MR 60 mg or lansoprazole 30 mg. However, this subgroup analysis is considered exploratory since this comparison between the two active treatment doses was neither pre-specified nor appropriately powered.

### Maintenance of Healed EE (Section 3.4)

Having received active treatment in the healing EE studies, the subjects with healed EE by Week 8 entered into the maintenance studies. Two double-blind, multicenter, randomized, placebo-controlled, 3-arm maintenance of healed EE studies were conducted to compare the efficacy and safety of dexlansoprazole MR with that of placebo. Each study was designed to stand as a single, large robust study and was powered to demonstrate statistical superiority of each dexlansoprazole MR dose compared with placebo using an overall 0.0025 (0.05<sup>2</sup>) level of significance instead of the typical 0.05 mainly due to the fact that 30 mg and 90 mg doses of dexlansoprazole MR were only investigated in one of these two studies. The primary measure of efficacy was maintenance of healed EE by Month 6. The secondary efficacy endpoints were: relief of daytime and nighttime (24-hour) heartburn and relief of nighttime heartburn over the treatment period. Both crude rate and time-to-event (life-table) methods were used for estimating the maintenance of healed EE rates while the crude rate analysis was the primary analysis. The sponsor claimed that this crude rate analysis was conservative because subjects who prematurely discontinued with their last endoscopy showing no recurrence were considered to have recurred. However, this strategy was used for both treatment and placebo groups, whether or not it was conservative in terms of the treatment comparisons requires further investigation by sensitivity analyses.

The sponsor claimed that the results of the studies showed that dexlansoprazole MR was highly effective in the maintenance of healed EE since all three doses of dexlansoprazole MR (30 mg, 60 mg, and 90 mg) were superior to placebo in maintaining healed EE. The sponsor also claimed that dexlansoprazole MR 60 mg demonstrated a therapeutic advantage compared with the lower dexlansoprazole MR 30 mg dose on maintaining healed EE in more difficult to treat subjects (moderate to severe EE patients and patients who needed longer treatment duration for healing EE). However, since the study that evaluated the dexlansoprazole MR 30 mg and 60 mg (Study T-EE05-135) started later than the one that evaluated 60 mg and 90 mg (Study T-EE04-086) most of the patients with longer treatment duration for healing EE are enrolled into Study T-EE05-135 and hence the claimed efficacy difference between two doses on this subgroup may be biased. The sponsor further claimed that Study T-EE04-086 demonstrated that dexlansoprazole MR 90 mg did not provide additional clinical benefit on maintenance of healed EE over that of dexlansoprazole MR 60 mg. It should be noted that any comparison between any two active treatment groups is only exploratory and not confirmatory.

The sponsor also made statistical claims on the secondary endpoints, stating that all dexlansoprazole MR doses were highly effective in relieving heartburn and statistically significant superior to placebo for the percentage of 24-hour heartburn-free days and the percentage of days without nighttime heartburn during the treatment period.

### **3.2 Overview of Safety**

This review will only briefly discuss the safety assessments from this application. For more details on the safety of dexlansoprazole MR, refer to the clinical review.

The safety of dexlansoprazole MR was assessed in preclinical studies, phase 1 studies, and in phase 3 studies in subjects with EE, in subjects with healed EE, and in subjects with symptomatic GERD. Adverse events (AEs) were summarized by patient-month (PM) of exposure for the study groups of all phase 3 studies combined.

A total of 4794 subjects received at least one dose of dexlansoprazole MR (30 mg to 300 mg) in the phase 1 studies and the phase 3 studies. A total of 4270 subjects received dexlansoprazole MR 30 mg, 60 mg, or 90 mg in the phase 3 studies, 1363 subjects received lansoprazole 30 mg in the phase 3 healing of EE studies, and 896 subjects received placebo in the phase 3 symptomatic GERD or maintenance of healed EE studies. A total of 524 subjects received at least one dose of dexlansoprazole MR in the phase 1 studies. During these studies, 283 subjects received dexlansoprazole MR in single-dose studies and 241 subjects received dexlansoprazole MR in multiple-dose studies. A total of 651 subjects received dexlansoprazole MR doses of 30 mg, 60 mg, or 90 mg for at least six months (24 weeks) and 203 subjects received dexlansoprazole MR doses of either 60 mg or 90 mg for at least one year (48 weeks).

In the phase 3 program, the number of subjects per 100 PM who prematurely discontinued was 28.3, 7.4, 5.9, 5.6, and 4.2 in the placebo, dexlansoprazole MR 30 mg, 60 mg, 90 mg, and lansoprazole 30 mg treatment groups, respectively. In all phase 3 studies combined, among dexlansoprazole MR-treated subjects, adjusted for exposure, the most frequently reported (at least one subject/100 PM) treatment-emergent AEs were Diarrhea, Upper Respiratory Tract Infections, Gastrointestinal and Abdominal Pains, Nausea and Vomiting Symptoms, Headaches NEC (not elsewhere classified), Flatulence, and Bloating and Distension. In the uncontrolled, long-term safety study, Upper Respiratory Tract Infection was among the most frequently reported AEs.

Seven subjects (five on dexlansoprazole MR 60 mg [0.09/100 PM], one on dexlansoprazole MR 90 mg [0.02/100 PM], and one on lansoprazole 30 mg [0.06/100 PM]) died in the phase 3 studies. All deaths were considered by the investigator to be not related to study drug. A total of 61 subjects experienced nonfatal serious adverse events (SAEs) in the phase 3 studies. Adjusting for exposure, the number of subjects per 100 PM with at least one treatment-emergent, nonfatal SAE ranged from 0.43 to 0.54 across the dexlansoprazole MR treatment groups, was 0.39 in the lansoprazole 30 mg treatment group and 0.19 in the placebo group. The majority of the nonfatal SAEs were considered by the investigator to be not related to study drug. In all phase 3 studies combined, after adjusting for exposure, the number of subjects per 100 PM with at least one treatment-emergent AE leading to premature discontinuation of study drug was 0.96, 1.48, 1.46 in dexlansoprazole MR 30 mg, 60 mg, 90 mg treatment groups, respectively, and was 1.00 in the lansoprazole 30 mg treatment group, and 3.86 in the placebo group.

A total of 13 serious cardiovascular adverse events were reported in 7 out of 4270 dexlansoprazole MR subjects, 1 of 1363 lansoprazole subjects, and 1 of 896 placebo subjects. There were no cardiac-related deaths in dexlansoprazole MR phase 1 or phase 3 clinical studies. There were no events of Hip Fracture or Vertebral Fracture reported in any of the phase 1 or phase 3 clinical studies.

### **3.3 Evaluation of the Healing EE Indication**

One of the three proposed indications for dexlansoprazole MR is healing of EE and symptom relief of subjects with EE. Two identical phase 3, randomized, active-controlled, double-blind, 3-arm, multicenter studies were conducted to support the healing of EE indication (Studies T-EE04-084 and T-EE04-085).

#### **3.3.1 Evaluation of Efficacy**

In each of the healing EE studies, enrollment was targeted to include approximately 70% of subjects with Grade A or B and approximately 30% of subjects with Grade C or D (of which 7% were to be Grade D). Therefore, once subjects with Grade A or B comprised approximately 70% of total projected enrollment, primarily subjects with Grade C or D would be enrolled.

##### **3.3.1.1 Study Design and Endpoints**

Studies T-EE04-084 and T-EE04-085 were both phase 3, randomized, double-blind, active-controlled, multicenter, 3-arm studies with up to 8-week treatment periods. The studies were designed to evaluate healing of EE and relief of GERD-related symptoms and to compare the efficacy and safety of dexlansoprazole MR 60 mg QD and 90 mg QD with that of delayed-release lansoprazole 30 mg QD.

In each study, subjects with endoscopically confirmed EE were randomly assigned in a 1:1:1 ratio to receive one of the following treatments: lansoprazole 30 mg QD, dexlansoprazole MR 60 mg QD, or dexlansoprazole MR 90 mg QD. The study drug assignment was stratified by baseline EE grade and the randomization was fairly equally balanced between the three treatment groups within each stratum.

Patients with endoscopic Barrett's esophagus and/or definite dysplastic changes in the esophagus were excluded from the studies. If any suspicious Barrett's esophagus was seen during screening and the principal investigator was confident that the subject would be confirmed with Barrett's esophagus, the subject could be automatically excluded. Otherwise, any suspicious Barrett's esophagus seen during screening endoscopy was biopsied and sent to a local pathology laboratory. Subjects were discontinued if the screening biopsy was positive and Final Visit procedures were performed except the endoscopy. Subjects with indeterminate dysplasia due to severe inflammation could be enrolled and rebiopsied at the next endoscopy.

Subjects self-administered one capsule of blinded study drug once daily in the morning before breakfast and returned for study visits after four and eight weeks (if not healed at four weeks) of treatment. At these visits, study drug was collected and/or dispensed, GERD symptoms were assessed, concomitant medication use was reviewed, AEs were assessed, and QOL questionnaires were completed.

An endoscopy was performed at Week 4. If the subject's EE was healed, the subject completed the study, and Final Visit procedures were performed. If the subject's EE was not healed, the

subject continued in the study for an additional four weeks. For those subjects who continued in the study, an endoscopy was also performed at Week 8.

If subjects successfully completed the study (i.e., EE was healed), they were eligible for enrollment in a 6-month maintenance study (Study T-EE05-135 or T-EE04-086) if a study was available at their site.

The primary efficacy variable was the percentage of subjects who had complete healing of EE over eight weeks as assessed by endoscopy. The secondary efficacy variables were (1) the percentage of subjects who had complete healing of EE over four weeks as assessed by endoscopy; and (2) the percentage of subjects with baseline LA Grade C or D (moderate or severe) who had complete healing of EE over eight weeks as assessed by endoscopy.

Additional (exploratory) efficacy variables included the percentage of subjects with baseline LA Grade C or D who had complete healing of EE by Week 4, as assessed by endoscopy, the percentage of subjects who had complete healing of EE over eight weeks as assessed by endoscopy by Baseline LA Grade (A, B, C, D).

A total of 1950 subjects with documented EE during screening were planned to be enrolled into each healing of EE study to ensure 1560 subjects complete the study (assuming a 20% dropout rate). Given the non-inferiority margin of dexlansoprazole MR to lansoprazole on healing EE rate at Week 8 being proposed as 10%, the sample size of 520 subjects per treatment group would provide at least 95% power at the 0.025 level of significance to meet the non-inferiority criteria between a dexlansoprazole MR dose and lansoprazole 30 mg assuming equal EE healing rates (87%) at Week 8. This sample size would also provide at least 80% power at the 0.025 level of significance to detect a 6% difference for superiority between a dexlansoprazole dose (93%) and lansoprazole 30 mg (87%) in the EE healing rates at Week 8. The lansoprazole healing rate was estimated from prior lansoprazole studies based on life-table method, which was originally proposed as the primary analysis for the healing EE studies. See Section 3.3.1.3 for further details on the statistical methodology.

### **3.3.1.2 Patient Disposition, Demographic and Baseline Characteristics**

The two healing EE studies enrolled a total of 4092 subjects at 188 sites in the U.S. and 118 sites outside of the U.S. (non-U.S.). Of the 4059 ITT (intent-to-treat) subjects, 2929 participated at U.S. sites and 1130 participated at non-U.S. sites. Approximately 71% of enrolled subjects had EE with LA Grade A or B, and 29% had LA Grade C or D (of which 6% were Grade D).

#### ***Study T-EE04-084***

Study T-EE04-084 had the first dose administered on December 2, 2005 and the last procedure on January 30, 2007. While 1950 were planned, the study enrolled 2038 subjects in 150 sites (95 sites in the U.S. and 55 sites throughout Australia, Bulgaria, Canada, Czech Republic, Estonia, Germany, India, Israel, Latvia, Lithuania, New Zealand, Poland, Russia, Slovakia, South Africa, and Ukraine). Out of these enrolled subjects, 14 subjects who had confirmed endoscopic Barrett's esophagus and/or definite dysplastic changes in the esophagus after enrollment and two subjects who did not have valid baseline endoscopic EE reading were excluded from ITT

population. Out of 2022 ITT subjects, 93 did not have adequate follow up data and so were excluded for the primary crude healing rate analyses. In total, 1929 (94.65%) of enrolled subjects were included in the primary analyses.

About 10% (211/2038) of subjects had at least one protocol deviation during this study. A total of 164 subjects (8% of the study population) were enrolled without meeting all of the inclusion/exclusion criteria. Seven subjects (less than 1% of the study population) developed withdrawal criteria but were not withdrawn from the study. All seven of these subjects were confirmed with Barrett's esophagus during the study (two subjects at screening and five subjects during treatment) and completed the study. In addition, four subjects (less than 1% of the study population) who were healed at the Week 4 Visit were not discontinued from the study as outlined in the protocol. A total of 50 subjects (2% of the study population) received an excluded concomitant medication during the study. A total of three subjects (less than 1% of the study population) who were assigned to three different treatment arms received wrong doses than assigned by randomization and remained on the received doses throughout the study. For analyses, these subjects were included in the treatment group corresponding to the study drug actually received.

Overall, there were slightly more enrolled subjects who were male (54.5%) than female and the majority were White (87.5%). The average age was 47.5 years, and the average BMI was 29.8 kg/m<sup>2</sup>, which is deemed overweight. There were 680, 668, and 690 subjects who received dexlansoprazole MR 60 mg, 90 mg, and lansoprazole 30 mg, respectively. Approximately 70.51% subjects had LA Classification Grade A or B, and 29.39% Grade C or D (5.79% Grade D). They are relatively well-balanced among treatment groups. For the 1929 subjects included in the primary and secondary crude healing rate analyses, demographic characteristics were similar to those in the all-subjects population. Out of those, 639, 634, and 656 subjects received dexlansoprazole MR 60 mg, 90 mg, and lansoprazole 30 mg, respectively.

#### Study T-EE04-085

Study T-EE04-085 had the first dose administered on December 16, 2005 and the last procedure on January 22, 2007. While 1950 were planned, the study enrolled 2054 subjects in 156 sites (93 sites in the U.S. and 63 sites throughout Australia, Bulgaria, Canada, Colombia, Czech Republic, Estonia, Germany, Hungary, India, Israel, Latvia, Lithuania, New Zealand, Peru, Poland, Russia, Slovakia, South Africa, and Ukraine). Out of these subjects, 15 subjects who had confirmed endoscopic Barrett's esophagus and/or definite dysplastic changes in the esophagus after enrollment and two subjects who did not have valid baseline endoscopic EE reading were excluded from ITT population. Out of 2037 ITT subjects, 80 did not have adequate follow up data and so were excluded for the primary crude healing rate analyses. In total, 1957 (95.28%) of enrolled subjects were included in the primary analyses.

