CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-327

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-327 / 000
Drug Name:	PREVACID® (lansoprazole) Delayed-Release Capsules, 15mg
Indication(s):	(OTC) Treatment of frequent heartburn (occurs two or more days a week)
Applicant:	Novartis Consumer Health, Inc. (NCH)
Date(s):	Letter Date: 7/15/2008 Stamp Date: 7/16/2008 PDUFA Date: 5/15/2009
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Biometrics Division:	Division of Biometrics 3
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Keywords: Clinical studies, data imputation, intent-to-treat, multiple endpoints, NDA review, nonparametric / distribution-free tests, post-hoc / prospective analyses, sensitivity analyses

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

PREVACID® (lansoprazole) delayed-release capsules, 15 mg, QD, 14-day treatment, is effective in the treatment of frequent heartburn (occurs two or more days a week) by increasing the proportion of 24-hour days with no heartburn over a 14-day of treatment period as compared to placebo. This conclusion is based on the data from three randomized and well-controlled studies. [

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1.2 Brief Overview of Clinical Studies

Novartis Consumer Health, Inc. (NCH) submitted the NDA for the over-the-counter (OTC) marketing of lansoprazole delayed-release capsules, 15 mg for the treatment of frequent heartburn (occurs two or more days a week).

NCH has conducted three adequate and well-controlled studies in an OTC population which support the safe and effective use of lansoprazole delayed-release capsules, 15 mg for the treatment of frequent heartburn. The three clinical studies were all multicenter, double-blind, randomized, placebo-controlled, two or three-arm trials of a similar design. The primary objectives of Study PRSW-GN-301, hereafter called Study 301, and Study PRSW-GN-302, hereafter called Study 302, were to demonstrate that repeated doses of lansoprazole 15 mg in the morning, once a day, are effective in increasing the proportion of 24-hour days with no heartburn during 14 days of treatment. The primary objective of Study PRSW-GN-305, hereafter called Study 305, was to demonstrate that this dosing regimen increased the proportion of nighttimes without heartburn over 14 days of treatment.

Included subjects had heartburn occurring on a minimum of two or more days per week over the past month if their heartburn was left untreated. In Study 305 only, subjects were required to have nighttime heartburn on at least two days per week over the past month. Subjects with a history of erosive esophagitis (EE) verified by endoscopy, or gastroesophageal reflux disease (GERD) diagnosed by a physician and confirmed by endoscopy, were excluded. Subjects received lansoprazole 15 mg/day, placebo, or, in Study 305 only, lansoprazole 30 mg/day. Study 305 was not intended to support efficacy of 30 mg for the current NDA but rather was the initial assessment of the 30 mg dose as part of the Rx-to-OTC development program.

1.3 Statistical Issues and Findings

The sponsor had modified the primary and secondary endpoints, and missing data handling strategies during the courses of the trials. The primary analysis method was also revised after unblinding the data for Studies 301 and 302. These changes tend to add unnecessary difficulty on interpretation of the data results. Due to the fact that the trials had been carefully conducted

with minimum amount of missing data, the final results on the primary endpoint of proportion of 24-hour days with no heartburn over 14 days of treatment are sufficient to support the labeling claim. However, the results on the endpoint of proportion of nighttimes with no heartburn over 14 days of treatment are not sufficient for any efficacy claims, because the statistical analyses were not adequately and prospectively planned out. Moreover, the clinical population for nighttime heartburn claims has not been fully characterized. The post-hoc modifications to the secondary endpoints have made it difficult to interpret statistical significance; however, the sponsor is not pursuing any labeling claims on these endpoints at this time.

2. INTRODUCTION

2.1 Background

PREVACID® (lansoprazole) Delayed-Release Capsule was approved for prescription (Rx) use in the U.S. on May 10, 1995. NCH has an agreement with TAP Pharmaceutical Products, Inc. (TAP), the holder of NDA 20-406 and IND 30,159 granting NCH full right of reference to the NDA and IND data in support of all application related to over-the counter use. TAP has authorized the Agency, in correspondence dated March 6, 2008, to cross-reference these data in support of NCH's programs. The letters were submitted to NCH IND 74,256 on March 10, 2008 in Serial No. 0032.

Regulatory History – NDA 20-406, PREVACID® (lansoprazole) Delayed-Release Capsules, 15 and 30 mg

Approval Date	Indication	Dose
05/10/1995	Short-Term Treatment of Active Duodenal Ulcer	15 mg
	Short-Term Treatment of Erosive Esophagitis	30 mg
	Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome	60 mg
04/08/1996	Maintenance of Healing of Erosive Esophagitis	15 mg
04/17/1997	Maintenance of Healed Duodenal Ulcers	15 mg
05/08/1997	Short-Term Treatment of Active Benign Gastric Ulcer	30 mg
04/23/1998	Short-Term Treatment of Symptomatic GERD	15 mg
07/20/1998	*H. pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence Triple Therapy: PREVACID/amoxicillin/clarithromycin	30 mg
11/30/2000	Healing of NSAID-Associated Gastric Ulcer	30 mg
07/31/2002	Pediatric (1-11 years of age) Short-Term Treatment of Symptomatic GERD and Short-Term Treatment of Erosive Esophagitis	15 mg /30 mg
06/17/2004	Pediatric (12-17 years of age) Short-Term Treatment of Symptomatic GERD • Nonerosive GERD • Erosive Esophagitis	 15mg 30mg

Source: Cover Letter Attachment

Other approved lansoprazole dosage forms and products include:

NDA #	Approval Date	Dosage Form / Indication	Dose
50-757	01/22/1999	PREVPAC® (lansoprazole 30 mg capsules, amoxicillin 500 mg capsules, USP, and clarithromycin 500 mg tablets, USP) for *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence	30 mg
21-281	05/03/2001	PREVACID® (lansoprazole) Delayed-Release Oral Suspension	15 mg/30 mg
21-428	08/30/2002	PREVACID® (lansoprazole) Delayed-Release Orally Disintegrating Tablets	15 mg/30 mg
21-566	05/27/2004	PREVACID® IV (lansoprazole) for Injection	30 mg
21-507	11/04/2003	PREVACID® NapraPAC™ (lansoprazole delayed-release capsules and naproxen tablets kit) for risk reduction of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID	15 mg/250 mg 15 mg/375 mg 15 mg/500 mg

Source: Cover Letter Attachment

Frequent heartburn has been established as an OTC condition, as evidenced by the approval of the current OTC proton pump inhibitor (PPI), Prilosec OTC® (NDA 21-229). It has been demonstrated that consumers can self-recognize and self-treat frequent heartburn over the 14-day course of treatment, without a healthcare practitioner's oversight. The sponsor claims that the misuse and abuse potential for lansoprazole is low. The sponsor further claims that lansoprazole has a well-established safety profile with a reasonable therapeutic index of safety that supports its use in an OTC population.

Three clinical placebo-controlled phase 3 efficacy studies had been submitted for review. The protocols for two identical clinical studies, PRSW-GN-301 and PRSW-GN-302, were submitted on May 5, 2006 under IND 74,256 (Serial No. 000) and then on November 15, 2006 the Statistical Analysis Plans (SAPs) for these two studies were submitted (Serial No. 008). The primary objective of these two studies was to demonstrate that repeated daily doses of 15 mg of lansoprazole once a day are effective in increasing the proportion of days with no heartburn during 14 days (24-hour days) of treatment as compared to placebo. On July 26, 2006 a Special Protocol Assessment (SPA) was filed for study PRSW-GN-305 to focus on frequent nighttime heartburn (Serial No. 003) and on July 30, 2007 the SAP for this study was filed (Serial No. 020). In this study only, the initial assessment of the 30 mg dose was conducted as part of the Rx-to-OTC development program and was not intended to support efficacy of 30 mg for the current NDA. No prior agreements were made with the sponsor regarding the validity of a nighttime heartburn claim.

2.2 Overview

Heartburn occurs when acidic stomach contents move into the esophagus from the stomach, causing a burning sensation in the chest or throat. Approximately 20% of adults in the U.S. suffer from heartburn at least once weekly. Most heartburn sufferers have events occurring both during the day and at night. A telephone survey conducted in 1000 heartburn sufferers on behalf of the American Gastroenterological Association (AGA) demonstrated that 78% of heartburn sufferers had nighttime heartburn: 65% had events during both day and night on a 24-hour basis, 13% of subjects had events only during bedtime, and 20% of heartburn sufferers had daytime events alone.