About 11% (236/2054) of subjects had at least one protocol deviation during this study. A total of 166 subjects (8% of the study population) were enrolled without meeting all of the inclusion/exclusion criteria. Only one subject (less than 1% of the study population) developed withdrawal criteria but were not withdrawn from the study. In particular, this subject had confirmed Barrett's esophagus on study Day 31 and remained in the study. In addition, three subjects (less than 1% of the study population) who were healed at the Week 4 Visit were not

discontinued from the study as outlined in the protocol. A total of 68 subjects (3% of the study population) received an excluded concomitant medication during the study. A total of 10 subjects (less than 1% of the study population) received wrong doses than assigned by randomization and eight of them remained on the received treatment throughout the study. The other two prematurely discontinued after 1 day and 26 days of treatment, respectively. Evaluation and statistical analyses of the data for these subjects were performed in accord with the corresponding treatment group of the study drug actually received.

Overall, there were slightly more enrolled subjects who were male (53.1%) than female and the majority were White (86.2%). The average age was 47.9 years, and the average BMI was 29.9 kg/m<sup>2</sup>. There were 694, 687, and 673 subjects who received dexlansoprazole MR 60 mg, 90 mg, and lansoprazole 30 mg, respectively. Approximately 71.18% subjects had LA Classification Grade A or B, and 28.72% Grade C or D (6.43% Grade D). They are relatively well-balanced among treatment groups. For the 1957 subjects included in the primary and secondary crude healing rate analyses, demographic characteristics were similar to those in the all-subjects population. Out of those, 657, 652, and 648 subjects received dexlansoprazole MR 60 mg, 90 mg, and lansoprazole 30 mg, respectively.

### **3.3.1.3 Statistical Methodologies**

As prespecified in the protocol and the original statistical analysis plan (SAP), the primary analysis for the primary and secondary efficacy endpoints was based on life-table methods, and for those endpoints, crude rate analysis was considered supportive. Based on a recommendation from the FDA at the pre-NDA meeting on October 1, 2007, the primary analysis for the primary and secondary endpoints was changed to crude rate analysis, and analysis based on life-table methods with log-rank tests as supportive. Since a time-to-event type of response is not of great clinical interest, and life-table analysis is only a supportive finding, this review will primarily focus on the crude rate analyses.

All sponsor's efficacy analyses were done on the appropriate ITT population proposed by the sponsor. The general ITT population was defined as all subjects who had documented EE at the screening endoscopy, did not have confirmed Barrett's esophagus or definite dysplastic changes at baseline, were randomized and received at least one dose of study drug. A subject was considered to have documented EE if the last endoscopy within 28 days on or before the first day of study drug showed LA Grade of A, B, C, or D. For the primary and secondary efficacy analyses of the crude healing rate, only ITT subjects with data from at least one post-baseline endoscopy were included. Base on this definition, this population should be better characterized as the modified ITT (mITT) population and such will be used in this review to distinguish it from the general ITT population.

As specified in the SAP, the primary efficacy endpoint, healing rate of EE by Week 8, was assessed using a closed testing procedure by first assessing non-inferiority of the dexlansoprazole MR doses to lansoprazole. Those dexlansoprazole MR doses shown to be non-inferior to lansoprazole were then tested for superiority to lansoprazole using CMH (Cochran-Mantel-Haenszel) test with Baseline LA EE Grade as strata. As proposed by the sponsor, the non-inferiority assessment of the primary efficacy endpoint was determined by calculating 95% large

sample normal approximation confidence intervals (CIs) for the differences between the healing rates of each dexlansoprazole MR dose and those of lansoprazole 30 mg. If the lower bound of that CI was greater than -10%, non-inferiority would be concluded. However, the sponsor did not provide any justification of this non-inferiority margin of 10%. Moreover, mITT population was used for both non-inferiority and superiority testing while Per-Protocol (PP) population, which was not defined in the protocol, is commonly considered more appropriate for the non-inferiority testing. For this review, the lower bounds of CIs will be under scrutiny instead of a simple comparison to -10%. Moreover, the non-inferiority test will be conducted using a PP population as commonly defined.

#### Control of Type I Error

When comparing two doses of dexlansoprazole MR to lansoprazole 30 mg, the sponsor proposed to control the overall significance level of 0.05 using Hochberg's method. In particular, the comparison was proposed to be done in the following sequential order using a closed testing procedure within each step.

1. Non-inferiority to lansoprazole was to be declared for both dexlansoprazole MR doses if the lower bounds of both 95% CIs of differences were greater than -10%. If non-inferiority to lansoprazole could not be declared for both doses, but the lower bound of the 95% CI was greater than -10% for one of the doses, then a 97.5% CI would be calculated for the difference between that dose and lansoprazole. If the lower bound of this 97.5% CI was greater than -10%, then non-inferiority for only that dose would be declared.
2. If both dexlansoprazole MR doses were shown to be non-inferior to lansoprazole and so were compared with lansoprazole for superiority, superiority of a dexlansoprazole MR dose to lansoprazole would be declared if the p-value was less than or equal to the critical significance level based on Hochberg's method. More specifically, the p-values from the pairwise comparisons between dexlansoprazole MR and lansoprazole would be ordered and the larger p-value would be compared with 0.05. If the larger p-value was less than or equal to 0.05, both doses of dexlansoprazole MR would be considered statistically superior to lansoprazole. If the larger p-value was greater than 0.05, the corresponding dexlansoprazole MR dose would not be considered statistically superior to lansoprazole. The smaller p-value would then be compared with  $0.05/2 = 0.025$ . If the smaller p-value was less than or equal to 0.025, that dexlansoprazole MR dose would be considered statistically superior to lansoprazole. Otherwise, none of the doses would be considered statistically superior to lansoprazole. If only one dexlansoprazole MR dose was shown to be non-inferior to lansoprazole, superiority of that dose to lansoprazole would be declared if the p-value was less than or equal to 0.05.

The additional comparison between the dexlansoprazole MR groups was made at a significance level of 0.05 without adjustment. The reason given by the sponsor was that it was not a primary assessment in these studies. However, this comparison can only serve as an exploratory finding whether or not the statistical significance has been reached.

For those dexlansoprazole MR doses shown to be non-inferior to lansoprazole, the two secondary efficacy endpoints were then assessed for superiority to lansoprazole. To maintain an

overall significance level at 0.05, the sponsor proposed to control multiplicities for the two secondary efficacy endpoints using Hommel-Simes method within a treatment group in addition to Hochberg's method for each comparison of dexlansoprazole MR dose to lansoprazole by endpoint. In particular, within each dexlansoprazole MR dose that was found to be non-inferior to lansoprazole, the p-values from the comparisons versus lansoprazole for both secondary efficacy variables would be grouped into families. The 0.05 level of significance within each family would be controlled using adjusted p-values from Hommel-Simes closed test. If both dexlansoprazole MR doses were declared non-inferior to lansoprazole, comparisons between dexlansoprazole MR and lansoprazole within a secondary efficacy variable would be conducted using the adjusted p-values, and the 0.05 level of significance would be controlled using Hochberg's method. If only one dexlansoprazole MR dose was declared non-inferior to lansoprazole, then the adjusted p-values in the single family would be compared with 0.05. The sponsor also compared dexlansoprazole MR 60 mg QD with 90 mg QD at a significance level of 0.05 without a multiplicity adjustment, although this additional comparison is exploratory.

The formerly described multiplicity adjusting testing procedure proposed by the sponsor has questionable validity. Firstly, if only one dose of dexlansoprazole MR was declared non-inferior to lansoprazole, only the remaining significance level of 0.025 instead of the full significance level of 0.05 should be carried over to the next family (i.e., superiority comparisons on primary and secondary endpoints in this case). Secondly, after declaring non-inferiority for any dose(s) of dexlansoprazole MR comparing with lansoprazole, the sponsor proceeded to test superiority on both primary and secondary endpoints with the full significance level of 0.05 for each endpoints group, there was no multiplicity adjustment at this step. Finally, the use of two different closed testing procedures, each with the full significance level of 0.05, within each dose and variable separately did not control the significance level for the whole secondary endpoints family at 0.05. In this review, the unadjusted p-values will be presented and multiplicity will be adjusted using the conservative Bonferroni method and gatekeeping procedure.

#### *Handling of Missing Values and Sensitivity Analyses*

The primary analyses were based on the crude rates determined by the proportion of subjects whose EE was healed by Week 8, as assessed by endoscopy (LA Grade = 0). ITT subjects who had at least one post-baseline endoscopic assessment were included in the analyses. Additionally, endoscopies that were conducted longer than 7 days after the last dose of study drug were not included in the analyses. The crude healing rates were calculated by dividing the number of healed subjects by the number of subjects with at least one post-baseline endoscopy assessment. Subjects who were healed by Week 4 (between Day 2 and 42) were carried forward as healed to Week 8. Subjects who were not declared as healed by the Week 4 endoscopy assessment and did not have Week 8 endoscopic assessment were considered not healed by Week 8. Subjects endoscopically proven to be healed between Day 43 and 70 were considered as healed by Week 8. Subjects who were healed according to the endoscopic assessments that were conducted after Day 70 were considered as not healed on the day of earlier endoscopic assessment. Subjects who were not healed according to the endoscopic assessments that were conducted after Day 70 were considered as not healed by Week 8. If a subject had more than one endoscopic assessment within an interval, then the last endoscopy was used.

For non-inferiority testing, a PP population needs to be defined. Conventionally, it is defined as all ITT subjects with no major protocol deviations. In this review, it is specifically defined as all ITT subjects who fully complied with the study drug and had either endoscopic assessment data between Day 2 and 42 if healed by Week 4 or also had endoscopic assessment data between Day 43 and 70 if not healed by Week 4.

The following sensitivity analyses using the crude healing rates were performed by the sponsor for the primary efficacy endpoint for each study and the data pooled over studies:

- Including subjects who were not healed by the Week 4 endoscopy and did not have Week 8 endoscopy data by considering them healed at Week 8. Crude healing rates from each treatment group were compared using CMH tests with baseline LA EE Grade as strata.
- Week 8 crude healing rates were compared between treatment groups using Fisher's exact test ignoring the baseline LA Grade.

In this review, results from more sensitivity analyses, including a worst-case scenario, are presented. Moreover, more testing methods will be investigated, such as Binomial Exact test and Chi-Square test ignoring the baseline LA Grade.

### **3.3.1.4 Results and Conclusions**

#### Primary Analyses

Both 95% normal approximation CIs for the differences between the healing EE rate of each dexlansoprazole MR dose and that of lansoprazole 30 mg excluded zero for Study T-EE04-084. However, for Study T-EE04-085 the same result only held for dexlansoprazole MR 90 mg. The lower bound of the 95% CI comparing dexlansoprazole MR 60 mg with lansoprazole was below zero as shown in Table 3.2. Although the proposed non-inferiority margin of -10% lacks justification, the small value of the difference is supportive of the non-inferiority claim. This reviewer applied Bonferroni method to adjust for multiplicity using a 97.5% CI. All the CIs still excluded zero except for that from the difference between the healing rate of dexlansoprazole MR 60 mg and that of lansoprazole in Study T-EE04-085. The same analysis was conducted on the PP population, which is defined as all ITT subjects who completed the study with valid endoscopy assessments. Using this definition did not change the interpretation of the CIs. The smallest lower confidence bound from these different methods was -2.15% and the conclusion that both doses of dexlansoprazole MR are non-inferior to lansoprazole still holds. The CIs on the differences of healing rates are summarized in the table below.

**Table 3.2. Treatment Differences on Week 8 Crude Healing Rates of EE**

Study	Method		Dexlansoprazole MR 60 mg vs. Lansoprazole	Dexlansoprazole MR 90 mg vs. Lansoprazole
<b>mITT population</b>				
Study T-EE04-084	Dexlansoprazole % (n/N) – Lansoprazole % (n/N) = Difference %		85.29 (545/639) – 78.96 (518/656) = 6.33%	85.80 (544/634) – 78.96 (518/656) = 6.84%
	95% CI	Normal approximation <sup>a</sup>	(2.17%, 10.48%)	(2.70%, 10.98%)
		Normal approximation with continuity correction	(2.02%, 10.64%)	(2.55%, 11.13%)
		Exact	(2.15%, 10.52%)	(2.68%, 11.01%)
	97.5% CI	Normal approximation	(1.57%, 11.08%)	(2.11%, 11.57%)
		Normal approximation with continuity correction	(1.42%, 11.23%)	(1.96%, 11.73%)
Exact		(1.55%, 11.11%)	(2.09%, 11.61%)	
Study T-EE04-085	Dexlansoprazole % (n/N) – Lansoprazole % (n/N) = Difference %		86.91 (571/657) – 84.57 (548/648) = 2.34%	89.42 (583/652) – 84.57 (548/648) = 4.85%
	95% CI	Normal approximation <sup>a</sup>	(-1.45%, 6.14%)	(1.20%, 8.50%)
		Normal approximation with continuity correction	(-1.60%, 6.29%)	(1.05%, 8.65%)
		Exact	(-1.46%, 6.17%)	(1.19%, 8.54%)
	97.5% CI	Normal approximation	(-2.00%, 6.68%)	(0.68%, 9.02%)
		Normal approximation with continuity correction	(-2.15%, 6.83%)	(0.52%, 9.18%)
Exact		(-2.01%, 6.72%)	(0.67%, 9.08%)	
<b>PP population</b>				
Study T-EE04-084	Dexlansoprazole % (n/N) – Lansoprazole % (n/N) = Difference %		87.86 (543/618) – 81.23 (515/634) = 6.63%	88.58 (543/613) – 81.23 (515/634) = 7.35%
	95% CI	Normal approximation	(2.65%, 10.62%)	(3.40%, 11.30%)
		Normal approximation with continuity correction	(2.49%, 10.78%)	(3.24%, 11.46%)
		Exact	(2.64%, 10.65%)	(3.39%, 11.34%)
	97.5% CI	Normal approximation	(2.08%, 11.19%)	(2.84%, 11.86%)
		Normal approximation with continuity correction	(1.92%, 11.35%)	(2.68%, 12.02%)
Exact		(2.07%, 11.24%)	(2.81%, 11.91%)	
Study T-EE04-085	Dexlansoprazole % (n/N) – Lansoprazole % (n/N) = Difference %		89.87 (568/632) – 86.69 (547/631) = 3.19%	91.67 (583/636) – 86.69 (547/631) = 4.98%
	95% CI	Normal approximation	(-0.36%, 6.73%)	(1.57%, 8.39%)
		Normal approximation with continuity correction	(-0.52%, 6.89%)	(1.41%, 8.55%)
		Exact	(-0.37%, 6.77%)	(1.56%, 8.45%)
	97.5% CI	Normal approximation	(-0.87%, 7.24%)	(1.08%, 8.88%)
		Normal approximation with continuity correction	(-1.03%, 7.40%)	(0.92%, 9.04%)
Exact		(-0.88%, 7.30%)	(1.07%, 8.96%)	

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer's Table

Note that the sponsor used the unstratified data for the non-inferiority tests but used stratified data for the superiority tests. This may not have been the most proper analysis approach, but it appears to be a conservative one, and the difference in analyses should be taken into consideration when interpreting the tests results for non-inferiority and superiority claims. Table 3.3 shows the percentages of mITT subjects who had complete healing of EE over eight weeks as assessed by endoscopy and the p-values for superiority testing. While other tests, including Fisher's Exact test, Pearson's Chi-square tests, and Binomial Exact test, were investigated, only the results from CMH tests are presented because they rendered more conservative p-values.