Lansoprazole is a PPI that has been used in the treatment of peptic ulcer disease and other gastrointestinal conditions where the inhibition of gastric acid secretion may be beneficial. Lansoprazole has been approved for prescription use for the management of duodenal ulcer, gastric ulcer, GERD, EE, and pathological hypersecretory conditions.

The target indication of lansoprazole 15 mg for OTC use is the short-term treatment of frequent heartburn, in adults aged 18 years and older. Frequent heartburn is defined as heartburn episodes occurring at least two days per week in the preceding month if left untreated. The proposed dosing regimen of lansoprazole for OTC use is 15 mg once daily for 14 days co-administered with water prior to breakfast. This is consistent with the dosing regimen utilized in the phase 3 studies of the present OTC development program as well as in prescription studies previously conducted to assess the treatment of heartburn in patients with GERD.

The pharmacology, and clinical safety and efficacy of lansoprazole are well characterized and extensively reported in the literature. Lansoprazole, available in 15 and 30 mg dosage strengths, has been approved for prescription use in the U.S. since 1995.

The clinical development program of lansoprazole 15 mg for OTC use consists of three large, placebo-controlled, adequately powered, phase 3 trials in subjects with frequent heartburn. Overall, the objective of the program was to demonstrate that repeated daily morning doses of 15 mg of lansoprazole once a day are effective in increasing the proportion of days with no heartburn during 14 days (24-hour days) of treatment as compared to placebo in frequent heartburn sufferers. All three studies were conducted in the target population intended for OTC use of lansoprazole 15 mg in the management of frequent heartburn. The treatment period of 14 days is consistent with that currently approved for OTC omeprazole in the management of frequent heartburn. In addition to the 15 mg dose, the safety and efficacy of the 30 mg once daily dose were also investigated in Study 305 on an exploratory basis for the management of heartburn symptoms in the target population.

The safety and efficacy of lansoprazole in the management of frequent heartburn were evaluated in a total of 1986 patients. Out of those, 861 received lansoprazole 15 mg, 277 received lansoprazole 30 mg, and 848 received placebo for 14 consecutive days.

In all three studies, eligible subjects underwent a screening and heartburn medication washout period prior to entering the single-blind placebo run-in period, each one week in duration. Following the successful completion of the run-in period and having met all required entry criteria, subjects were randomized in equal ratio to receive the active or placebo treatments for 14 days during the double-blind treatment period, to be followed immediately by the 7-day single-blind placebo follow-up period. No dose adjustment during the double-blind treatment period was allowed. The 7-day period immediately following the conclusion of study drug administration was used to assess the potential for withdrawal and rebound effects, as well as the persistence of efficacy of lansoprazole 15 mg in the same population.

2.3 Data Sources

Materials reviewed include study reports (Studies 301, 302, and 305) and integrated study reports. This application was submitted in electronic Common Technical Document (eCTD) format, with SAS datasets and programs provided, to EDR at \\Cdsesub1\evsprod\NDA022327.

3. STATISTICAL EVALUATION

Three placebo-controlled trials, Studies 301, 302, and 305, were conducted to evaluate the efficacy of lansoprazole 15 mg once daily for 14 days in the treatment of frequent heartburn on a short-term basis. In addition, the efficacy of lansoprazole 30 mg once daily for 14 days was also investigated in Study 305 on an exploratory basis for the treatment of frequent heartburn. A summary of the three placebo-controlled trials is provided in the following table.

Table 3.1. Summary of placebo-controlled phase 3 studies

Study No. / # of Sites	Study objective, population	Planned patients	Treatment duration	Dosage of double-blind treatment	Efficacy endpoints
PRSW-GN-301/ 35 study sites	Efficacy/ safety in subjects with frequent heartburn	576, randomized 1:1 to lansoprazole 15 mg or placebo	7 day placebo run-in period, 14 day placebo-controlled treatment period, 7 day placebo follow-up period	Lansoprazole 15 mg/day or matching placebo	Primary: proportion of 24-hour days with no heartburn over 14 days. Secondary: proportion of nighttimes with no heartburn over 14 days; proportion of days with no heartburn over Days 1-2; proportion of subjects with no heartburn on Day 1.
PRSW-GN-302/ 37 study sites	Efficacy/ safety in subjects with frequent heartburn	576, randomized 1:1 to lansoprazole 15 mg or placebo	7 day placebo run-in period, 14 day placebo-controlled treatment period, 7 day placebo follow-up period	Lansoprazole 15 mg/day or matching placebo	Primary: proportion of 24-hour days with no heartburn over 14 days. Secondary: proportion of nighttimes with no heartburn over 14 days; proportion of days with no heartburn over Days 1-2; proportion of subjects with no heartburn on Day 1.
PRSW-GN-305/ 53 study sites	Efficacy/ safety in subjects with frequent heartburn	864, Randomized 1:1:1 to lansoprazole 15 mg, lansoprazole 30 mg or placebo	7 day placebo run-in period, 14 day, placebo-controlled treatment period, 7 day placebo follow-up period	Lansoprazole 15 mg/day, lansoprazole 30 mg/day or matching placebo	Primary: proportion of nighttimes with no heartburn over 14 days. Secondary: proportion of 24-hour days with no heartburn over 14 days; proportion of subjects with no heartburn on Day 1.

Source: Modules 2.7.3 – Summary of Clinical Efficacy, Table 1-2

3.1 Overview of Efficacy

All three pivotal studies were multicenter, double-blind, randomized, placebo-controlled, 2- or 3-arm trials of identical general design as in the figure below, whose primary objective was to demonstrate that repeated doses of lansoprazole 15 mg in the morning, once daily, are effective in increasing the proportion of 24-hour days (Studies 301 and 302) or nighttimes (Study 305) with no heartburn during 14 days of treatment, as compared to placebo, in the target population. Subjects included had heartburn occurring on a minimum of two or more days a week over the past month if their heartburn was left untreated. In Study 305 only, subjects were required to have nighttime heartburn on at least two days per week over the past month. Subjects with a

history of EE verified by endoscopy, or GERD diagnosed by a physician and confirmed by endoscopy, were excluded. Subjects received lansoprazole 15 mg/day, placebo or, in Study 305 only, lansoprazole 30 mg/day.

Figure 3.1. General study design

← **Screening** →	← **Run-in** →	← **Treatment** →		← **Follow-up** →
Heartburn medication wash out	Single-blind placebo	Randomization (Double-blind treatment)	End of Double-blind treatment	End of Single-blind placebo follow-up
Day -14 (±2)	Day -8 (+4)	Day 1	Day 16 (+4)	Day 24 (+4)
Visit 1	Visit 2	Visit 3	Visit 4	Visit 5

Source: Modules 2.5 – Clinical Overview, Figure 1-1

In Studies 301 and 302, the primary efficacy variable was the proportion of 24-hour days with no heartburn during the 14-day treatment period. The sponsor claimed that this endpoint is consistent with the intended OTC indication and potential label for the product – the treatment of frequent heartburn over a 14-day course of therapy, which is consistent with the currently approved OTC PPI. Secondary efficacy variables were the proportion of nighttimes with no heartburn over a 14-day treatment period, the proportion of 24-hour days with no heartburn over Days 1-2 and the proportion of subjects with no 24-hour heartburn during Day 1. Together, these variables assess the overall efficacy of lansoprazole 15 mg in reducing the frequency of heartburn, and the onset of effect.

Since the focus of Study 305 was frequent nighttime heartburn, the primary efficacy variable was the proportion of nighttimes with no heartburn during the 14-day treatment period, while the proportion of 24-hour days with no heartburn during the 14-day treatment period was a secondary efficacy variable. In common with Studies 301 and 302, the proportion of subjects with no 24-hour heartburn during Day 1 was a secondary efficacy variable.

In all studies, the analysis on the Intent to Treat (ITT) set, defined as all randomized subjects who took at least one dose of study medication, and had at least one post-baseline efficacy assessment (diary recording of the occurrence and severity of heartburn) was considered the primary efficacy analysis. The proportions of 24-hour days and nighttimes with no heartburn over 14-day of treatment, expressed as percentages, were analyzed using analysis of covariance (ANCOVA) model including treatment and center as factors and frequency of heartburn (24-hour or nighttime, as appropriate) during the run-in phase as a covariate. The proportion of 24-hour days with no heartburn over Days 1-2 and the proportion of subjects with no 24-hour heartburn during Day 1 were analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by center.