**Table 3.3. Week 8 Crude Healing Rates of EE (mITT population)**

Study	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N) (95% Exact CI)	p-value	
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dexlansoprazole MR 60 mg vs. Lansoprazole	Dexlansoprazole MR 90 mg vs. Lansoprazole
Study T-EE04-084	85.29% (545/639) (82.30%, 87.95%)	(b) (4)	78.96% (518/656) (75.64%, 82.02%)	0.0043 (CMH) <sup>a</sup> 0.0054 (CMH with continuity correction)	(b) (4)
Study T-EE04-085	86.91% (571/657) (84.09, 89.39)	(b) (4)	84.57 (548/648) (81.55, 87.26)	0.2338 (CMH) <sup>a</sup> 0.2671 (CMH with continuity correction)	(b) (4)

<sup>a</sup> The results concur with those from the sponsor

Source: Reviewer's Table

It can be observed that Study T-EE04-085 had better performance in healing EE than Study T-EE04-084 for all three treatment groups, especially for the lansoprazole arm. Since the healing rate was substantially larger in Study T-EE04-085 than that in Study T-EE04-084 for the active control (lansoprazole) arm, the treatment benefits of dexlansoprazole MR observed in Study T-EE04-084 could not be replicated by Study T-EE04-085. It can be seen that dexlansoprazole MR 60 mg could not be shown superior to lansoprazole in Study T-EE04-085.

For dexlansoprazole MR 90 mg, it seems that the superiority to lansoprazole could be demonstrated in both studies using the multiplicity adjustment with Hochberg's method proposed by the sponsor. However, if using a gatekeeping procedure, after the non-inferiority test, the significance level of 0.05 would be carried over and then split for two testing families: superiority tests and secondary endpoints tests. Then using Bonferroni method, for each dose the comparison should be tested using significance level of 0.0125, which would mean the p-value of comparison between dexlansoprazole 90 mg and lansoprazole in Study T-EE04-085 would not be statistically significant. Even if Hochberg's method was used at this step, since the superiority testing family only shared a significance level of 0.025, the statistical significance for neither dose comparison could be established.

For the primary analysis, this reviewer also used the general ITT population and imputed all the missing values as failures. As expected, all the healing rates for all treatment arms in both studies dropped, more so for dexlansoprazole MR arms (about 5%) than for lansoprazole arms (about 3%), although the percentages of the subjects with no post-baseline endoscopy were fairly similar across treatment arms (about 4-6%). However, the p-values were vastly different from the ones based on the mITT population. In particular, the comparison results were statistically insignificant between each dexlansoprazole dose and lansoprazole for Study T-EE04-085 with both p-values greater than 10%. For Study T-EE04-084, the p-value for the comparison between dexlansoprazole 90 mg and lansoprazole was (b) (4) (CMH with continuity correction), which was statistically significant. However, the p-value for the comparison between dexlansoprazole 60 mg and lansoprazole was 0.0319 (CMH) or 0.0376 (CMH with continuity correction), while statistically significant, is not considered supportive for a superiority claim, as previously discussed.

It is this reviewer's conclusion that the multiplicity adjustment approach proposed by the sponsor was erroneous. Several valid alternatives were investigated and superiority for neither dose of

dexlansoprazole MR could be established in Study T-EE04-085, especially when the ITT population was used. Although one may argue that there might be a statistically significant difference comparing dexlansoprazole 90 mg with lansoprazole under certain valid multiple comparison adjustment procedure, this superiority conclusion would only be marginal and not supportive of a clinical effect that would be sufficient for a labeling claim.

Secondary Analyses

For the secondary efficacy endpoint of EE healing by Week 4, more than 64% of mITT subjects in each treatment group were healed. However, there are no statistically significant differences between treatment groups that could be concluded for either dose even using the Hommel-Simes adjusted p-values and Hochberg’s method proposed by the sponsor. Using this proposed multiplicity adjustment procedure, there would be a statistically significant difference for the secondary efficacy endpoint of EE healing by Week 8 for mITT subjects with baseline LA EE Grade C or D comparing dexlansoprazole 60 mg with lansoprazole in Study T-EE04-084 only. However, this statistical significance could not be repeated in Study T-EE04-085 and so no substantial efficacy could be established. Similar results were obtained using the unmodified ITT population. The results based on the mITT population for secondary efficacy endpoints are summarized in the table below and again only the results from the most conservative CMH tests are presented.

**Table 3.4. Secondary Endpoints for Healing EE Studies (mITT population)**

Endpoint	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N) (95% Exact CI)	p-value	
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dexlansoprazole MR 60 mg vs. Lansoprazole	Dexlansoprazole MR 90 mg vs. Lansoprazole
<b>Study T-EE04-084</b>					
Week 4	66.20% (423/639) (62.38%, 69.86%)	(b) (4)	64.79% (425/656) (61.00%, 68.44%)	0.7051 (CMH) <sup>a</sup> 0.7502 (CMH with continuity correction)	(b) (4)
Week 8 C or D	79.67% (145/182) (73.08%, 85.26%)		65.00% (130/200) (57.95%, 71.59%)	0.0017 (CMH) <sup>a</sup> 0.0025 (CMH with continuity correction)	
<b>Study T-EE04-085</b>					
Week 4	69.71% (458/657) (66.04%, 73.21%)		65.43% (424/648) (61.63%, 69.09%)	0.1001 (CMH) <sup>a</sup> 0.1133 (CMH with continuity correction)	
Week 8 C or D	77.84% (151/194) (71.33%, 83.47%)		78.95% (150/190) (72.46%, 84.51%)	0.7680 (CMH) <sup>a</sup> 0.8663 (CMH with continuity correction)	

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer’s Table

The only statistical significance was, as stated before, for comparison between dexlansoprazole MR 60 mg and lansoprazole in Study T-EE04-084 on the endpoint of EE healing by Week 8 for mITT subjects with baseline LA EE Grade C or D. Using Bonferroni method and splitting the significance level of 0.025 four ways (two doses and two endpoints), a p-value of 0.0017 or 0.0025 could still be considered as statistically significant (at the significance level of 0.00625). However, as mentioned earlier, this significance could not be replicated by the other study. The

formulation of dexlansoprazole MR was developed in the hope of resulting in acceleration of healing EE with better response for more severe EE grades. Evidently, compared to lansoprazole, neither dose of dexlansoprazole MR appears to have accelerated healing of EE or had better response for more severe EE grades patients.

The supportive analyses of life-table methods and log-rank tests on time-to-event responses had higher estimates for the healing EE rates than those from crude rate methods. Although life-table method used all ITT subjects and crude rate results presented above were based on the mITT population, life-table method assumes that the censored subjects have the same response pattern as the observed subjects while crude rate method assumes all censored subjects as failures. Thus, life-table methods are more lenient on handling drop-outs and usually render higher point estimates. The results are summarized in the Appendix (Table A.1). It can be observed that there is no strong evidence of dexlansoprazole MR hastening the healing of EE than lansoprazole.

#### *Sensitivity Analyses*

Sensitivity analyses based on different missing data handling strategies were further studied on the primary and two key secondary endpoints. One sensitivity analysis was to include subjects who were not healed by the Week 4 endoscopy and did not have Week 8 endoscopy data by considering them to be healed at Week 8 for all treatment arms. This sensitivity analysis was performed by the sponsor. The other sensitivity analysis was a worst-case scenario where to include subjects who were not healed by the Week 4 endoscopy and did not have Week 8 endoscopy data as healed for lansoprazole arm but not healed for dexlansoprazole arms.

The results for the non-inferiority tests are summarized in the Appendix (Table A.2) with only 95% normal approximation CIs presented. For the non-inferiority tests, only the results based on the mITT population are presented because both sensitivity analyses generated the same results as those from the primary analysis for the PP population. This is due to the fact that the patients who were not healed by Week 4 and either had no Week 8 endoscopy or had Week 8 endoscopy after study Day 70 were excluded from the PP population.

The results for the superiority tests are summarized in the table below. For the superiority tests, crude healing EE rates by Week 4 are not presented because the results were not altered by the sensitivity analyses due to the fact that all mITT subjects had the Week 4 endoscopy. It can be observed that the results from the first sensitivity analysis were slightly better than, while the results from the worst-case analysis were clearly worse than those from the primary analysis. However, it should be kept in mind when interpreting the results that the first sensitivity analysis may be too lenient while the worst-case analysis overly conservative.

**Table 3.5. Crude Healing Rates of EE (mITT population)**

Endpoint	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N) (95% Exact CI)	p-value	
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dexlansoprazole MR 60 mg vs. Lansoprazole	Dexlansoprazole MR 90 mg vs. Lansoprazole
<b>Prematurely Discontinued Before Healing Considered as Healed</b>					
<b>Study T-EE04-084</b>					
Week 8	88.26% (564/639) (85.51%, 90.66%)	(b) (4)	81.71% (536/656) (78.53%, 84.59%)	0.0014 (CMH) <sup>a</sup> 0.0019 (CMH with continuity correction)	(b) (4)
Week 8 C or D	83.52% (152/182) (77.31%, 88.59%)		68.50% (137/200) (61.57%, 74.87%)	0.0008 (CMH) 0.0012 (CMH with continuity correction)	
<b>Study T-EE04-085</b>					
Week 8	90.26% (593/657) (87.73%, 92.42%)		86.88% (563/648) (84.04%, 89.39%)	0.0556 (CMH) <sup>a</sup> 0.0680 (CMH with continuity correction)	
Week 8 C or D	82.47% (160/194) (76.38%, 87.55%)		81.05% (154/190) (74.75%, 86.36%)	0.7303 (CMH) 0.8334 (CMH with continuity correction)	
<b>Worst-Case Scenario</b>					
<b>Study T-EE04-084</b>					
Week 8	85.29% (545/639) (82.30%, 87.95%)	(b) (4)	81.71% (536/656) (78.53%, 84.59%)	0.1114 (CMH) 0.1296 (CMH with continuity correction)	(b) (4)
Week 8 C or D	79.67% (145/182) (73.08%, 85.26%)		68.50% (137/200) (61.57%, 74.87%)	0.0158 (CMH) 0.0216 (CMH with continuity correction)	
<b>Study T-EE04-085</b>					
Week 8	86.91% (571/657) (84.09%, 89.39%)		86.88% (563/648) (84.04%, 89.39%)	0.9838 (CMH) 0.9838 (CMH with continuity correction)	
Week 8 C or D	77.84% (151/194) (71.33%, 83.47%)		81.05% (154/190) (74.75%, 86.36%)	0.4161 (CMH) 0.4934 (CMH with continuity correction)	

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer's Table

Additional Analyses

Various additional secondary endpoints, including Week 4 healing rates of EE for subjects with baseline LA EE Grade C or D, were evaluated by the sponsor. However, there were no statistically significant differences that could be concluded for the additional secondary endpoints.

Exploratory comparisons between two dexlansoprazole MR groups were conducted by the sponsor and there were no statistically significant findings. It can be observed that dexlansoprazole MR 90 mg had very little benefit over 60 mg on the healing rates of EE.

Moreover, the higher dose did not result in better performance on more severe (baseline LA EE Grade C or D) patients.

### 3.3.2 Evaluation of Safety

In the phase 3 healing of EE studies, the percentage of subjects with at least one treatment-emergent AE was 30.4%, 28.1% and 27.8% in dexlansoprazole MR 60 mg QD, 90 mg QD, and lansoprazole 30 mg QD treatment groups, respectively. The most frequently reported (at least 4% of subjects in any treatment group by MedDRA HLT) treatment-emergent AE was Diarrhoea (4.1% in each dexlansoprazole MR treatment group and 3.2% in lansoprazole treatment group). The incidence of treatment-related AEs was low among three treatment groups within each AE. For more details on the safety of dexlansoprazole MR, refer to the clinical team’s review.

### 3.3.3 Integrated Efficacy Analysis

The efficacy results based on the data pooling over two phase 3 healing of EE studies are summarized in the table below for the crude rate analyses and in the Appendix (Table A.1) for life-table method. Since both doses of dexlansoprazole MR had numerically higher healing EE rates than lansoprazole in both studies for efficacy and combining two studies together could provide higher power to detect the difference between two treatments, it would be more likely to see statistically significant differences in this integrated analysis. However, even with this advantage, there was still no visible benefit of dexlansoprazole MR compared with lansoprazole on the healing rates of EE. There was a statistically significant difference between dexlansoprazole MR 90 mg and lansoprazole on Week 8 crude healing rate of EE for mITT subjects with baseline LA EE Grade C or D, which was inconsistent with the findings from individual studies (a statistically significant difference between dexlansoprazole MR 60 mg and lansoprazole in Study T-EE04-084 only). Evidently, this statistical significance resulted from the aforementioned advantage of higher power from the pooled data.