A total of 1986 ITT subjects were randomized to receive lansoprazole 15 mg (861), lansoprazole 30 mg (277), or placebo (848). Treatment groups in each trial were balanced in baseline demographic and disease characteristics and number of patients. There were few major protocol deviations (19, 20, and 28 subjects in Studies 301, 302, and 305, respectively). They were distributed evenly across treatments, and did not affect the quality of the data. Less than 5% of subjects discontinued from each study. The sponsor claimed that discontinuations were mostly

due to withdrawal of consent or loss of follow-up, occurred at an equal rate with all treatments, and did not influence the conclusions drawn from the data.

The mean percentage of 24-hour days with no heartburn was consistently 14%-20% higher with lansoprazole 15 mg than with placebo in all three studies ($p < 0.0001$). The mean percentage of nighttimes with no heartburn over 14 days was approximately 4% higher with lansoprazole 15 mg than with placebo in Studies 301 and 302, and 14% in Study 305. Seventy percent (70%) of lansoprazole-treated subjects in Studies 301 and 302 had at least one heartburn-free 24-hour day during Days 1-2, as compared with 56-57% of placebo-treated subjects ($p \leq 0.0006$); and the advantage of lansoprazole over placebo in the proportion of subjects who had no 24-hour heartburn on Day 1 was 13-17% across three studies ($p \leq 0.0011$).

Overall, the sponsor claimed that the data from the three pivotal trials showed that lansoprazole 15 mg, once daily, in the morning, is efficacious for the treatment of frequent heartburn, regardless of the time of day that the symptoms occurred, in the target population of OTC subjects, showing consistent superiority compared to placebo. The sponsor further claimed that there was a significant difference in favor of the active groups compared to placebo for the proportion of subjects with no heartburn during Day 1 (the 24 hours following the first dose); thus demonstrating that the onset of the full effect of treatment was rapid.

3.2 Overview of Safety

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

Adverse Clinical Events

The safety profile of lansoprazole in various prescription indications is documented from the clinical and post-marketing perspectives. Over 10000 patients worldwide had been treated with lansoprazole in clinical trials involving various dosages and durations of treatment. Since the initial marketing approval of PREVACID® in the U.S. in May 1995, the estimated sales through June 2007 were ——— prescriptions. b(4)

The key safety population comprised of 1986 subjects in the three placebo-controlled clinical studies who received at least one dose of the study medication. These three studies were conducted in the OTC population utilizing the same study design and treatment duration. This population consisted of adult subjects aged 18 years or older with a history of frequent heartburn.

The majority of the subjects in all three treatment groups received study drugs for 14 days (76.2%, 82.7%, and 76.1%, respectively, for 15 mg lansoprazole, 30 mg lansoprazole, and placebo) while only about 5% of the subjects received no more than 11 days of study treatment. Overall, 1138 subjects from the three pivotal trials received at least one dose of the active treatment, of whom 861 received 15 mg lansoprazole once daily and 277 received 30 mg once daily. Based on the number of days of lansoprazole treatment received for each subject in the key safety population, the total number of administered doses was 11546 for lansoprazole 15 mg and 3765 for lansoprazole 30 mg. For the placebo, the total number of administered doses was 11418.

Adverse events (AEs) were collected during the placebo run-in, double-blind treatment, and placebo follow-up periods of the three studies. Overall, the frequencies of AEs were low among the three treatment groups during all three treatment periods, with the highest incidence rate observed for lansoprazole 30 mg (11.2%) during the double-blind treatment period. During the double-blind treatment period, more subjects in all three treatment groups reported adverse experiences compared to the other two treatment periods. The incidence rate of the lansoprazole 30 mg group was the highest and slightly higher than that reported for lansoprazole 15 mg (11.2% vs. 10.2%). The incidence rate among the placebo subjects was the lowest (8.3%) compared to that of the two active treatment groups.

The most common AEs were diarrhea, headache, nausea, and nasopharyngitis. There were no deaths and few SAEs (seven in all three studies) during the double-blind treatment period, which were distributed evenly across groups and not considered drug-related. Only 16 subjects in total discontinued for AE(s) (less than 1% of the 1986 subjects included in the three safety analysis sets), and only eight of these subjects had AE(s) suspected of a relationship to study treatment. The only AE that was attributable to treatment with active drug was diarrhea (1-2% incidence over 14 days).

There were two deaths in the follow-up period of the trials. One was in the 15 mg lansoprazole treatment group and the other in the placebo group. Neither was thought related to the administration of study medication. An analysis of subgroup rates of AEs based on age groups (less than 65 years and no less than 65 years), gender and race did not reveal any consistent AE clustering suggestive of a particular risk for any subgroup.

Post-Marketing Experience

Lansoprazole has been marketed globally for over 18 years (International Birth Date [IBD] Dec. 31, 1990). It was first approved as a prescription drug on May 10, 1995 and is currently marketed in 93 countries. As of December 2007, the global patient exposure was estimated to be over ——— which includes all formulations world wide. b(4)

The analysis of AEs reported for lansoprazole entered into the TAP safety database during the time period May 10, 1995 to Sep. 30, 2007 revealed 9776 cases involving 17768 MedDRA AE preferred terms. There were 215 reports of death among these 9776 cases. The majority of cases with death as an outcome provided documentation of confounding factors such as significant medical history (cancer, cardiac disorders, renal impairment, etc.), multiple concomitant medications or co-suspect drugs possibly contributing to the outcome of death. The remaining cases provided limited clinical information and so causality could not be determined. A review of the 214 reports with an outcome of death did not reveal any safety signal or trend.

Overall, for the TAP safety data, the sponsor concluded that no new or unexpected findings have emerged from this analysis of the safety profile of lansoprazole. The majority of reported events were not serious and the most frequent events were related to the Gastrointestinal System Organ Class (SOC) (diarrhea, nausea, and abdominal pain) or drug ineffectiveness.

3.3 Evaluation of Efficacy

Studies 301 and 302 started and ended around the same time, June 2006 to January 2007. Study 305 initiated subsequently after the other two pivotal studies in January 2007 and ended in August 2007.

The statistical analysis plans (SAPs) for Studies 301 and 302 were finalized in November 2006 and incorporated some major changes, including changes in the primary and secondary efficacy endpoints, and an addition of a sequential testing procedure. Although these changes were made before data lock and unblinding, they were too late to be amended in the protocols and caused inconsistencies between the two documents (protocol and SAP). After data unblinding, the sponsor changed the primary analysis on the secondary efficacy endpoint, proportion of nighttimes with on heartburn over 14 days of treatment, from ANCOVA with original data to ANCOVA with ranked data (the nonparametric additional analysis). The reason of this change was the alleged heteroscedasticity (non-normality of the residual) of the data discovered during the data analysis. This resulted in a change in the conclusion for the superiority (lansoprazole 15 mg vs. placebo) on this endpoint from statistically insignificant ($p = 0.0501$) to significant ($p = 0.0029$) in Study 301. For Study 302 this did not affect the conclusion since the p-value only changed from 0.0003 to less than 0.0001.

The SAP for Study 305 was finalized in July 2007. The aforementioned major changes, including the one made after unblinding Studies 301 and 302 data, were incorporated in both SAP and protocol (in Amendment 3). Consequently, the primary analysis for the primary endpoint was nonparametric ANCOVA with parametric ANCOVA as supportive. The p-values from both analyses were less than 0.0001 for both comparisons between lansoprazole (15 mg and 30 mg) and placebo.

3.3.1 Study Design and Endpoints

Studies 301 and 302

Studies 301 and 302 were two identical, multicenter, double-blind, randomized, parallel group, placebo-controlled studies to investigate the safety and efficacy of lansoprazole 15 mg once daily, in preventing frequent heartburn with a 1-week screening and heartburn medication wash out period, a 1-week placebo run-in period, a 2-week placebo-controlled treatment period, and a 1-week placebo follow-up period. For each study, it was planned to randomize a total of 576 subjects with frequent heartburn (288 per group) in order to yield 546 subjects. Enrollment was planned to stop when the overall target number of subjects was reached.

The primary objective of each study was to demonstrate that repeated daily doses of 15 mg of lansoprazole, once daily, are effective in increasing the proportion of days with no heartburn during 14 days of treatment as compared to placebo. The screening period was to allow heartburn medication wash out; the placebo run-in period was to allow the evaluation of the frequent heartburn, and compliance with daily medication dosing and diary completion; the treatment period was to allow double-blinded comparison of placebo and lansoprazole treatment groups. There was a one week follow-up period in order to assess the time to recurrence of heartburn.

The trials enrolled male and female subjects, who were at least 18 years old, with frequent heartburn occurring a minimum of two or more days a week over the past month if their heartburn was left untreated. The patients randomized were the ones had the presence of heartburn on at least two days per week during the run-in phase, had missed no more than one day entries in the run-in diary, and had returned for the baseline (randomization) visit no more than two days after scheduled date. Subjects with either endoscopic EE or confirmed GERD were excluded at randomization.

Subjects were supplied with 1-week, 2-week, and 1-week study medication at the beginning of run-in, treatment, and follow-up period, respectively. Placebo capsule was taken orally once daily for seven days during the single-blind run-in period, and once daily for seven days during the single-blind follow-up period. Placebo or lansoprazole 15 mg capsule was taken once daily for 14 days during the double-blind treatment period. The capsule should be swallowed whole with a glass of water once a day before eating, preferably in the morning with breakfast, but in any case before noon. The Gelusil® antacid tablets could be taken according to the label instructions when necessary for the relief of acute heartburn, but no sooner than one hour after study medication was taken. Subjects were encouraged not to use the rescue medication unless absolutely necessary for the relief of acute heartburn.

At the end of the placebo run-in period, eligible subjects was to be randomized in a 1:1 ratio in a double-blind fashion to one of the two treatment groups: lansoprazole 15 mg and placebo. The randomization scheme was set up in blocks, and within block, the randomization numbers were assigned equally to the two treatment groups. It was planned that the data from all centers that participate would be combined. The anticipated number of centers was 28.

Most measures of efficacy were derived from data recorded in the subject IVRS (Interactive Voice Response System) diary after a daily self-assessment. Subjects were given instructions to complete the IVRS diary in the morning for the previous 24-hour period on a daily basis for all phases of the study. The diary was designed to collect information on the occurrence of daytime and nighttime heartburn episodes, maximum heartburn severity, and rescue medication consumption for the previous 24 hours. In addition, the date and time of study medication consumption were also recorded.

As specified in the protocols, the primary evaluation was the period between the first dose (Day 1) and the end of the double-blind treatment period, i.e. Days 1-14 for 24-hour days. "No heartburn over 24 hours" on each of Days 1-14 was defined as the combined experience of daytime and nighttime heartburn. On Day 1, evaluation of daytime heartburn began with the first dose of study medication. On Days 2-14, evaluation of daytime heartburn began upon getting out of bed. The evaluation of nighttime heartburn ended with the next dose of study medication which was to be taken immediately after the subject had awoken and completed the diary.

The protocols specified that the proportion of subjects in each treatment group with no heartburn on each day of the two-week double-blind treatment period would be summarized and presented graphically. P-values for each day would be presented based on an analysis using the CMH test

stratified by center. In addition, the proportion of subjects in each treatment group with each total number of heartburn free days would be presented.

The protocols also specified that two treatment groups would be compared by fitting an ANCOVA to the percent of days with the indicated outcome using treatment and center as factors and the proportion of baseline heartburn days as a covariate. An analogous nonparametric ANCOVA was specified in the protocols to be performed in support of the parametric procedure.

The two secondary efficacy variables specified in the protocols were the proportion of nighttimes with no heartburn over the 14 days treatment period (proportion of days with no nighttime heartburn), and the proportion of subjects with no heartburn during Day 1. Along with them, the other efficacy variables specified were:

- the proportion of 24-hour days with no heartburn during Days 1-4, 1-3, 1-2, and Day 1,
- heartburn severity during 14 days of treatment during the nighttime and 24-hour day,
- the first 24-hour day with no heartburn,
- the first 24-hour day with no heartburn for which there is no heartburn on every subsequent 24-hour day through Day 14,
- the average duration of consecutive heartburn-free 24-hour days during 14 days of treatment,
- the longest duration of consecutive heartburn-free 24-hour days during 14 days of treatment,
- subject global assessment questionnaires,
- the proportion of 24-hour days with no heartburn during seven days of the placebo follow-up period,
- the first 24-hour day with heartburn during the placebo follow-up period,
- the first 24-hour day with heartburn during the placebo follow-up period for subjects with no heartburn on Day 14 of the 14-day treatment period.

The associated SAPs specified the primary efficacy variable to be the proportion of days with no heartburn during the treatment phase of the study (Days 1-14). Although the primary variable in the SAPs was different than the one specified in the protocols, the originally planned daily treatment comparison using the CMH test stratified by center was not appropriate without any multiplicity adjustment specified. In lieu of that, the later proposed primary variable was acceptable.

The SAPs also changed the proportion of 24-hour days with no heartburn during Days 1-2 of the treatment phase from an tertiary ("other") efficacy variable to a secondary efficacy variable, and added time to confirmed response (two different definitions of confirmed response) as new secondary efficacy variables. Those changes were not appropriate; however, the sponsor is not pursuing any labeling claims on any of these endpoints at this point. The conclusions on these efficacy variables should be drawn with caution.

The sample size was determined to detect a difference of approximately 15%, between lansoprazole 15 mg and placebo, in the percentage of days with the outcome of no heartburn over 24 hours during the first 14 days of dosing. A standard deviation of approximately 49.5% was taken based on some references. A two group t-test for comparison of the treatment means

with a 0.05 two-sided significance level would have 90% power when the sample size in each group was 230. The sample size of 576 subjects (288 per group) would allow for a combined early discontinuation and non-evaluability rate of 20%.

In the SAPs, sample size justification for the original critical secondary efficacy variables (specified in the protocol) was added as described below. As mentioned earlier, the sponsor was confident that the sample size of 576 subjects (288 per group) should have provided at least 230 subjects per group in the ITT set.

- Assuming that the percentage of nighttimes with no heartburn over 14 days of treatment had the same standard deviation (approximately 49.5%) as the percentage of 24-hour days with no heartburn over the same period, a sample size of 230 subjects would provide 90% power to detect an approximate 15% difference between lansoprazole 15 mg and placebo on this parameter (probability of type I error = 0.05, two-sided test).
- A sample of 230 subjects would also provide at least 90% power to detect a difference of 15% in the proportion of subjects with no heartburn on Day 1 (probability of type I error = 0.05, two-sided test).

Study 305

Study 305 was similar to Studies 301 and 302 in terms of the study design. Lansoprazole 30 mg once daily was added as the third arm in this study. Also with 288 patients per group, it was planned to randomize 864 subjects in order to yield 690 subjects. The primary objective of this study was to demonstrate that repeated daily doses of 15 or 30 mg of lansoprazole once daily are effective in increasing the proportion of days (24-hour periods) with no *nighttime heartburn* during 14 days of treatment as compared to placebo.

The study subjects enrolled were mostly under the same inclusion and exclusion criteria as in Studies 301 and 302, except that for Study 305, at randomization the subject must have had the presence of *nighttime heartburn* on no less than two days per week during the run-in phase. The eligible subjects were randomized in a 1:1:1 ratio to one of the three treatment groups. The anticipated number of centers was 42.

Both the protocol and SAP for Study 305 specified the primary endpoint as the proportion of nighttimes with no heartburn during 14 days of treatment; and the secondary endpoints as the proportion of 24-hour days with no heartburn during 14 days of treatment and the proportion of subjects with no heartburn during Day 1. The other efficacy variables for this study were similar to the ones for Studies 301 and 302 except that the focus switched from heartburn in 24-hour day to that in nighttime.

All the comparisons were between each active treatment and placebo without multiplicity adjustment for multiple doses comparisons. Also note that the sponsor anticipated 15% treatment effect on all three original efficacy variables for sample size justification. Therefore, the sample size calculation was nearly identical to the other two pivotal studies.

3.3.2 Patient Disposition, Demographic and Baseline Characteristics

In total, 1709 subjects from Studies 301, 302, and 305 received either lansoprazole 15 mg or placebo during treatment period. Out of those patients, 1500 (88%) were aged less than 65 years, and 209 (12%) subjects were aged 65 years or older. The minimum age for inclusion in the studies was 18 years, but there was no upper age limit; the oldest subject randomized was aged 90 years. The male to female ratio among those patients was approximately 1:2. In particular, 1094 (64%) subjects were female and 615 (36%) were male. In total, 1196 (70%) of those subjects were Caucasian, 240 (14%) were Hispanic and 273 (16%) were Black, Asian, or other races. Study drug administration compliance rates were greater than 99% for all treatment groups in all three studies.