**Table 3.6. Crude Healing Rates of EE for Integrated Data (mITT population)**

Endpoint	Dexlansoprazole MR		Lansoprazole 30	p-value	
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)	mg QD % (n/N) (95% Exact CI)	Dexlansoprazole MR 60 mg vs. Lansoprazole	Dexlansoprazole MR 90 mg vs. Lansoprazole
Week 8	86.11% (1116/1296) (84.11%, 87.95%)	(b) (4)	81.75% (1066/1304) (79.54%, 83.81%)	0.0033 (CMH) <sup>a</sup> 0.0039 (CMH with continuity correction)	(b) (4)
Week 4	67.98% (881/1296) (65.36%, 70.51%)		65.11% (849/1304) (62.45%, 67.70%)	0.1541 (CMH) <sup>a</sup> 0.1669 (CMH with continuity correction)	
Week 8 C or D	78.72% (296/376) (74.24%, 82.75%)		71.79% (280/390) (67.05%, 76.21%)	0.0299 (CMH) <sup>a</sup> 0.0369 (CMH with continuity correction)	

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer’s Table

### **3.4 Evaluation of the Maintenance of Healed EE Indication**

One of the three proposed indications for dexlansoprazole MR is maintenance of healed EE. The sponsor states that a frequently used approach for maintenance of healed EE is to step down to a lower dose than that used for healing EE. The sponsor also states that although the majority of patients will be maintained with a step-down dose, patients with more severe disease may obtain additional benefit from continuing treatment with the standard healing dose. Based on this, the sponsor studied three doses of dexlansoprazole MR (30 mg, 60 mg, and 90 mg) were used in the phase 3 clinical studies for the maintenance of healed EE evaluation.

#### **3.4.1 Evaluation of Efficacy**

The dexlansoprazole MR clinical program originally consisted of two identical phase 3, randomized, controlled, 6-month studies (T-EE04-086 and T-EE04-087) designed to assess the safety and efficacy of dexlansoprazole MR 60 mg QD and 90 mg QD vs. placebo for the maintenance of healed EE indication. After these two studies started, the sponsor claimed that PK/PD data from phase 1 studies supported the inclusion of a 30 mg dose in the development plan for the maintenance of healed EE indication. This resulted in adding another randomized, controlled, 6-month, phase 3 study (T-EE05-135) before the original two studies ended, which compared dexlansoprazole MR 30 and 60 mg QD vs. placebo. Studies T-EE04-086 and T-EE04-087 were then combined into a single large study around March 2006, as indicated in the protocol amendment 3, hereinafter referred to as Study T-EE04-086.

##### **3.4.1.1 Study Design and Endpoints**

Studies T-EE04-086 and T-EE05-135 were both phase 3, randomized, double-blind, multicenter, placebo-controlled studies designed to compare the efficacy and safety of dexlansoprazole MR with that of placebo, in maintaining healing in subjects with healed EE from two previous studies, T-EE04-084 and T-EE04-085, which evaluated endoscopic healing of EE. On Day -1 (the Final Visit of Studies T-EE04-084 and T-EE04-085), subjects were assigned in a 1:1:1 ratio to receive either placebo or one of the two dexlansoprazole MR doses QD.

During the 6-month Treatment Period, subjects self-administered study drug orally QD before breakfast. Subjects documented the daily presence and maximum severity of daytime and nighttime heartburn symptoms and use of rescue medication throughout the study via a twice-daily diary. Subjects returned for study visits after 1, 3, and 6 months of treatment, and underwent various procedures at each visit, including an endoscopy. Subjects who showed recurrence of EE by endoscopy at any visit were discontinued from study drug.

The primary efficacy variable was the percentage of subjects who maintained healed EE for six months as assessed by endoscopy. The secondary efficacy variables were (1) the percentage of days with neither daytime nor nighttime heartburn (24-hour heartburn-free days) during the treatment period as assessed by daily diary; and (2) the percentage of nights without heartburn during the treatment period as assessed by daily diary.

Additional (exploratory) efficacy variables included the percentage of subjects who maintained healed EE at Month 1 or Month 3 as assessed by endoscopy and time to recurrence among those who experienced a recurrence.

A total of 450 subjects with documented healed EE at Day -1 were planned to be enrolled into Studies T-EE04-086 and T-EE04-087 combined and also in Study T-EE05-135 to ensure 360 subjects complete the study (assuming a 20% dropout rate). The sample size of 120 subjects per treatment group would provide at least 95% power at the 0.00125 level of significance to detect a 45% difference between a dexlansoprazole MR dose (70%) and placebo (25%) in maintenance of EE healing over six months. The test of this primary efficacy variable used Hochberg's method at the 0.0025 significance level; however, the use of 0.00125 in the power calculation was to ensure power even if only one of the doses was effective. The placebo rate was estimated from prior lansoprazole studies for EE maintenance based on life-table method, which was originally proposed as the primary analysis for the maintenance studies. See Section 3.4.1.3 for further details on the statistical methodology.

### **3.4.1.2 Patient Disposition, Demographic and Baseline Characteristics**

The two maintenance studies enrolled a total of 896 subjects at 180 sites in the U.S. and 19 sites outside of the U.S. Of these, 842 subjects participated at U.S. sites and 54 participated at sites outside of the U.S.

#### *Study T-EE04-086*

Study T-EE04-086 had the first dose administered on January 4, 2006 and the last procedure on November 14, 2006. While 450 were planned, 451 subjects were randomized and received study drug (237 in T-EE04-086 and 214 in T-EE04-087) in 105 sites in the U.S. with 107 investigators, including the two who were replaced by new investigators. Out of these enrolled subjects, no subjects had a gap of more than seven days between the EE healing studies and this maintenance study and a total of 402 (89.14%) were included in the primary crude rate efficacy analyses.

About 9% (39/451) of subjects had at least one protocol deviation during this study. A total of three subjects (1% of the study population) were enrolled without meeting all of the inclusion/exclusion criteria. Three subjects (1% of the study population) developed withdrawal criteria but were not withdrawn from the study. Two of these subjects were determined to have Barrett's esophagus and the other one had a relapse of EE during the study (at least seven days prior to the last dose of study drug). These subjects completed the study. A total of 31 subjects (7% of the study population) received an excluded concomitant medication during the study. Two subjects received the wrong treatment during the course of the study since the site dispensed a kit with a different treatment from the randomization assignment. They were included in the treatment group of the actual dose they received in all analyses.

Approximately half of the enrolled subjects were male (52.1%) and the majority were White (87.6%). The average age was 48.9 years, and the average BMI was 31.1 kg/m<sup>2</sup>. There were 159, 152, and 140 subjects who received dexlansoprazole MR 60 mg, 90 mg, and placebo, respectively. For the 402 subjects included in the primary crude maintenance of healed EE rate analyses, demographic characteristics were similar to those in the all-subjects population. Out of

those, 152, 138, and 112 subjects received dexlansoprazole MR 60 mg, 90 mg, and placebo, respectively.

Table A.3 in the Appendix presents the counts of the primary crude rate mITT subjects healed by Week 4 and Week 8 for different healing EE study characteristics (healing EE study number, treatment received in healing EE study, and baseline EE grades in healing EE study) breakdown. Subjects were evenly distributed among three healing EE treatment groups (dexlansoprazole MR 60 mg, 90 mg, and lansoprazole 30 mg QD) with the highest percentage (35.07%; 141/402) from dexlansoprazole MR 90 mg arm in the healing EE studies. About the same percentage of subjects within each healing EE treatment group was healed by Week 8. All three maintenance healed EE treatment groups had similarly low percentages (8% - 9%) of subjects with healing EE treatment duration of eight weeks. A total of 211 subjects were from Study T-EE04-084 and 191 from Study T-EE04-085. Approximately 23% subjects had pre-healing EE Grade C or D and 4% subjects Grade D. However, the subjects with pre-healing EE Grade A had the highest percentage of subjects healed by Week 8 (9.55%; 15/157) while the percentage of subjects healed by Week 8 was 7.19% (11/153), 6.58% (5/76), and 6.67% (1/15) for pre-healing EE Grade B, C, and D group, respectively. A total of 32 (7.96%) subjects were healed by Week 8.

#### Study T-EE05-135

Study T-EE05-135 had the first dose administered on May 19, 2006 and the last procedure on May 21, 2007. While 450 were planned, 445 subjects were randomized and received study drug in 94 sites (75 sites in the U.S. and 19 sites throughout Australia, Canada, the Czech Republic, Estonia, India, Latvia, Lithuania, Poland, and the Slovak Republic). Note that all subjects were from U.S. sites and more sites were involved for Study T-EE04-086. Out of these enrolled subjects, 10 subjects had a gap of more than seven days between the EE healing studies and this maintenance study and a total of 387 (86.97%) were included in the primary crude rate efficacy analyses.

About 6% (28/445) of subjects had at least one protocol deviation during this study. A total of two subjects (less than 1% of the study population) were enrolled without meeting all of the inclusion/exclusion criteria. All subjects who satisfied withdrawal criteria were withdrawn from the study. A total of 25 subjects (6% of the study population) received an excluded concomitant medication during the study. One subject randomized to dexlansoprazole MR 60 mg QD treatment group, received the lower dose of dexlansoprazole MR, 30 mg, for six days. The sponsor stated that it is unlikely receiving the lower dose of dexlansoprazole MR for six days had any affect on any other assessments of efficacy. The subject remained healed during the study.

Approximately half of the enrolled subjects were male (48.3%) and the majority were White (89.9%). The average age was 48.2 years, and the average BMI was 30.6 kg/m<sup>2</sup>. There were 140, 158, and 147 subjects who received dexlansoprazole MR 30 mg, 60 mg, and placebo, respectively. For the 387 subjects included in the primary crude maintenance of healed EE rate analyses, demographic characteristics were similar to those in the all-subjects population. Out of those, 125, 143, and 119 subjects received dexlansoprazole MR 30 mg, 60 mg, and placebo, respectively.

Table A.4 in the Appendix presents the counts of the primary crude rate mITT subjects healed by Week 4 and Week 8 for different healing EE study characteristics (healing EE study number, treatment received in healing EE study, and baseline EE grades in healing EE study) breakdown. This study enrolled one subject in the placebo group who had her EE healed by Week 9 in Study T-EE04-084 dexlansoprazole 90 mg arm. This subject was included in the primary crude maintenance rate analysis but excluded for this summary. Subjects were evenly distributed among three healing EE treatment groups (dexlansoprazole MR 60 mg, 90 mg, and lansoprazole 30 mg QD) with the highest percentage (36.01%; 139/386) from dexlansoprazole MR 90 mg arm in the healing EE studies. About the same percentage of subjects within each healing EE treatment group was healed by Week 8. Three maintenance healed EE treatment groups had similar percentage of subjects with healing EE treatment duration of eight weeks, which was approximately 26%, 24%, and 22% for dexlansoprazole MR 30 mg, 60 mg, and placebo group, respectively. A total of 212 subjects were from Study T-EE04-084 and 174 from Study T-EE04-085. Greater percentage (approximately 27%) of subjects than Study T-EE04-086 had pre-healing EE Grade C or D and 4% subjects Grade D. However, different from Study T-EE04-086, the subjects with pre-healing EE Grade D had the highest percentage of subjects healed by Week 8 (35.29%; 6/17) while the percentage of subjects healed by Week 8 was 14.89% (21/141), 28.06% (39/139), and 30.34% (27/89) for pre-healing EE Grade A, B, and C group, respectively. In general, comparing with Study T-EE04-086, much higher percentage (24.09%; 93/386) subjects were healed by Week 8 in this study.

### 3.4.1.3 Statistical Methodologies

The two double-blind, randomized, placebo-controlled maintenance of healed EE studies were each powered to demonstrate the statistical superiority of the dexlansoprazole MR doses compared with placebo as if each trial was a single study. Thus, to achieve a higher level of significance, the sponsor planned to control the two-sided type I error rate at 0.0025.

As prespecified in the protocol and original SAP for each of study T-EE05-135 and T-EE04-086, the primary analysis for the primary efficacy endpoint was based on life-table methods, and the crude rate analysis was considered as supportive. Following a request from the FDA at the Pre-NDA meeting on October 1, 2007, the primary analysis for the primary endpoint was changed to crude rate analysis and analysis based on life-table methods with log-rank tests considered supportive.

The sponsor's efficacy analyses were performed on the appropriate ITT population proposed by the sponsor. Subjects who had endoscopically proven EE, were randomized in Study T-EE04-084 or Study T-EE04-085, were healed and did not have a gap in dosing more than seven days before entering the maintenance study (T-EE05-086 or T-EE04-135) were included in the general ITT population. Subjects who were ITT and also had at least one endoscopy in the maintenance study were included for the primary analysis of the primary efficacy endpoint of maintenance of healed EE. Base on this definition, this population should be better characterized as the modified ITT (mITT) population and such will be used in this review to distinguish it from the general ITT population. All ITT subjects were included in the percentage of subjects with maintenance of healed EE by life-table methods. Separate mITT populations for the secondary

efficacy analyses were defined as all ITT subjects who completed at least one of the appropriate heartburn Yes/No questions during the treatment period.

The sponsor assessed the following two secondary efficacy variables in the following sequential order:

- The mean percentage of days without daytime or nighttime heartburn over six months as assessed by daily diary.
- The mean percentage of days without nighttime heartburn over six months as assessed by daily diary.

Comparisons between dexlansoprazole MR and placebo for each secondary variable were made with Wilcoxon rank-sum tests by the sponsor. For each dexlansoprazole MR dose that was found to be superior to placebo for the primary efficacy variable, evaluation of the first secondary variable was performed. Evaluation of the second secondary variable was then performed only for the dexlansoprazole MR doses that were superior to placebo for the first secondary efficacy variable. Since the comparisons for the two variables were done sequentially, adjustments for multiplicity were only made for assessing the two dexlansoprazole MR doses within each variable.

#### Control of Type I Error

For each efficacy variable, the comparisons of each dexlansoprazole MR dose to placebo used Hochberg's method to control the overall significance level of two-sided 0.0025 with the multiple comparisons. If both dexlansoprazole MR doses were declared superior to placebo in the primary efficacy analysis, the 0.0025 level of significance for the secondary efficacy variables were to be controlled using Hochberg's method within each variable. If only one dexlansoprazole dose was declared superior to placebo, then the p-values for the secondary efficacy variables were to be compared with 0.0025. Note that this procedure was erroneous since in the latter situation only the unspent portion of the significance level, 0.00125 ( $=0.0025/2$ ), should be carried over to the comparisons on the secondary efficacy variables. The sponsor also conducted comparisons between the two dexlansoprazole MR doses for each efficacy variable with no adjustment to the 0.0025 level of significance. This comparison can only be considered exploratory.