The differences in inclusion criteria did not lead to any differences between studies in the subjects' reports of their historical frequency of heartburn (approximately 4.0 days per week in the last month). Subjects enrolled in Study 305 were more likely than those in Studies 301 and 302 to rate their most intense episode of heartburn experienced in the last month as severe. Very high proportions ($\geq$ 92%) of subjects in all arms of all studies had taken prescription or OTC treatment for heartburn over the previous five years. The proportion of subjects reporting that lying down triggered heartburn symptoms was 57% in Studies 301 and 302 versus 73% in Study 305. Approximately 74% of the subjects enrolled in Studies 301 and 302 reported at least one episode of nighttime heartburn during the run-in phase. Moreover, all the subjects in Study 305, while 51% and 52% subjects in Studies 301 and 302, respectively, experienced at least two nighttime heartburns during the seven day run-in period. There were no differences between subjects enrolled in Studies 301 and 302 regarding the proportion of subjects who experienced 24-hour heartburn and nighttime heartburn during the 7-day run-in phase. However, the mean number of 24-hour days with heartburn during the run-in phase increased from 4.9 days in Studies 301 and 302 to 5.7 days in Study 305, whereas the mean number of nighttimes with heartburn increased from 2.2 to 4.6 as expected per the inclusion requirement of at least two nighttimes with heartburn during the run-in phase in Study 305.

Study 301

Study 301 had the first patient screened on June 08, 2006, and last patient completed on January 29, 2007. There were 576 subjects enrolled in 35 centers in the U.S. Out of those, 564 were included in the safety analysis set and the ITT set. There were 272 (96%) of 282 subjects treated with lansoprazole 15 mg and 274 (97%) of 282 subjects treated with placebo completed the study to the end of the double-blind treatment phase. There were 269 (95%) and 271 (96%) subjects in the two groups, respectively, completed the entire study to the end of the follow-up phase. There was no major difference in the discontinuation rate or in the reasons for discontinuation between treatment groups. The most common reasons for premature discontinuation were withdrawal of consent (four subjects in the lansoprazole 15 mg group and five subjects in the placebo group) and loss to follow-up (five subjects in the lansoprazole 15 mg group and two subjects in the placebo group). Two subjects in each group discontinued due to AE(s).

Ten (4%) subjects treated with lansoprazole 15 mg and nine (3%) subjects treated with placebo had a major protocol violation. Seven and three subjects in the two groups, respectively,

recorded diary data for less than seven days during the treatment phase of the study. Two subjects treated with lansoprazole 15 mg and four subjects treated with placebo received treatment for an incorrect randomization number. These subjects have been analyzed according to the treatment actually received. A total of 155 (55%) subjects in the lansoprazole 15 mg group and 145 (51%) subjects in the placebo group had one or more minor protocol violations. The most common of these was a Screening Visit being made before Day -16 or after Day -12 (29% of subjects in the lansoprazole 15 mg group and 27% of subjects in the placebo group). The second most common minor protocol violation was missing diary data for two or more days in the run-in phase or for any day in the treatment phase of the study (26% and 22% of subjects in the lansoprazole 15 mg and placebo groups, respectively).

The 564 subjects included in the safety and ITT set ranged in age from 18 to 90 years (mean 47 years). The majority (60%) of these subjects were aged from 40 to 65 years. Female subjects comprised 64% of the total. Sixty-nine percent (69%) of subjects were Caucasian, 14% were Hispanic, and 10% were Black. The treatment groups were comparable at baseline with respect to their demographic characteristics.

Study 302

Study 302 had the first patient screened on June 09, 2006, and last patient completed on January 24, 2007. There were 576 subjects enrolled in 36 centers in the U.S. Out of those, 570 were included in the safety analysis set and the ITT set. There were 279 (97%) of 288 subjects treated with lansoprazole 15 mg and 270 (96%) of 282 subjects treated with placebo completed the study to the end of the double-blind treatment phase. There were 276 (96%) and 269 (95%) subjects in the two groups, respectively, completed the entire study to the end of the follow-up phase. There was no major difference in the discontinuation rate or in the reasons for discontinuation between treatment groups. The most common reasons for premature discontinuation were as well withdrawal of consent (three subjects in the lansoprazole 15 mg group and five subjects in the placebo group) and loss to follow-up (three subjects in the lansoprazole 15 mg group and five subjects in the placebo group). Five subjects in total (three in the lansoprazole 15 mg group and two in the placebo group) discontinued due to AE(s).

Nine (3%) subjects treated with lansoprazole 15 mg and 11 (4%) subjects treated with placebo had a major protocol violation. Five and seven subjects in the two groups, respectively, recorded diary data for less than seven days during the treatment phase of the study. Two subjects treated with lansoprazole 15 mg and four subjects treated with placebo received treatment for an incorrect randomization number. These subjects have been analyzed according to the treatment actually received. A total of 127 (44%) subjects in the lansoprazole 15 mg group and 129 (46%) subjects in the placebo group had one or more minor protocol violations. The most common minor protocol violation was missing diary data for two or more days in the run-in phase or for any day in the treatment phase of the study (18% and 22% of subjects in the lansoprazole 15 mg and placebo groups, respectively). The second most common one was a Screening Visit being made before Day -16 or after Day -12 (17% of subjects in the lansoprazole 15 mg group and 19% of subjects in the placebo group).

The 564 subjects included in the safety and ITT set ranged in age from 18 to 84 years (mean 49 years). The majority (61%) of these subjects were aged from 40 to 65 years. Female subjects

comprised two-thirds of the total. Seventy-five percent (75%) of subjects were Caucasian, 13% were Hispanic, and 11% were Black. The treatment groups were also comparable at baseline with respect to their demographic characteristics.

Study 305

Study 305 had the first patient screened on January 29, 2007, and last patient completed on August 16, 2007. There were 864 subjects enrolled in 53 centers in the U.S. Out of those, 852 were included in the safety analysis set and the ITT set. There were 281 (97%) of 291 subjects treated with lansoprazole 15 mg, 273 (96%) of 284 subjects treated with placebo, and 265 (96%) of 277 subjects treated with lansoprazole 30 mg completed the study to the end of the double-blind treatment phase. There were 278 (96%), 272 (96%), and 264 (95%) subjects in the three groups, respectively, completed the entire study to the end of the follow-up phase. There was no major difference in the discontinuation rate or in the reasons for discontinuation across treatment groups. The most common reason for premature discontinuation was withdrawal of consent (four subjects in the lansoprazole 15 mg group, five subjects in the placebo group, and eight subjects in the lansoprazole 30 mg group). Ten subjects in total (three in the lansoprazole 15 mg group, three in the placebo group, and four in the lansoprazole 30 mg group) discontinued due to AE(s).

Nine (3%) subjects treated with lansoprazole 15 mg, 12 (4%) subjects treated with placebo, and seven (3%) subjects treated with lansoprazole 30 mg had a major protocol violation. Six, four, and two subjects in the three groups, respectively, recorded diary data for less than seven days during the treatment phase of the study. Two subjects treated with lansoprazole 15 mg, six subjects treated with placebo, and four subjects treated with lansoprazole 30 mg used a disallowed concomitant medication during the study. A total of 111 (38%) subjects in the lansoprazole 15 mg group, 114 (40%) subjects in the placebo group, and 103 (37%) subjects in the lansoprazole 30 mg had one or more minor protocol violations. The most common of these was a Screening Visit being made before Day -16 or after Day -12 (17% of subjects in the lansoprazole 15 mg group, 19% of subjects in the placebo group, and 17% of subjects in the lansoprazole 30 mg group). The second most common minor protocol violation was missing diary data for two or more days in the run-in phase or for any day in the treatment phase of the study (16%, 16%, and 14% of subjects in the lansoprazole 15 mg, 30 mg, and placebo groups, respectively).

The 852 subjects included in the safety and ITT set ranged in age from 18 to 85 years (mean 48 years). The majority (60%) of these subjects were aged from 40 to 65 years. Female subjects comprised 63% of the total. Two-thirds of subjects were Caucasian, 15% were Hispanic, and 14% were Black. The treatment groups were also comparable at baseline with respect to their demographic characteristics.