#### Handling of Missing Values and Sensitivity Analyses

The crude rate analysis at Month 6 of the primary efficacy variable was the primary analysis. The sponsor calculated the percentage of subjects who maintained healed EE per endoscopy by each of Month 1, 3, and 6, for each treatment group, for the mITT population. The interval for Month 1, 3, and 6 was defined as Day 2 to 35, Day 36 to 105, and Day 106 to 195, respectively. Subjects with an endoscopy showing recurrence anywhere in the interval were considered as recurred for the visit. Those subjects who did not have a recurrence of EE and did not complete the study were included in the analysis according to their last endoscopy date. If the last endoscopy that showed no recurrence was during the predefined visit window (Days 21 to 35 for Month 1, Days 75 to 105 for Month 3, and Days 165 to 195 for Month 6), the subjects were considered maintained EE during that visit but included for any later visits as having recurrence. Subjects who prematurely discontinued with the final endoscopy showing no recurrence in the early part of the interval for Month 1, 3, or 6 could not be considered to have evidence of no

recurrence for that visit. Thus, those subjects were assumed as having recurred for that visit. Subjects who had a recurrence after the visit window for Month 6 were still considered to have recurred at Month 6. However, among all the ITT subjects from the two maintenance studies there was no subject with a recurrence after Day 195 recorded in the study. Pairwise comparisons between treatment groups of the percentages at Month 1, 3, and 6 were made with Fisher's exact tests by the sponsor.

The sponsor performed a sensitivity analysis on the primary efficacy endpoint by recalculating the maintenance rates while considering all subjects who prematurely discontinued without known recurrence to have no recurrence by the end of six months. The other sensitivity analysis performed by the sponsor for the crude rate analysis included subjects who had a gap of more than seven days between the EE healing studies and the maintenance studies. However, additional sensitivity analyses including a worst-case scenario analysis should have been carried out. These and the efficacy analyses using other testing methods than Fisher's exact tests were conducted by this reviewer and are presented below.

### 3.4.1.4 Results and Conclusions

#### Primary Analyses

In both studies, both doses of dexlansoprazole MR were statistically significantly superior to placebo in maintaining healed EE. The table below shows the percentage of mITT subjects who maintained healed EE throughout six months as assessed by endoscopy and the p-values from Fisher's exact tests for treatment comparisons. Pearson's Chi-square tests and Binomial Exact tests generated nearly the same p-values. For this table, subjects who prematurely discontinued with last endoscopy showing no recurrence were considered as recurred.

**Table 3.7. Month 6 Maintenance of Healed EE Rates (mITT population)**

Study	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
Study T-EE04-086	NA	(b) (4) (b) (4) (b) (4)	(b) (4) (b) (4) (b) (4)	14.29% 16/112 (8.39%, 22.16%)	NA	(b) (4)	(b) (4)
Study T-EE05-135	66.40% 83/125 (57.40%, 74.60%)	(b) (4) (b) (4) (b) (4)	(b) (4)	14.29% 17/119 (8.55%, 21.88%)	<0.0001	(b) (4)	(b) (4)

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer's Table

(b) (4) all doses of dexlansoprazole MR had higher 6-month maintenance of healed EE rates than placebo using either Hochberg's or Bonferroni method for the multiplicity adjustment.

For the primary analysis, this reviewer also used the general ITT population and imputed all the missing values as recurred. As expected, all the maintenance rates for all treatment arms in both studies dropped. However, the treatment comparison results were similar to those from using the mITT population.

Secondary Analyses

For the secondary efficacy endpoints of the percentage of 24-hour heartburn-free days and the percentage of heartburn-free nights according to subjects' twice-daily diary, ITT subjects in all treatment groups had five to six days with heartburns and four to five nights with heartburns, on average, over the seven days before the maintenance studies. After treatment, all doses showed statistically significant difference comparing with placebo for both secondary endpoints on mITT subjects. All statistical significances were strong using either Hochberg's or Bonferroni method for the multiplicity adjustment. The p-values presented in the table below are from Wilcoxon rank-sum tests while two-sample t-tests generated nearly the same small p-values. Similar results were obtained using the general ITT population by imputing missing data as having heartburns. The results for secondary efficacy endpoints based on the mITT population are summarized in the table below. It can be observed that Study T-EE05-135 had slightly higher placebo response than T-EE04-086.

**Table 3.8. Secondary Endpoints for Maintenance of Healed EE Studies (mITT population)**

Endpoint	Dexlansoprazole MR			Placebo N Median Mean (SD)	p-value <sup>a</sup>		
	30 mg QD N Median Mean (SD)	60 mg QD N Median Mean (SD)	90 mg QD N Median Mean (SD)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Study T-EE04-086</b>							
24-hour Heartburn-Free Days	NA	(b) (4)		133 19.23% 29.54% (29.29)	(b) (4)		
Nighttime Heartburn-Free Days	NA			133 50.00% 48.28% (35.26)	NA		
<b>Study T-EE05-135</b>							
24-hour Heartburn-Free Days	132 96.09% 83.25% (26.56)			141 28.57% 36.02% (31.97)	<0.0001		
Nighttime Heartburn-Free Days	132 98.83% 88.72% (22.57)			141 71.43% 57.10% (36.79)	<0.0001		

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer's Table

Table A.5 in the Appendix summarizes the results for the crude maintenance of healed EE rates by Month 1 and 3 based on the mITT population. The treatment comparison results were similar to those from Month 6 analysis except that Study T-EE05-135 had slightly higher maintenance rates than T-EE04-086 for placebo group.

The supportive analyses of life-table methods and log-rank tests on time-to-event responses had similar results as those from crude rate methods. The results are summarized in the Appendix (Table A.6). As discussed earlier for the healing studies, life-table methods are more lenient on treating censored subjects and rendered higher estimates for the maintenance of healed EE rates.

Sensitivity Analyses

The sponsor performed sensitivity analyses of the primary efficacy results to different missing data handling assumptions. One sensitivity analysis performed by the sponsor is to consider all mITT subjects who prematurely discontinued without known recurrence to have no recurrence by the end of six months. Another sensitivity analysis performed by this reviewer is the worst-case scenario which includes mITT subjects who prematurely discontinued without known recurrence as having no recurrence by the end of six months for placebo arm but as having a recurrence for dexlansoprazole arms. Another sensitivity analysis done by the sponsor for the crude rate endpoint includes subjects who had a gap of more than seven days between the EE healing studies and the maintenance studies.

The results are summarized in the table below. Note that including subjects who had a gap of more than seven days between the EE healing studies and the maintenance studies in the mITT population for the crude healing rate analysis did not alter the results for Study T-EE04-086 since there were no such subjects. However, the results from this sensitivity analysis for Study T-EE05-135 were slightly different from the sponsor’s results because the sponsor’s analysis only included nine out of ten subjects with a gap of more than seven days (excluding one placebo subject) while the reviewer’s analysis included all ten subjects. The results from all these sensitivity analyses do not exhibit unusual variation in the estimates and do not change the efficacy conclusions based on the sponsor’s primary analysis.

**Table 3.9. Sensitivity Analyses on Month 6 Maintenance of Healed EE Rates (mITT population)**

Study	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Prematurely Discontinued Before Recurrence Considered as Not Recurred<sup>a</sup></b>							
Study T-EE04-086	NA	(b) (4)	(b) (4)	22.32% 25/112 (15.00%, 31.16%)	NA	(b) (4)	(b) (4)
Study T-EE05-135	75.20% 94/125 (66.68%, 82.49%)	(b) (4)	(b) (4)	27.73% 33/119 (19.92%, 36.68%)	<0.0001	(b) (4)	(b) (4)
<b>Worst-Case</b>							
Study T-EE04-086	NA	(b) (4)	(b) (4)	22.32% 25/112 (15.00%, 31.16%)	NA	(b) (4)	(b) (4)
Study T-EE05-135	66.40% 83/125 (57.40%, 74.60%)	(b) (4)	(b) (4)	27.73% 33/119 (19.92%, 36.68%)	<0.0001	(b) (4)	(b) (4)
<b>Including Subjects with a Gap of &gt;7 Days</b>							
Study T-EE04-086	NA	(b) (4)	(b) (4)	14.29% 16/112 (8.39%, 22.16%)	NA	(b) (4)	(b) (4)
Study T-EE05-135	66.41% 85/128 (57.52%, 74.51%)	(b) (4)	(b) (4) 8	14.05% 17/121 (8.40%, 21.54%)	<0.0001	(b) (4)	(b) (4)

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer’s Table

#### Additional Analyses

Additional secondary endpoints were evaluated by the sponsor. However, these are all considered exploratory findings (b) (4) [REDACTED]. These results will not be further discussed in this review.

Exploratory comparisons between dexlansoprazole MR groups were also conducted by the sponsor, and there were no statistically significant findings. It should be observed from the above tables (Tables 3.7 and 3.9) that higher dose(s) of dexlansoprazole MR had very minimum, if any, clinical benefit over lower dose(s) on the maintenance of healed EE rates.

#### **3.4.2 Evaluation of Safety**

In the phase 3 maintenance of healed EE studies, lower number of subjects per 100 PM of exposure in each dexlansoprazole MR treatment group (10.35, 10.93, 9.65 for 30 mg, 60 mg, and 90 mg, respectively) compared with placebo group (15.80) had at least one treatment-emergent AE. A dose-dependent pattern was observed in the incidence of treatment-emergent Diarrhea (0.78, 1.21, and 1.46 per 100 PM in dexlansoprazole MR 30 mg, 60 mg, and 90 mg treatment group, respectively, compared with 0.39 per 100 PM for placebo). For more details on the safety of dexlansoprazole MR, refer to the clinical team's review.

#### **3.4.3 Integrated Efficacy Analysis**

Due to differences between the two maintenance studies in trial conduct and patients' characteristics, it may not be meaningful to conduct an analysis on the pooled data from these two studies. The sponsor stated that a statistically significant imbalance between the maintenance studies was shown in the percentage of subjects with healed EE after four or eight weeks of treatment from the healing EE studies. However, this imbalance may be due to the fact that Study T-EE05-135 began the enrollment much later than Study T-EE04-086 and so most of the subjects with 8-week healed EE were enrolled in the former study. Since dexlansoprazole 30 mg was only studied in Study T-EE05-135 and 90 mg in T-EE04-086, the 30 mg group had much higher percentage of subjects with healed EE after eight weeks than the 90 mg group. Thus a pooled analysis may be biased and should be interpreted carefully. Additionally, pooled analyses should only be considered as exploratory.

Because only dexlansoprazole MR 60 mg QD dose and placebo were evaluated in both studies, for the integration of data from Studies T-EE04-086 and T-EE05-135 the only meaningful comparison would be between dexlansoprazole MR 60 mg and placebo. The efficacy results based on data pooling over two phase 3 maintenance of healed EE studies are summarized in the Appendix (Table A.7). The results were consistent with those from individual studies.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Evaluation of the Healing EE Indication

For the healing EE studies, subgroup analyses on the primary efficacy variable were conducted by the sponsor for the following factors for each study and the integrated analysis on data pooled over Studies T-EE04-084 and T-EE04-085:

- 1) Baseline LA Grade (A, B, C, D)
- 2) Baseline LA Grade A and B combined, C and D combined
- 3) Age (<45, 45-<65, ≥65 years old)
- 4) Race (Caucasian, Black, Other)
- 5) Gender (male, female)
- 6) Body mass index (BMI) (<25, 25-<30, ≥30 kg/m<sup>2</sup>)
- 7) Smoking status (smoker, non-/ex-smoker)
- 8) Alcohol use (drinker, non-/ex-drinker)
- 9) Caffeine use (caffeine user, caffeine nonuser)
- 10) Baseline diary recorded heartburn
- 11) Baseline GERD symptom investigator assessment of heartburn
- 12) Investigative sites from U.S. versus non-U.S.
- 13) Study drug compliance (<90% and ≥90%)
- 14) Rescue medication usage (<50% and ≥50% of days)
- 15) Combined baseline LA Grade (A and B, C and D) by U.S. versus non-U.S. investigative sites.

The results from 1), 2), and 12) are discussed in Section 4.1.2. The results from 3), 4), and 5) are discussed in Section 4.1.1 below. For the other factors, the efficacy results were very similar across the subgroups. Moreover, the results for these factors are not of great clinical interest and so they will not be further discussed in this review.

#### 4.1.1 Gender, Race and Age

The subgroup results from the primary endpoint efficacy analyses on subgroups of gender, race, and age are summarized in the table below. It can be observed that female subjects had higher placebo response rates than the male subjects. Moreover, there seems to be no significant treatment difference based on the overlapping CIs for the female subjects while for male subjects the treatment effect is more promising. Caucasian subjects had better treatment effect than the other races. However, the sample sizes for the other races were too small to draw a reliable conclusion. As expected, younger patients had higher placebo response rates and better treatment effect than older patients. The oldest group, however, only had very limited number of patients and so the results for this subgroup may be biased. Although some subgroups may have more promising clinical benefit from the dexlansoprazole MR than the other subgroups, all these results are only exploratory.