3.3.3 Statistical Methodologies

Three analysis populations were defined in all three protocols.

- The safety analysis set, used for all safety analyses, includes all subjects who take at least one dose of double-blind study medication.

- The Intent-to-Treat (ITT) set, used for primary efficacy analysis, includes all randomized subjects who were dispensed the study medication, and have at least one post-baseline efficacy assessment (diary recording of the occurrence and severity of heartburn).
- The per-protocol set (PPS) includes subjects in the ITT set who do not violate the protocol in any way liable to influence the efficacy outcome. The PPS was determined and documented in the SAP only after data base lock and before the study was unblinded. The protocol stated that the only results presented for PPS would be the analyses of the primary efficacy endpoint. Later the SAP added analyses of subject disposition, protocol violations, and baseline data for this set.

For the purpose of the efficacy analyses, the treatment period had been defined as the 14 consecutive days which started with the first day after randomization on which the subject recorded that they took study medication (Day 1), whether or not diary data were missing on any day. The last day of the treatment period occurred no later than the day of the follow-up visit (Visit 4).

While the protocols did not specify the analysis of the 7-day follow-up period, the SAPs defined the analysis in two ways:

- The first analysis used the seven consecutive days immediately following the end of 14 days of treatment (or assumed treatment), whether or not the subject had started the placebo treatment.
- The second analysis used the seven day period during which the subject took the placebo treatment, even if there was an interval of one or more days between the end of the treatment phase and the start of placebo follow-up treatment.

The protocols for Studies 301 and 302 indicated that for the primary efficacy variable, the proportion of subjects in each treatment group with no heartburn on each day of the two-week double-blind treatment period would be summarized and presented graphically. P-values for each day would be presented based on analysis using the CMH test stratified by center. In addition, the proportion of subjects in each treatment group with each total number of heartburn free days would be presented. The protocols also indicated that the two treatment groups would be compared by fitting an ANCOVA to the percent of days with the indicated outcome using treatment and center as factors and the proportion of baseline heartburn days as a covariate. The SAPs for these two studies identified the latter as the primary analysis. Both the protocols and SAPs for Studies 301 and 302 had indicated the ANCOVA model as the primary analysis for the secondary efficacy variable of the proportion of nighttimes with no heartburn over the 14 day treatment period, while the CMH test for the other secondary variable(s) when applicable.

Both the protocols and SAPs for Studies 301 and 302 indicated that for efficacy variable of proportion of 24-hour days or nighttimes without heartburn during the 14-day treatment period, an analogous nonparametric ANCOVA would be performed in support of the parametric procedure where the percentage of 24-hour days or nighttimes with no heartburn was ranked prior to analysis. The SAPs for these two trials also specified that all primary, supportive and sensitivity analyses for the primary and secondary efficacy endpoints would be repeated with mild heartburn treated as no heartburn.

During the analysis of the percentage of nighttimes with no heartburn over 14 days of treatment for Study 301, the sponsor claimed that it was noted the p-values obtained from the primary parametric analysis (0.0501) and the supportive nonparametric analysis (0.0029) were noticeably different. The sponsor further claimed that this finding was a signal that the assumptions underlying analysis of variance (normally distributed errors with constant variance) had potentially been violated. Hence the sponsor made checks on these two assumptions, re-ran the parametric ANCOVA, and conducted tests of normality on the residuals. The sponsor then claimed that the results indicated the non-normality of the residuals. Further supportive analyses on the data heteroscedasticity were conducted by the sponsor, who therefore concluded that the percentage of nighttimes with no heartburn was proven to be non-normally distributed with non-constant variance and decided to use the allegedly more valid results from the nonparametric ANCOVA for this efficacy endpoint. The argument is persuasive from an academic perspective; however, the nonparametric model was only prespecified as a supportive analysis for Study 301, not a back-up analysis when non-normality or heteroscedasticity of the data happened. The randomness of choosing the primary analysis after unblinding the data prevents its usage in this clinical trial setting. The sponsor should be encouraged to plan ahead in the future in case of data violations of the model assumptions.

The sponsor specified that for Study 305, the nonparametric ANCOVA would be performed as the primary analysis of the primary endpoint (the percentage of nighttimes with no heartburn during the 14-day treatment period) and the parametric ANCOVA would be performed as a supportive analysis; and the opposite for one of the two secondary endpoints (the proportion of 24-hour days with no heartburn during 14 days of treatment). For the other secondary endpoint of the proportion of subjects with no heartburn during Day 1 and some other efficacy endpoints, the CMH test stratified by center was specified as the primary analysis. The SAP for this study also specified that all primary, supportive and sensitivity analyses for the primary and secondary efficacy endpoints would be repeated with mild heartburn treated as no heartburn.

Control of Type I Error

The type I error rate was two-sided 0.05 for the primary analysis on the primary efficacy variable. In all three protocols, it was planned that the majority of the primary, secondary, and tertiary efficacy variables would be analyzed independently of one another. The only sequential analysis planned to protect the overall type I error rate was of the proportion of 24-hour days (Studies 301, 302, and 305) or nighttimes (Study 305) with no heartburn during (a) Days 1 through 4, (b) Days 1 through 3, (c) Days 1 through 2, and (d) Day 1.

The SAPs for Studies 301 and 302 indicated that due to the number of efficacy variables, it was decided that the primary, secondary, and two new tertiary efficacy variables would be analyzed sequentially. These variables, and their order in the sequential analysis, were:

1. The proportion of 24-hour days with no heartburn during 14 days of treatment (primary efficacy variable);
2. The proportion of nighttimes with no heartburn during 14 days of treatment (secondary efficacy variable);
3. The proportion of 24-hour days with no heartburn during Days 1 through 2 of the treatment phase (new secondary efficacy variable);

4. The proportion of subjects with no heartburn during Day 1 (secondary efficacy variable);
5. The time to confirmed response, defined as four consecutive 24-hour days with no heartburn (new efficacy variable);
6. The time to confirmed response, defined as seven consecutive 24-hour days with no heartburn (new efficacy variable).

For these two studies, in order to protect the type I error rate for the comparison of treatments, it was planned that tests of significance for variables 2-6 in the ordering would be conducted for descriptive purposes only, unless each previous comparison had shown a statistically significant difference between treatments at the two-sided 0.05 significance level. The sponsor claimed that a statistically significant difference between treatments for one or more of variables 3-6 would support the claim and time frame of "full effect". This testing procedure along with the ordering of the variables were specified only in SAP with addition of three new efficacy variables at the end stage of these two trials, and so none of the secondary or tertiary variables should be considered for labeling claims.

The SAP for Study 305 indicated that the primary and secondary efficacy variables would be analyzed sequentially when comparing lansoprazole 15 mg and placebo. The variables included in the sequential analysis, and their order in it, were:

1. The proportion of nighttimes with no heartburn during 14 days of treatment (primary efficacy variable);
2. The proportion of 24-hour days with no heartburn during 14 days of treatment (secondary efficacy variable);
3. The proportion of subjects with no heartburn during Day 1 (secondary efficacy variable).

For this study, in order to protect the type I error rate for the comparison of lansoprazole 15 mg and placebo, each of the comparisons would have a formal inferential assessment for statistical significance at the two-sided 0.05 significance level only when all previous comparisons had been statistically significant at the same significance level. Note that although the sponsor did not intent to pursue marketing of lansoprazole 30 mg at this time, the primary analysis included the comparison between the 30 mg dose of lansoprazole and placebo on the primary efficacy variable of the proportion of nighttimes with no heartburn during 14 days of treatment. Somehow this comparison was omitted in the sequential testing procedure by the sponsor. Before proceeding to secondary variables testing, appropriate multiplicity adjustment on the treatment comparisons of the primary variable between each dose of lansoprazole and placebo should be employed.

Handling of Missing Values and Sensitivity Analyses

The sponsor claimed that the IVRS system used to collect the subjects' diary data prevented the recording of incomplete or inconsistent data for a day. This meant, allegedly, that it was not possible for a subject to have data for the daytime and missing data for the nighttime, or vice versa. The extent and nature of missing efficacy data were examined during a review of the data prior to unblinding. For all efficacy endpoints for which the proportion of days (either 24-hour days or nighttimes) with no heartburn (y) was calculated over a specific number of days ($t \geq 2$), the following formula was specified by all three protocols to be utilized when there were a number of days (m) with missing information:

- If $m < t/2$ then y = (number of days with no heartburn)/(t-m);
- If $m \geq t/2$ then y = (number of days with no heartburn) + m×(baseline proportion of days with no heartburn)/t.

This method is similar to baseline observation carried forward (BOCF) method, which is an acceptable imputation technique in this situation. Although more missing data handling strategies, such as treating all missing days as days with heartburn, should be investigated, the results are expected to be consistent given the very limited amount of missing data in the three pivotal studies.

The SAPs added more details to the aforementioned imputation method for each efficacy endpoint. More specifically, for the primary endpoint (Studies 301 and 302: the proportion of 24-hour days with no heartburn during 14 days of treatment; Study 305: the proportion of nighttimes with no heartburn during 14 days of treatment), the following formula were used when there were a number of days or nighttimes (m) with missing information:

- (Subgroup 1) If $0 \leq m < 7$ then y = (number of 24-hour days or nighttimes with no heartburn)/(14-m);
- If $m \geq 7$
  - (Subgroup 2) and the subject discontinued due to lack of efficacy then y = (number of 24-hour days or nighttimes with no heartburn) + m×(proportion of 24-hour days or nighttimes with no heartburn during the run-in phase)/14;
  - (Subgroup 3) and the subject did not discontinue due to lack of efficacy then y = (number of 24-hour days or nighttimes with no heartburn) + m×(average proportion of 24-hour days or nighttimes with no heartburn for all subjects in Subgroups 1 and 2 for the associated treatment group)/14.

Missing data for the secondary endpoint of proportion of nighttimes (Study 301 and 302) or 24-hour days (Study 305) with no heartburn during 14 days of treatment were handled in a similar manner to the primary efficacy endpoint. The addition of the last subgroup (Subgroup 3) changed the original BOCF nature to somewhat imputing the missing data with average of observed data. Although this method is still acceptable in general, the original imputation method should be utilized for treatment comparisons as well to investigate consistency.

In all three studies, for the ITT evaluation of the efficacy variable of proportion of 24-hour days or nighttimes without heartburn over 14-day of treatment, an additional sensitivity analysis was performed excluding subjects with less than seven 24-hour days or nighttimes of data. It was planned that a further sensitivity analysis, excluding subjects who did not have complete 24-hour days or nighttimes data over the entire 14-day treatment period, would be performed if at least 5% of subjects had less than seven 24-hour days of data, but the latter did not occur for either efficacy variable.

3.3.4 Results and Conclusions

Primary Analyses

The primary efficacy variable in Studies 301 and 302, the proportion of 24-hour days with no heartburn over 14 days of treatment, was the first secondary efficacy variable in Study 305; while the primary efficacy variable in Study 305, the proportion of nighttimes with no heartburn over 14 days of treatment, was the first secondary efficacy variable in Studies 301 and 302. Both variables are therefore presented as primary efficacy variables in this section.

The results of the primary efficacy variable in Studies 301 and 302, the proportion of heartburn-free 24-hour days over the 14-day treatment phase of the study, are presented in Table 3.2 below. The lansoprazole 30 mg group was included as a third, exploratory, arm in Study 305. Although counted as an additional comparison, the small p-values ensure the significance for the comparison between lansoprazole 15 mg and placebo with or without multiplicity adjustment. The comparison between lansoprazole 15 mg and 30 mg was not prespecified and the result of it is presented here only for descriptive purposes.

Table 3.2. Proportion (%) of 24-hour days with no heartburn over 14 days of treatment (ITT population)

Study No. / Statistics	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg	Parametric p-value[a]	Nonparametric p-value[b]
Study 301					
N	282	282			
Mean (95% C.I.)	59.9 (56.4, 63.4)	45.7 (42.4, 49.0)	–	< 0.0001	< 0.0001
Median	64.3	50.0			
Min – Max	0.0 – 100.0	0.0 – 100.0			
Study 302					
N	288	282			
Mean (95% C.I.)	64.7 (61.1, 68.2)	45.0 (41.6, 48.4)	–	< 0.0001	< 0.0001
Median	71.4	50.0			
Min – Max	0.0 – 100.0	0.0 – 100.0			
Study 305					
N	291	284	277		
Mean (95% C.I.)	49.7 (45.8, 53.6)	29.5 (26.2, 32.8)	50.9 (46.7, 55.1)	(1) < 0.0001[c]	(1) < 0.0001[c]
Median	57.1	24.1	57.1	(2) < 0.0001[c]	(2) < 0.0001[c]
Min – Max	0.0 – 100.0	0.0 – 100.0	0.0 – 100.0	(3) 0.7686[c]	(3) 0.7952[c]

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

[b] Nonparametric p-value is based on a supportive nonparametric ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

[c] (1) p-value for comparison of lansoprazole 15 mg and placebo.
(2) p-value for comparison of lansoprazole 30 mg and placebo.
(3) p-value for comparison of lansoprazole 15 mg and lansoprazole 30 mg.

Source: Reviewer's Table (the results concur with those from the sponsor)

In subjects treated with lansoprazole 15 mg, the mean percentage of 24-hour days with no heartburn was 59.9%, 64.7%, and 49.7% in Studies 301, 302, and 305, respectively. Comparing to the large differences in the mean percentage of heartburn-free days between studies, the treatment effect was relatively constant: 14.2%, 19.7%, and 20.2%, respectively. In all three studies, lansoprazole 15 mg was highly significantly superior to placebo ($p < 0.0001$) whether parametric or nonparametric ANCOVA model was utilized. The sponsor claimed that the lower

absolute percentages of heartburn-free days observed in subjects treated with lansoprazole 15 mg or placebo in Study 305 can be explained by the fact that the subjects in this study had more frequent 24-hour heartburn days during the run-in phase, on 5.7 of the 7 days, as compared with 4.9 of the 7 days in subjects in the other two studies. It should be noted that the largest treatment effect, both in absolute terms (20.2%) and in relative terms (an increase of 68% in the percentage of heartburn-free 24-hour days in comparison with placebo), was observed in Study 305. The reason for this may depend on the subjects' demographical differences or the fact that Study 305 was conducted chronically after the other two studies, which may cause some study conduct differences.

The results of the primary efficacy variable in Study 305, the proportion of heartburn-free nighttimes over the 14-day treatment phase of the study, are presented in Table 3.3 below. Again, lansoprazole 30 mg was included as a third, exploratory, arm in Study 305. The comparison between lansoprazole 15 mg and 30 mg was as well not prespecified and the result of it is presented here only for descriptive purposes.

Table 3.3. Proportion (%) of nighttimes with no heartburn over 14 days of treatment (ITT population)

Study No. / Statistics	Lansoprazole 15 mg	Placebo	Lansoprazole 30 mg	Parametric p-value[a]	Nonparametric p-value[b]
Study 301					
N	282	282			
Mean (95% C.I.)	79.5 (76.5, 82.5)	76.3 (73.3, 79.4)	–	0.0501	0.0029
Median	90.3	85.7			
Min – Max	0.0 – 100.0	0.0 – 100.0			
Study 302					
N	288	282			
Mean (95% C.I.)	81.6 (78.8, 84.5)	77.0 (74.0, 80.0)	–	0.0003	< 0.0001
Median	91.7	85.7			
Min – Max	0.0 – 100.0	0.0 – 100.0			
Study 305					
N	291	284	277		
Mean (95% C.I.)	61.7 (57.7, 65.6)	47.8 (44.1, 51.5)	61.3 (57.2, 65.4)	(1) < 0.0001[c]	(1) < 0.0001[c]
Median	71.4	50.0	71.4	(2) < 0.0001[c]	(2) < 0.0001[c]
Min – Max	0.0 – 100.0	0.0 – 100.0	0.0 – 100.0	(3) 0.6452[c]	(3) 0.6610[c]

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

[b] Nonparametric p-value is based on a supportive nonparametric ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

[c] (1) p-value for comparison of lansoprazole 15 mg and placebo.
(2) p-value for comparison of lansoprazole 30 mg and placebo.
(3) p-value for comparison of lansoprazole 15 mg and lansoprazole 30 mg.