**Table 4.1. Week 8 Crude Healing Rates of EE by Gender, Race, and Age  
(mITT population)**

Factor Category	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 60 mg vs. Lansoprazole	Dex MR 90 mg vs. Lansoprazole	Dex MR 60 mg vs. Dex MR 90 mg
<b>Study T-EE04-084</b>						
<b>Gender as strata</b>						
Male	84.2% (303/360) (80.0%, 87.8%)	(b) (4)	73.4% (254/346) (68.4%, 78.0%)	0.003	(b) (4)	
Female	86.7% (242/279) (82.2%, 90.5%)		85.2% (264/310) (80.7%, 88.9%)			
<b>Race as strata</b>						
Caucasian	84.5% (480/568) (81.3%, 87.4%)		77.3% (443/573) (73.7%, 80.7%)	0.004		
Black	100.0% (28/28) (NA)		100.0% (26/26) (NA)			
Other	86.0% (37/43) (72.1%, 94.7%)		86.0% (49/57) (74.2%, 93.7%)			
<b>Age (years) as strata</b>						
<45	82.7% (206/249) (77.5%, 87.2%)	(b) (4)		0.006	(b) (4)	
45-<65	86.3% (284/329) (82.1%, 89.8%)					
≥65	90.2% (55/61) (79.8%, 96.3%)					
<b>Study T-EE04-085</b>						
<b>Gender as strata</b>						
Male	86.2% (306/355) (82.2%, 89.6%)			0.229		
Female	87.7% (265/302) (83.5%, 91.2%)					

<sup>a</sup> P-values for each subgroup factor are using CMH tests with baseline LA EE Grade and each subgroup factor as strata. Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Healing EE: T-EE04-084 Study Report, Table 14.2.2.3, 14.2.2.4, and 14.2.2.5; T-EE04-085 Study Report, Table 14.2.2.3, 14.2.2.4, and 14.2.2.5; Integrated Summary of Efficacy, Table 8.2.7.3, 8.2.7.4, and 8.2.7.5

**Table 4.1. (Cont'd) Week 8 Crude Healing Rates of EE by Gender, Race, and Age (mITT population)**

Factor Category	Dexlansoprazole MR		Lansoprazole	p-value <sup>a</sup>		
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)	30 mg QD % (n/N) (95% Exact CI)	Dex MR 60 mg vs. Lansoprazole	Dex MR 90 mg vs. Lansoprazole	Dex MR 60 mg vs. Dex MR 90 mg
<b>Race as strata</b>						
	(b) (4)			(b) (4)		
Caucasian	86.4% (491/568) (83.4%, 89.2%)		84.7% (476/562) (81.5%, 87.6%)	0.205		
Black	91.2% (31/34) (76.3%, 98.1%)		93.8% (30/32) (79.2%, 99.2%)			
Other	89.1% (49/55) (77.8%, 95.9%)		77.8% (42/54) (64.4%, 88.0%)			
<b>Age (years) as strata</b>						
<45	86.6% (206/238) (81.6%, 90.6%)		82.1% (229/279) (77.1%, 86.4%)	0.246		
45-<65	87.9% (290/330) (83.9%, 91.2%)		86.6% (265/306) (82.3%, 90.2%)			
≥65	84.3% (75/89) (75.0%, 91.1%)		85.7% (54/63) (74.6%, 93.3%)			
<b>Integrated Analysis</b>						
<b>Gender as strata</b>						
	(b) (4)			(b) (4)		
Male	85.2% (609/715) (82.4%, 87.7%)		77.6% (540/696) (74.3%, 80.6%)	0.003		
Female	87.3% (507/581) (84.3%, 89.9%)		86.5% (526/608) (83.5%, 89.1%)			
<b>Race as strata</b>						
Caucasian	85.5% (971/1136) (83.3%, 87.5%)		81.0% (919/1135) (78.6%, 83.2%)	0.003		
Black	95.2% (59/62) (86.5%, 99.0%)		96.6% (56/58) (88.1%, 99.6%)			
Other	87.8% (86/98) (79.6%, 93.5%)		82.0% (91/111) (73.6%, 88.6%)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with baseline LA EE Grade and each subgroup factor as strata.  
Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Healing EE: T-EE04-084 Study Report, Table 14.2.2.3, 14.2.2.4, and 14.2.2.5; T-EE04-085 Study Report, Table 14.2.2.3, 14.2.2.4, and 14.2.2.5; Integrated Summary of Efficacy, Table 8.2.7.3, 8.2.7.4, and 8.2.7.5

**Table 4.1. (Cont'd) Week 8 Crude Healing Rates of EE by Gender, Race, and Age (mITT population)**

Factor Category	Dexlansoprazole MR		Lansoprazole	p-value <sup>a</sup>		
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)	30 mg QD % (n/N) (95% Exact CI)	Dex MR 60 mg vs. Lansoprazole	Dex MR 90 mg vs. Lansoprazole	Dex MR 60 mg vs. Dex MR 90 mg
Age (years) as strata		(b) (4)		(b) (4)		
<45	84.6% (412/487) (81.1%, 87.7%)		78.3% (436/557) (74.6%, 81.6%)	0.007		
45-<65	87.1% (574/659) (84.3%, 89.6%)		83.7% (517/618) (80.5%, 86.5%)			
≥65	86.7% (130/150) (80.2%, 91.7%)		87.6% (113/129) (80.6%, 92.7%)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with baseline LA EE Grade and each subgroup factor as strata. Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Healing EE: T-EE04-084 Study Report, Table 14.2.2.3, 14.2.2.4, and 14.2.2.5; T-EE04-085 Study Report, Table 14.2.2.3, 14.2.2.4, and 14.2.2.5; Integrated Summary of Efficacy, Table 8.2.7.3, 8.2.7.4, and 8.2.7.5

#### 4.1.2 Other Special/Subgroup Populations

The results from the efficacy analyses on the subgroups of different baseline LA EE grades are summarized in the Appendix (Table A.8). The results were consistent with those from the primary efficacy analysis with higher healing rates for the lower grade(s) compared with the higher grade(s).

Since there were non-U.S. sites involved in both studies, the results from the efficacy analyses on the subgroups of investigative sites from U.S. vs. non-U.S. are summarized in the Appendix (Table A.9). The results were similar to those from the primary efficacy analysis with slightly higher healing rates for the U.S. investigative sites than the non-U.S. sites. The difference was larger for dexlansoprazole MR 60 mg QD and lansoprazole 30 mg QD groups than for dexlansoprazole MR 90 mg group.

#### 4.2 Evaluation of the Maintenance of Healed EE Indication

For the maintenance of healed EE studies, subgroup analyses on the primary efficacy variable were conducted by the sponsor for the following factors for each study and the integrated analysis on data pooled over Studies T-EE04-086 and T-EE05-135:

- 1) Age (<45, 45-<65, ≥65 years old)
- 2) Race (Caucasian, Black, Other)
- 3) Gender (male, female)
- 4) Body mass index (BMI) (<25, 25-<30, ≥30 kg/m<sup>2</sup>)
- 5) Smoking status (smoker, non-/ex-smoker)
- 6) Alcohol use (drinker, non-/ex-drinker)
- 7) Caffeine use (caffeine user, caffeine nonuser)
- 8) *Helicobacter pylori* (*H. pylori*) status (positive, negative)

- 9) Overall study drug compliance (<80%, 80%-<90%, ≥90%)
- 10) GERD Symptoms Investigator Assessment of Heartburn at Day -1 (none, mild, moderate, severe, very severe)
- 11) Investigative site
- 12) Baseline LA EE Grade in healing of EE study (A, B, C, D; A and B combined; C and D combined)
- 13) Duration of treatment in healing of EE study (4 weeks, 8 weeks)
- 14) Treatment in healing of EE study (dexlansoprazole MR 60 mg QD, dexlansoprazole MR 90 mg QD, lansoprazole 30 mg QD)
- 15) Rescue medication usage (<50% and ≥50% of days)

The results from 1), 2), and 3) are discussed in Section 4.2.1 below. The results from 11), 12), 13) and 14) are discussed in Section 4.2.2. For the other factors, the efficacy results were very similar across the subgroups. Moreover, the results for these factors are not of great clinical interest and so they will not be further discussed in this review.

#### 4.2.1 Gender, Race and Age

In both Study T-EE04-086 and Study T-EE05-135, and in the integrated analysis, the efficacy results for subgroups of gender, race and age were fairly similar to those from the primary efficacy analysis. The subgroup results on the primary endpoint of Month 6 maintenance of healed EE rate are summarized in the table below. Although some subgroups may seem to have larger treatment effect than the other subgroups, the treatment differences on the maintenance rates were all statistically significant for the subgroups with reasonable sample sizes. Some age and race subgroups had too few subjects to have reliable results. All these results are considered exploratory.

**Table 4.2. Month 6 Maintenance of Healed EE Rates by Gender, Race, and Age (mITT population)**

Factor Category	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Study T-EE04-086</b>							
<b>Gender as strata</b>							
		(b) (4)			(b) (4)		
Male	NA				10.3% (6/58) (3.9%, 21.2%)	NA	
Female	NA				18.5% (10/54) (9.3%, 31.4%)		

<sup>a</sup> P-values for each subgroup factor are using CMH tests with each subgroup factor as strata.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Maintenance of Healed EE: T-EE04-086 Study Report, Table 14.2.1.1, 14.2.1.2, and 14.2.1.3; T-EE05-135 Study Report, Table 14.2.1.1, 14.2.1.2, and 14.2.1.3; Integrated Summary of Efficacy, Table 8.2.7.1, 8.2.7.2, and 8.2.7.3

**Table 4.2. (Cont'd) Month 6 Maintenance of Healed EE Rates by Gender, Race, and Age (mITT population)**

Factor Category	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Study T-EE04-086</b>							
<b>Race as strata</b>							
Caucasian	NA	(b) (4)		13.0% (13/100) (7.1%, 21.2%)	NA	(b) (4)	
Black	NA			25.0% (2/8) (3.2%, 65.1%)			
Other	NA			25.0% (1/4) (0.6%, 80.6%)			
<b>Age (years) as strata</b>							
<45	NA			13.2% (5/38) (4.4%, 28.1%)	NA	(b) (4)	
45-<65	NA			14.9% (10/67) (7.4%, 25.7%)			
≥65	NA			14.3% (1/7) (0.4%, 57.9%)			
<b>Study T-EE05-135</b>							
<b>Gender as strata</b>							
Male	66.7% (42/63) (53.7%, 78.0%)	(b) (4)		14.3% (8/56) (6.4%, 26.2%)	<0.0001	(b) (4)	
Female	66.1% (41/62) (53.0%, 77.7%)			14.3% (9/63) (6.7%, 25.4%)			
<b>Race as strata</b>							
Caucasian	65.8% (77/117) (56.5%, 74.3%)			14.9% (17/114) (8.9%, 22.8%)	<0.0001	(b) (4)	
Black	66.7% (2/3) (9.4%, 99.2%)			0.0% (0/4) (NA)			
Other	80.0% (4/5) (28.4%, 99.5%)			0.0% (0/1) (NA)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with each subgroup factor as strata.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Maintenance of Healed EE: T-EE04-086 Study Report, Table 14.2.1.1, 14.2.1.2, and 14.2.1.3; T-EE05-135 Study Report, Table 14.2.1.1, 14.2.1.2, and 14.2.1.3; Integrated Summary of Efficacy, Table 8.2.7.1, 8.2.7.2, and 8.2.7.3

**Table 4.2. (Cont'd) Month 6 Maintenance of Healed EE Rates by Gender, Race, and Age (mITT population)**

Factor Category	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Age (years) as strata</b>		(b) (4)			(b) (4)		
<45	57.4% (27/47) (42.2%, 71.7%)			25.6% (10/39) (13.0%, 42.1%)	<0.0001		
45-<65	74.6% (50/67) (62.5%, 84.5%)			7.4% (5/68) (2.4%, 16.3%)			
≥65	54.5% (6/11) (23.4%, 83.3%)			16.7% (2/12) (2.1%, 48.4%)			
<b>Integrated Analysis</b>							
<b>Gender as strata</b>							
Male	66.7% (42/63) (53.7%, 78.0%)			12.3% (14/114) (6.9%, 19.7%)	<0.0001		
Female	66.1% (41/62) (53.0%, 77.7%)			16.2% (19/117) (10.1%, 24.2%)			
<b>Race as strata</b>							
Caucasian	65.8% (77/117) (56.5%, 74.3%)			14.0% (30/214) (9.7%, 19.4%)	<0.0001		
Black	66.7% (2/3) (9.4%, 99.2%)			16.7% (2/12) (2.1%, 48.4%)			
Other	80.0% (4/5) (28.4%, 99.5%)			20.0% (1/5) (0.5%, 71.6%)			
<b>Age (years) as strata</b>		(b) (4)			(b) (4)		
<45	57.4% (27/47) (42.2%, 71.7%)			19.5% (15/77) (11.3%, 30.1%)	<0.0001		
45-<65	74.6% (50/67) (62.5%, 84.5%)			11.1% (15/135) (6.4%, 17.7%)			
≥65	54.5% (6/11) (23.4%, 83.3%)			15.8% (3/19) (3.4%, 39.6%)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with each subgroup factor as strata.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Maintenance of Healed EE: T-EE04-086 Study Report, Table 14.2.1.1, 14.2.1.2, and 14.2.1.3; T-EE05-135 Study Report, Table 14.2.1.1, 14.2.1.2, and 14.2.1.3; Integrated Summary of Efficacy, Table 8.2.7.1, 8.2.7.2, and 8.2.7.3

#### 4.2.2 Other Special/Subgroup Populations

The results from the efficacy analyses on the subgroups of different healing EE study characteristics are summarized in the Appendix (Table A.10). The results were relatively consistent with those from the primary efficacy analysis. The two doses, dexlansoprazole MR 60 mg and 90 mg, had similar performance across the subgroups in Study T-EE04-086. It can be observed that in Study T-EE05-135 dexlansoprazole MR 60 mg had numerically higher maintenance rates than 30 mg for the subgroup of subjects with pre-healing EE Grade C or D and the subgroup of subjects with healed EE in eight weeks while the results reversed for the subgroup of subjects with pre-healing EE Grade A or B and the subgroup of subjects with healed EE in four weeks. However, the sample size for each subgroup was too small to generate reliable results.

From a statistical perspective, an efficacy benefit of the 60 mg dose over the 30 mg dose could not be demonstrated by the phase 3 study data. The maintenance rates observed for subjects healed with dexlansoprazole MR 90 mg QD were slightly higher than those for subjects healed with dexlansoprazole MR 60 mg QD or lansoprazole 30 mg QD. However, the differences were relatively small and decreasing with the dose received in the maintenance studies. Especially for subjects received dexlansoprazole 90 mg QD in Study T-EE04-086, subjects healed with dexlansoprazole MR 90 mg QD did not have any improvement on maintenance rates compared with the other subjects. In conclusion, added benefit of 90 mg dexlansoprazole MR over dexlansoprazole MR 60 mg and/or lansoprazole 30 mg could not be established contrary to what the sponsor stated.

Since there were non-U.S. sites involved in Study T-EE05-135 only, the efficacy analyses on the subgroups of investigative sites from U.S. vs. non-U.S. were performed by this reviewer and the results are summarized in the Appendix (Table A.11). The results from U.S. sites were similar to those from the primary efficacy analysis for both Study T-EE04-086 and T-EE05-135 while non-U.S. sites had higher maintenance rates for dexlansoprazole MR 60 mg QD and placebo groups, and lower maintenance rates for dexlansoprazole MR 30 mg QD group. However, the number of patients from non-U.S. sites was too small to draw any reliable conclusion.

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## 5. SUMMARY AND CONCLUSIONS

The doses of dexlansoprazole MR studied in the phase 3 trials are generally higher than those of approved lansoprazole for all three indications, and the dual delayed release formation of dexlansoprazole was supposed to extend the duration of drug exposure and maintain pharmacologically active levels of drug over a longer time period. In general, this more potent treatment of dexlansoprazole MR should have improved and hastened healing of EE compared with lansoprazole. However, based on the data from the two phase 3 EE healing studies (T-EE04-084 and T-EE04-085), the improvement in efficacy of either dexlansoprazole MR 60 mg or 90 mg QD over lansoprazole 30 mg QD was minimal to none. In particular, the higher dose of dexlansoprazole MR did not show better healing of EE for more severe subjects. The superiority of dexlansoprazole MR 90 mg over lansoprazole, as claimed by the sponsor, was based on an invalid multiplicity adjustment, and no clinical benefit of dexlansoprazole MR 90 mg over 60 mg could be observed in the clinical studies. The evidence does however strongly support the claim that dexlansoprazole MR is non-inferior to lansoprazole for the indication of healing of EE.

(b) (4) the results support the conclusion that all three doses of dexlansoprazole MR showed statistically significant improvement in maintenance rates compared with placebo. However, (b) (4), all three doses of dexlansoprazole MR had very similar efficacy across all subgroups with the treatment difference between 60 mg and 30 mg slightly larger than that between 60 mg and 90 mg. (b) (4)

(b) (4)

(b) (4)

In conclusion, (b) (4), dexlansoprazole MR 60 mg and 90 mg QD showed treatment effects similar to lansoprazole, but no added clinical benefit over lansoprazole were indicated. For maintenance of healed EE, dexlansoprazole MR showed clinical improvement in efficacy compared with placebo. There were no clinically meaningful treatment differences among the dexlansoprazole MR doses for either indication.

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## APPENDIX

**Table A.1. Healing Rates of EE by Life Table (ITT population)**

Endpoint	Dexlansoprazole MR		Lansoprazole 30 mg QD (N) % (95% CI)	p-value	
	60 mg QD (N) % (95% CI)	90 mg QD (N) % (95% CI)		Dexlansoprazole MR 60 mg vs. Lansoprazole	Dexlansoprazole MR 90 mg vs. Lansoprazole
<b>Study T-EE04-084</b>		<b>(b) (4)</b>		<b>(b) (4)</b>	
Week 8	(673) 92.3% (90.0%, 94.7%)		(684) 86.1% (83.0%, 89.2%)	0.060	
Week 4	(673) 77.0% (73.5%, 80.5%)		(684) 76.5% (73.0%, 80.0%)	0.896	
Week 8 C or D	(191) 88.9% (83.7%, 94.2%)		(208) 74.5% (67.3%, 81.6%)	0.011	
<b>Study T-EE04-085</b>					
Week 8	(685) 93.1% (90.9%, 95.3%)		(672) 91.5% (89.0%, 93.9%)	0.167	
Week 4	(685) 80.1% (76.8%, 83.3%)		(672) 77.0% (73.4%, 80.5%)	0.117	
Week 8 C or D	(199) 87.6% (82.2%, 92.9%)		(194) 87.7% (82.4%, 93.0%)	0.727	
<b>Integrated</b>					
Week 8	(1358) 92.7% (91.1%, 94.4%)		(1356) 88.9% (87.0%, 90.9%)	0.021	
Week 4	(1358) 78.6% (76.2%, 81.0%)		(1356) 76.7% (74.2%, 79.2%)	0.287	
Week 8 C or D	(390) 88.2% (84.5%, 92.0%)		(402) 81.5% (77.0%, 86.0%)	0.037	

Source: Modules 2.7.3 – Summary of Clinical Efficacy - Healing of EE, Table 2.7.b, Table 2.7.c, Table 2.7.p, Table 2.7.q, and Table 2.7.r

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**Table A.2. Sensitivity Analyses for Treatment Differences on Week 8 Crude Healing Rates of EE (mITT population)**

Study	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N)	Difference (dex-lanso) % (95% CI)	
	60 mg QD % (n/N)	90 mg QD % (n/N)		Dexlansoprazole MR 60 mg vs. Lansoprazole	Dexlansoprazole MR 90 mg vs. Lansoprazole
<b>Prematurely Discontinued Before Healing Considered as Healed<sup>a</sup></b>					
Study T-EE04-084	88.26% (564/639)	(b) (4)	81.71% (536/656)	6.56% (2.69%, 10.43%)	(b) (4)
Study T-EE-4-085	90.26% (593/657)		86.88% (563/648)	3.38% (-0.07%, 6.83%)	
<b>Worst-Case Scenario</b>					
Study T-EE04-084	85.29% (545/639)		81.71% (536/656)	3.58% (-0.45%, 7.62%)	
Study T-EE-4-085	86.91% (571/657)		86.88% (563/648)	0.03% (-3.63%, 3.69%)	

<sup>a</sup> The results concur with those from the sponsor  
Source: Reviewer's Table

**Table A.3. Primary Crude Rate mITT Subject Counts for Study T-EE04-086 (Healed by Week 4 / Healed by Week 8)**

Study	Trt	Prev Trt	Study T-EE04-084					Study T-EE04-085					Total				
			Baseline EE Grade				Total	Baseline EE Grade				Total	Baseline EE Grade				Total
			A	B	C	D		A	B	C	D		A	B	C	D	
60mg	60 mg	9 (9/0)	7 (6/1)	6 (6/0)	0 (0/0)	22 (21/1)	9 (8/1)	14 (10/4)	4 (3/1)	0 (0/0)	27 (21/6)	18 (17/1)	21 (16/5)	10 (9/1)	0 (0/0)	49 (42/7)	
		(b) (4)															
	Lanso	10 (10/0)	9 (8/1)	7 (5/2)	1 (1/0)	27 (24/3)	14 (14/0)	6 (5/1)	4 (4/0)	1 (1/0)	25 (24/1)	24 (24/0)	15 (13/2)	11 (9/2)	2 (2/0)	52 (48/4)	
		<b>Total</b>	28 (27/1)	30 (26/4)	19 (17/2)	2 (2/0)	79 (72/7)	31 (30/1)	28 (23/5)	12 (11/1)	2 (2/0)	73 (66/7)	59 (57/2)	58 (49/9)	31 (28/3)	4 (4/0)	152 (138/14)
90 mg	60 mg	(b) (4)															
		(b) (4)															
	Lanso	(b) (4)															
		<b>Total</b>	(b) (4)														
Placebo	60 mg	8 (6/2)	6 (6/0)	4 (4/0)	2 (2/0)	20 (18/2)	5 (5/0)	7 (7/0)	2 (2/0)	1 (1/0)	15 (15/0)	13 (11/2)	13 (13/0)	6 (6/0)	3 (3/0)	35 (33/2)	
		(b) (4)															
	Lanso	7 (6/1)	5 (5/0)	4 (4/0)	1 (1/0)	17 (16/1)	10 (7/3)	7 (7/0)	5 (5/0)	0 (0/0)	22 (19/3)	17 (13/4)	12 (12/0)	9 (9/0)	1 (1/0)	39 (35/4)	
		<b>Total</b>	22 (17/5)	19 (19/0)	13 (13/0)	3 (3/0)	57 (52/5)	26 (22/4)	21 (21/0)	7 (7/0)	1 (1/0)	55 (51/4)	48 (39/9)	40 (40/0)	20 (20/0)	4 (4/0)	112 (103/9)
Total	60 mg	29 (26/3)	24 (23/1)	14 (14/0)	3 (2/1)	70 (65/5)	21 (20/1)	27 (23/4)	9 (8/1)	2 (2/0)	59 (53/6)	50 (46/4)	51 (46/5)	23 (22/1)	5 (4/1)	129 (118/11)	
		(b) (4)															
	Lanso	24 (23/1)	22 (20/2)	15 (13/2)	4 (4/0)	65 (60/5)	29 (26/3)	24 (23/1)	12 (11/1)	2 (2/0)	67 (62/5)	53 (49/4)	46 (43/3)	27 (24/3)	6 (6/0)	132 (122/10)	
		<b>Total</b>	76 (68/8)	80 (75/5)	45 (42/3)	10 (9/1)	211 (194/17)	81 (74/7)	73 (67/6)	31 (29/2)	6 (6/0)	191 (176/15)	157 (142/15)	153 (142/11)	76 (71/5)	16 (15/1)	402 (370/32)

Source: Reviewer's Table

**Table A.4. Primary Crude Rate mITT Subject Counts for Study T-EE05-135  
(Healed by Week 4 / Healed by Week 8)**

Study		Study T-EE04-084					Study T-EE04-085					Total				
Trt	Prev Trt	Baseline EE Grade				Total	Baseline EE Grade				Total	Baseline EE Grade				Total
		A	B	C	D		A	B	C	D		A	B	C	D	
30mg	60 mg	(b) (4)														
	90 mg	(b) (4)														
	Lanso	9 (7/2)	4 (2/2)	4 (3/1)	3 (2/1)	20 (14/6)	5 (5/0)	5 (5/0)	4 (3/1)	1 (1/0)	15 (14/1)	14 (12/2)	9 (7/2)	8 (6/2)	4 (3/1)	35 (28/7)
	Total	28 (21/7)	21 (16/5)	15 (11/4)	8 (5/3)	72 (53/19)	19 (17/2)	18 (14/4)	14 (7/7)	2 (2/0)	53 (40/13)	47 (38/9)	39 (30/9)	29 (18/11)	10 (7/3)	125 (93/32)
60 mg	60 mg	(b) (4)														
	90 mg	(b) (4)														
	Lanso	(b) (4)														
	Total	(b) (4)														
Placebo	60 mg	(b) (4)														
	90 mg	(b) (4)														
	Lanso	5 (5/0)	3 (3/0)	5 (4/1)	0 (0/0)	13 (12/1)	9 (7/2)	10 (4/6)	2 (1/1)	0 (0/0)	21 (12/9)	14 (12/2)	13 (7/6)	7 (5/2)	0 (0/0)	34 (24/10)
	Total	26 (25/1)	22 (19/3)	16 (12/4)	2 (1/1)	66 (57/9)	18 (15/3)	25 (14/11)	9 (6/3)	0 (0/0)	52 (35/17)	44 (40/4)	47 (33/14)	25 (18/7)	2 (1/1)	118 (92/26)
Total	60 mg	(b) (4)														
	90 mg	(b) (4)														
	Lanso	24 (21/3)	20 (15/5)	12 (10/2)	3 (2/1)	59 (48/11)	18 (16/2)	26 (16/10)	13 (7/6)	2 (1/1)	59 (40/19)	42 (37/5)	46 (31/15)	25 (17/8)	5 (3/2)	118 (88/30)
	Total	79 (67/12)	74 (57/17)	47 (35/12)	12 (8/4)	212 (167/45)	62 (53/9)	65 (43/22)	42 (27/15)	5 (3/2)	174 (126/48)	141 (120/21)	139 (100/39)	89 (62/27)	17 (11/6)	386 (293/93)

Source: Reviewer's Table

**Table A.5. Month 1 and 3 Maintenance of Healed EE Rates (mITT population)**

Endpoint	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Study T-EE04-086</b>							
Month 1	NA	(b) (4)		30.4% 34/112 (22.0%, 39.8%)	NA	(b) (4)	
Month 3	NA	(b) (4)		16.1% 18/112 (9.8%, 24.2%)	NA	(b) (4)	
<b>Study T-EE05-135</b>							
Month 1	88.8% 111/125 (81.9%, 93.7%)	(b) (4)		42.9% 51/119 (33.8%, 52.3%)	<0.0001	(b) (4)	
Month 3	74.4% 93/125 (65.8%, 81.8%)	(b) (4)		22.7% 27/119 (15.5%, 31.3%)	<0.0001	(b) (4)	

Source: Modules 2.7.3 – Summary of Clinical Efficacy - Maintenance of Healed EE, Table 2.7.3.2.b and Table 2.7.3.2.d

**Table A.6. Maintenance of Healed EE Rates by Life Table (ITT population)**

Endpoint	Dexlansoprazole MR			Placebo % (95% CI)	p-value		
	30 mg QD % (95% CI)	60 mg QD % (95% CI)	90 mg QD % (95% CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Study T-EE04-086</b>							
N	NA	(b) (4)		140	(b) (4)		
Month 1	NA			38.6% (30.1%, 47.2%)	NA		
Month 3	NA			27.2% (18.6%, 35.9%)			
Month 6	NA			25.7% (17.0%, 34.4%)			
<b>Study T-EE05-135</b>							
N	137			145			
Month 1	89.3% (84.0%, 94.6%)			49.0% (40.5%, 57.6%)	<0.0001		
Month 3	80.2% (73.2%, 87.2%)			34.1% (25.3%, 42.9%)			
Month 6	74.9% (67.2%, 82.6%)			27.2% (18.3%, 36.0%)			

Source: Modules 2.7.3 – Summary of Clinical Efficacy - Maintenance of Healed EE, Table 2.7.3.2.b and Table 2.7.3.2.d

**Table A.7. Integrated Analysis on Primary and Key Secondary Endpoints (mITT population)**

Endpoint	Dexlansoprazole MR 60 mg QD	Placebo	p-value <sup>a</sup>
	% (n/N) (95% Exact CI)	% (n/N) (95% Exact CI)	
Month 6 Maintenance of Healed EE	66.44% (196/295) (60.74%, 71.81%)	14.29% (33/231) (10.04%, 19.47%)	<0.00001
	N Median Mean (SD)	N Median Mean (SD)	
24-hour Heartburn-Free Days	304 93.94% 79.10% (29.51)	274 22.22% 32.87% (30.81)	<0.00001
Nighttime Heartburn-Free Days	304 97.79% 86.61% (24.35)	274 58.82% 52.82% (36.26)	<0.00001

<sup>a</sup> The results concur with those from the sponsor

Source: Reviewer's Table

**Table A.8. Week 8 Crude Healing Rates of EE by Baseline LA EE Grade  
(mITT population)**

Study Baseline LA EE Grade	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N) (95% Exact CI)	p-value		
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 60 mg vs. Lansoprazole	Dex MR 90 mg vs. Lansoprazole	Dex MR 60 mg vs. Dex MR 90 mg
<b>Study T-EE04-084</b>						
A	89.9% (196/218) (85.1%, 93.6%)	(b) (4)	90.5% (199/220) (85.8%, 94.0%)	0.004 <sup>a</sup>	(b) (4)	
B	85.4% (204/239) (80.2%, 89.6%)		80.1% (189/236) (74.4%, 85.0%)			
C	81.5% (123/151) (74.3%, 87.3%)		67.7% (109/161) (59.9%, 74.8%)			
D	71.0% (22/31) (52.0%, 85.8%)		53.8% (21/39) (37.2%, 69.9%)			
A or B	87.5% (400/457) (84.1%, 90.4%)		85.1% (388/456) (81.5%, 88.2%)	0.004 <sup>b</sup>		
C or D	79.7% (145/182) (73.1%, 85.3%)		65.0% (130/200) (58.0%, 71.6%)			
<b>Study T-EE04-085</b>						
A	92.7% (204/220) (88.5%, 95.8%)		91.9% (193/210) (87.4%, 95.2%)	0.234 <sup>a</sup>		
B	88.9% (216/243) (84.2%, 92.5%)		82.7% (205/248) (77.4%, 87.2%)			
C	81.5% (123/151) (74.3%, 87.3%)		85.0% (125/147) (78.2%, 90.4%)			
D	65.1% (28/43) (49.1%, 79.0%)		58.1% (25/43) (42.1%, 73.0%)			
A or B	90.7% (420/463) (87.7%, 93.2%)		86.9% (398/458) (83.5%, 89.9%)	0.218 <sup>b</sup>		
C or D	77.8% (151/194) (71.3%, 83.5%)		78.9% (150/190) (72.5%, 84.5%)			

<sup>a</sup> P-values are using CMH tests with baseline LA EE Grade as strata.

<sup>b</sup> P-values are using CMH tests with combined baseline LA EE Grade as strata.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Healing EE: T-EE04-084 Study Report, Table 14.2.2.1 and 14.2.2.2; T-EE04-085 Study Report, Table 14.2.2.1 and 14.2.2.2; Integrated Summary of Efficacy, Table 8.2.7.1 and 8.2.7.2

**Table A.8. (Cont'd) Week 8 Crude Healing Rates of EE by Baseline LA EE Grade (mITT population)**

Study Baseline LA EE Grade	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N) (95% Exact CI)	p-value		
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 60 mg vs. Lansoprazole	Dex MR 90 mg vs. Lansoprazole	Dex MR 60 mg vs. Dex MR 90 mg
<b>Integrated Analysis</b>						
A	91.3% (400/438) (88.3%, 93.8%)	(b) (4)	91.2% (392/430) (88.1%, 93.7%)	0.003 <sup>a</sup>	(b) (4)	
B	87.1% (420/482) (83.8%, 90.0%)		81.4% (394/484) (77.6%, 84.8%)			
C	81.5% (246/302) (76.6%, 85.7%)		76.0% (234/308) (70.8%, 80.6%)			
D	67.6% (50/74) (55.7%, 78.0%)		56.1% (46/82) (44.7%, 67.0%)			
A or B	89.1% (820/920) (86.9%, 91.1%)		86.0% (786/914) (83.6%, 88.2%)	0.003 <sup>b</sup>		
C or D	78.7% (296/376) (74.2%, 82.8%)		71.8% (280/390) (67.0%, 76.2%)			

<sup>a</sup> P-values are using CMH tests with baseline LA EE Grade as strata.

<sup>b</sup> P-values are using CMH tests with combined baseline LA EE Grade as strata.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Healing EE: T-EE04-084 Study Report, Table 14.2.2.1 and 14.2.2.2; T-EE04-085 Study Report, Table 14.2.2.1 and 14.2.2.2; Integrated Summary of Efficacy, Table 8.2.7.1 and 8.2.7.2

**Table A.9. Week 8 Crude Healing Rates of EE by U.S. vs. non-U.S. Investigative Sites (mITT population)**

Study Sites	Dexlansoprazole MR		Lansoprazole 30 mg QD % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 60 mg vs. Lansoprazole	Dex MR 90 mg vs. Lansoprazole	Dex MR 60 mg vs. Dex MR 90 mg
<b>Study T-EE04-084</b>						
U.S.	86.2% (417/484) (82.8%, 89.1%)	(b) (4)	80.1% (390/487) (76.3%, 83.5%)	0.005	(b) (4)	
non-U.S.	82.6% (128/155) (75.7%, 88.2%)		75.7% (128/169) (68.6%, 82.0%)			
<b>Study T-EE04-085</b>						
U.S.	88.4% (396/448) (85.1%, 91.2%)		85.1% (387/455) (81.4%, 88.2%)	0.223		
non-U.S.	83.7% (175/209) (78.0%, 88.5%)		83.4% (161/193) (77.4%, 88.4%)			

<sup>a</sup> P-values are using CMH tests with baseline LA EE Grade and investigative sites from U.S. vs. non-U.S. as strata.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Healing EE: T-EE04-084 Study Report, Table 14.2.2.15; T-EE04-085 Study Report, Table 14.2.2.15; Integrated Summary of Efficacy, Table 8.2.7.14

**Table A.9. (Cont'd) Week 8 Crude Healing Rates of EE by U.S. vs. non-U.S. Investigative Sites (mITT population)**

Study Sites	Dexlansoprazole MR		Lansoprazole	p-value <sup>a</sup>		
	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)	30 mg QD % (n/N) (95% Exact CI)	Dex MR 60 mg vs. Lansoprazole	Dex MR 90 mg vs. Lansoprazole	Dex MR 60 mg vs. Dex MR 90 mg
<b>Integrated Analysis</b>						
U.S.	87.2% (813/932) (84.9%, 89.3%)	(b) (4)	82.5% (777/942) (79.9%, 84.9%)	0.003	<(b) (4)	█
non-U.S.	83.2% (303/364) (79.0%, 86.9%)	(b) (4)	79.8% (289/362) (75.3%, 83.8%)			

<sup>a</sup> P-values are using CMH tests with baseline LA EE Grade and investigative sites from U.S. vs. non-U.S. as strata.  
Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Healing EE: T-EE04-084 Study Report, Table 14.2.2.15; T-EE04-085 Study Report, Table 14.2.2.15; Integrated Summary of Efficacy, Table 8.2.7.14

**Table A.10. Month 6 Maintenance of Healed EE Rates by EE Healing Study Characteristics (mITT population)**

Factor Category	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Study T-EE04-086</b>							
<b>Pre-healing LA EE Grade as strata</b>							
A	NA	(b) (4)	(b) (4)	20.8% (10/48) (10.5%, 35.0%)	NA	(b) (4)	█
B	NA	(b) (4)	(b) (4)	12.5% (5/40) (4.2%, 26.8%)			
C	NA	(b) (4)	(b) (4)	0.0% (0/20) (NA)			
D	NA	(b) (4)	(b) (4)	25.0% (1/4) (0.6%, 80.6%)			
A or B	NA	(b) (4)	(b) (4)	17.0% (15/88) (9.9%, 26.6%)	NA	(b) (4)	█
C or D	NA	(b) (4)	(b) (4)	4.2% (1/24) (0.1%, 21.1%)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with each subgroup factor as strata.  
Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Maintenance of Healed EE: T-EE04-086 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; T-EE05-135 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; Integrated Summary of Efficacy, Table 8.2.7.11, 8.2.7.12, 8.2.7.13, and 8.2.7.14

**Table A.10. (Cont'd) Month 6 Maintenance of Healed EE Rates by EE Healing Study Characteristics (mITT population)**

Factor Category	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Duration of treatment in healing of EE study as strata</b>							
4 Weeks	NA	(b) (4)		13.6% (14/103) (7.6%, 21.8%)	NA	(b) (4)	
8 Weeks	NA			22.2% (2/9) (2.8%, 60.0%)			
<b>Treatment in healing of EE study as strata</b>							
Dex MR 60 mg	NA	(b) (4)		14.3% (5/35) (4.8%, 30.3%)	NA		
Dex MR 90 mg	NA			18.4% (7/38) (7.7%, 34.3%)			
Lanso 30 mg	NA			10.3% (4/39) (2.9%, 24.2%)			
<b>Study T-EE05-135</b>							
<b>Pre-healing LA EE Grade as strata</b>							
A	72.3% (34/47) (57.4%, 84.4%)	(b) (4)		25.0% (11/44) (13.2%, 40.3%)	<0.0001		
B	74.4% (29/39) (57.9%, 87.0%)			8.3% (4/48) (2.3%, 20.0%)			
C	55.2% (16/29) (35.7%, 73.6%)			8.0% (2/25) (1.0%, 26.0%)			
D	40.0% (4/10) (12.2%, 73.8%)			0.0% (0/2) (NA)			
A or B	73.3% (63/86) (62.6%, 82.2%)			16.3% (15/92) (9.4%, 25.5%)	<0.0001		
C or D	51.3% (20/39) (34.8%, 67.6%)			7.4% (2/27) (0.9%, 24.3%)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with each subgroup factor as strata.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Maintenance of Healed EE: T-EE04-086 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; T-EE05-135 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; Integrated Summary of Efficacy, Table 8.2.7.11, 8.2.7.12, 8.2.7.13, and 8.2.7.14

**Table A.10. (Cont'd) Month 6 Maintenance of Healed EE Rates by EE Healing Study Characteristics (mITT population)**

Factor Category	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Duration of treatment in healing of EE study as strata<sup>b</sup></b>							
4 Weeks	74.2% (69/93) (64.1%, 82.7%)	(b) (4)		15.2% (14/92) (8.6%, 24.2%)	<0.0001	(b) (4)	
8 Weeks	43.8% (14/32) (26.4%, 62.3%)			11.5% (3/26) (2.4%, 30.2%)			
<b>Treatment in healing of EE study as strata</b>							
Dex MR 60 mg	57.1% (28/49) (42.2%, 71.2%)	(b) (4)		8.6% (3/35) (1.8%, 23.1%)	<0.0001		
Dex MR 90 mg	75.6% (31/41) (59.7%, 87.6%)			14.0% (7/50) (5.8%, 26.7%)			
Lanso 30 mg	68.6% (24/35) (50.7%, 83.1%)			20.6% (7/34) (8.7%, 37.9%)			
<b>Integrated Analysis</b>							
<b>Pre-healing LA EE Grade as strata</b>							
A	72.3% (34/47) (57.4%, 84.4%)	(b) (4)		22.8% (21/92) (14.7%, 32.8%)	<0.0001	(b) (4)	
B	74.4% (29/39) (57.9%, 87.0%)			10.2% (9/88) (4.8%, 18.5%)			
C	55.2% (16/29) (35.7%, 73.6%)			4.4% (2/45) (0.5%, 15.1%)			
D	40.0% (4/10) (12.2%, 73.8%)			16.7% (1/6) (0.4%, 64.1%)			
A or B	73.3% (63/86) (62.6%, 82.2%)			16.7% (30/180) (11.5%, 22.9%)	<0.0001		
C or D	51.3% (20/39) (34.8%, 67.6%)			5.9% (3/51) (1.2%, 16.2%)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with each subgroup factor as strata.

<sup>b</sup> One subject in Study T-EE05-135 Placebo arm with treatment duration of 9 weeks in healing of EE study is excluded for this subgroup analysis.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Maintenance of Healed EE: T-EE04-086 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; T-EE05-135 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; Integrated Summary of Efficacy, Table 8.2.7.11, 8.2.7.12, 8.2.7.13, and 8.2.7.14

**Table A.10. (Cont'd) Month 6 Maintenance of Healed EE Rates by EE Healing Study Characteristics (mITT population)**

Factor Category	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)	90 mg QD % (n/N) (95% Exact CI)		Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 90 mg vs. Placebo
<b>Duration of treatment in healing of EE study as strata<sup>b</sup></b>							
4 Weeks	74.2% (69/93) (64.1%, 82.7%)	(b) (4)		14.4% (28/195) (9.8%, 20.1%)	<0.0001	(b) (4)	
8 Weeks	43.8% (14/32) (26.4%, 62.3%)			14.3% (5/35) (4.8%, 30.3%)			
<b>Treatment in healing of EE study as strata</b>							
Dex MR 60 mg	57.1% (28/49) (42.2%, 71.2%)	(b) (4)		11.4% (8/70) (5.1%, 21.3%)	<0.0001	(b) (4)	
Dex MR 90 mg	75.6% (31/41) (59.7%, 87.6%)			15.9% (14/88) (9.0%, 25.2%)			
Lanso 30 mg	68.6% (24/35) (50.7%, 83.1%)			15.1% (11/73) (7.8%, 25.4%)			

<sup>a</sup> P-values for each subgroup factor are using CMH tests with each subgroup factor as strata.

<sup>b</sup> One subject in Study T-EE05-135 Placebo arm with treatment duration of 9 weeks in healing of EE study is excluded for this subgroup analysis.

Source: Modules 5.3.5 – Reports of Efficacy and Safety Studies - Maintenance of Healed EE: T-EE04-086 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; T-EE05-135 Study Report, Table 14.2.1.12, 14.2.1.13, 14.2.1.14, and 14.2.1.15; Integrated Summary of Efficacy, Table 8.2.7.11, 8.2.7.12, 8.2.7.13, and 8.2.7.14

**Table A.11. Month 6 Maintenance of Healed EE Rates by U.S. vs. non-U.S. Investigative Sites for Study T-EE05-135 (mITT population)**

Sites	Dexlansoprazole MR			Placebo % (n/N) (95% Exact CI)	p-value <sup>a</sup>		
	30 mg QD % (n/N) (95% Exact CI)	60 mg QD % (n/N) (95% Exact CI)			Dex MR 30 mg vs. Placebo	Dex MR 60 mg vs. Placebo	Dex MR 30 mg vs. Dex MR 60 mg
U.S.	68.75% (77/112) (59.30%, 77.17%)	(b) (4)		13.21% (14/106) (7.41%, 21.17%)	<0.0001	(b) (4)	
non-U.S.	46.15% (6/13) (19.22%, 74.87%)			23.08% (3/13) (5.04%, 53.81%)			

<sup>a</sup> P-values are using CMH tests with investigative sites from U.S. vs. non-U.S. as strata.

Source: Reviewer's Table

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