Source: Reviewer's Table (the results concur with those from the sponsor)

The mean percentage of nighttimes with no heartburn in subjects treated with lansoprazole 15 mg was 79.5% in Study 301, 81.6% in Study 302, and 61.7% in Study 305. The treatment effect was 3.2%, 4.6%, and 13.9%, respectively. Nonparametric ANCOVA showed that lansoprazole 15 mg was significantly superior to placebo in all three studies ($p = 0.0029$, $p < 0.0001$, and $p < 0.0001$, respectively); however, the prespecified primary parametric ANCOVA only showed statistical significance in Studies 302 and 305 ($p = 0.0501$, $p = 0.0003$, and $p < 0.0001$, respectively). One may argue that even if ignoring the results from Study 301 the significance in

Study 305 was repeated in Study 302; but keep in mind that these two studies had fundamental differences in the study design as to the subjects enrolled and primary objective. Moreover, Study 305 was conducted sequentially after the other two studies; results from those studies likely influenced major changes in the protocol and SAP for Study 305. This also may have changed some aspects of study conduct for 305. ⌐

b(4)

1.

The results based on the PPS population were very similar to those based on the ITT population as well for both variables in all three studies.

Secondary Analyses

According to the sequential testing procedure proposed by the sponsor, the results for the other secondary efficacy endpoints presented in this section should only be considered descriptive for Study 301 due to its failure to show significance on the first secondary endpoint. Although for the other two studies the results could be considered supportive of efficacy claims, as discussed before, the fundamental differences between these two studies limited their usage.

The proportion of 24-hour days with no heartburn over Days 1-2 of the 14-day treatment period was a secondary efficacy variable in Studies 301 and 302 but a tertiary efficacy variable in Study 305. Nevertheless, it is included in the results presented in this section. The proportion of subjects with no heartburn for 24 hours on Day 1 of treatment was a secondary efficacy variable for all three studies.

Table 3.4 below shows that the differences between lansoprazole 15 mg and placebo in the proportions of subjects who were heartburn-free on at least one of the first two days in the 14-day treatment phase remained almost constant, 13%, 14%, and 17%, respectively, across Studies 301, 302, and 305. The differences between lansoprazole 15 mg and placebo in the proportions of subjects who were completely heartburn-free over Days 1-2 were also very similar: 10%, 14%, and 9%, respectively.

Table 3.4. Proportion of 24-hour days with no heartburn over Days 1-2 of the 14 days of treatment period (ITT population)

Number (proportion) of 24-hour days with no heartburn	Lansoprazole 15 mg		Placebo		Lansoprazole 30 mg		p-value[a]
	n	(%)	n	(%)	n	(%)	
Study 301	(N = 282)		(N = 282)				
0 (0%)	85	(30.1)	122	(43.3)			
1 (50%)	105	(37.2)	97	(34.4)	–	–	0.0006
2 (100%)	92	(32.6)	63	(22.3)			
Study 302	(N = 288)		(N = 282)				
0 (0%)	86	(29.9)	124	(44.0)			
1 (50%)	91	(31.6)	90	(31.9)	–	–	< 0.0001
2 (100%)	111	(38.5)	68	(24.1)			
Study 305	(N = 291)		(N = 284)		(N = 277)		
0 (0%)	138	(47.4)	182	(64.1)	125	(45.1)	(1) < 0.0001[b]
1 (50%)	94	(32.3)	70	(24.6)	78	(28.2)	(2) < 0.0001[b]
2 (100%)	59	(20.3)	32	(11.3)	74	(26.7)	(3) 0.2857[b]

[a] p-value is based on a CMH test stratified by center.
[b] (1) p-value for comparison of lansoprazole 15 mg and placebo.

(2) p-value for comparison of lansoprazole 30 mg and placebo.
(3) p-value for comparison of lansoprazole 15 mg and lansoprazole 30 mg.
Source: Modules 2.7.3 – Summary of Clinical Efficacy, Table 3-17

Table 3.5 below shows that in Studies 301 and 302, one-half of the subjects treated with lansoprazole 15 mg had no heartburn for 24 hours on Day 1 of treatment, as compared with 33% - 38% of the subjects in the placebo group.

Table 3.5. Proportion of subjects with no heartburn for 24 hours on Day 1 of treatment (ITT population)

Treatment	N	Proportion of subjects with no heartburn for 24 hours on Day 1			p-value[a]
		n	%	(95% C.I.)	
Study 301					
Lansoprazole 15 mg	282	142	50.4	(44.5, 56.2)	
Placebo	282	93	33.0	(27.5, 38.5)	
Difference between treatments:					
Lansoprazole 15 mg – Placebo			17.4	(9.2, 25.5)	< 0.0001
Study 302					
Lansoprazole 15 mg	288	146	50.7	(44.9, 56.5)	
Placebo	282	107	37.9	(32.3, 43.6)	
Difference between treatments:					
Lansoprazole 15 mg – Placebo			12.8	(4.6, 20.9)	0.0011
Study 305					
Lansoprazole 15 mg	291	103	35.4	(29.9, 40.9)	
Placebo	284	64	22.5	(17.7, 27.4)	
Lansoprazole 30 mg	277	101	36.5	(30.8, 42.1)	
Difference between treatments:					
Lansoprazole 15 mg – Placebo			12.9	(5.4, 20.3)	0.0005
Lansoprazole 30 mg – Placebo			13.9	(6.4, 21.5)	0.0004
Lansoprazole 15 mg – Lansoprazole 30 mg			-1.1	(-9.0, 6.8)	0.9764

[a] p-value is based on a CMH test stratified by center.
Source: Modules 2.7.3 – Summary of Clinical Efficacy, Table 3-18

For studies 301 and 302, there were two tertiary efficacy variables included in the sequential testing procedure following the above two secondary efficacy variables. These two variables were both time to confirmed response for 24-hour days with confirmed response defined in two ways: as four consecutive 24-hour days with no heartburn, and as seven consecutive 24-hour days with no heartburn. For both variables, the percentages of patients with confirmed responses on each treatment day were consistently about 10% more in the lansoprazole 15 mg arm than in the placebo arm. Using Wilcoxon survival techniques stratified by center, p-values were less than 0.0001 for both variables in both studies.

Sensitivity Analyses

The sponsor conducted a sensitivity analysis excluding subjects with less than seven 24-hour days or nighttimes of data. This reviewer performed several additional sensitivity analyses, such as a worst-case analysis, an analysis using the originally proposed imputation strategy, and an analysis treating all missing days as days with heartburns. As expected, due to the fact that only few subjects with missing or incomplete data, the results from the sensitivity analyses were nearly identical to the primary analyses. The conclusion still holds except that for Study 301, the p-value using parametric ANCOVA model of the treatment comparison on the proportion of nighttimes with no heartburn over 14 days of treatment was 0.0477 when excluding subjects with

data for less than seven nighttimes as opposed to 0.0501 in the primary analysis. The worst-case scenario, where imputing missing with failure in the treatment arm and with success in the placebo arm, rendered the least favorable p-values as usual and the only difference it caused was that for Study 302 the comparison between the two treatments on the proportion of nighttimes with no heartburn over 14 days of treatment was no longer statistically significant. In conclusion, the sensitivity analyses did not raise any concern on the validity of the primary analyses results.

Additional Analyses

The sponsor investigated various additional secondary and other efficacy variables. In addition, the sponsor conducted repeated analyses with mild heartburn treated as no heartburn. All the results were consistent with those from the primary analyses. There were no contradictory findings or safety signals. It is worth of mentioning that the results based on the follow-up phase data show lansoprazole 15 mg-treated subjects had comparable and similar behavior with placebo-treated subjects after 14 days of treatment in terms of heartburn recurrence.

3.4 Integrated Efficacy Analysis

A combined efficacy analysis was prespecified using data for lansoprazole 15 mg and placebo from the three large controlled phase 3 trials. However, the results presented below should only be considered exploratory and not supportive of any efficacy indications. Table 3.6 presents the results for the primary endpoint and the first secondary endpoint based on the pooled data from the three studies. The results were largely swayed by Study 305, which showed the largest treatment effect.

Table 3.6. Combined efficacy data (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	Parametric p-value[a]	Nonparametric p-value[b]
Proportion (%) of 24-hour days with no heartburn over 14 days of treatment				
N	861	848		
Mean (95% C.I.)	58.0 (55.9, 60.2)	40.0 (38.0, 42.0)	< 0.0001	< 0.0001
Median	64.3	42.9		
Min – Max	0.0 – 100.0	0.0 – 100.0		
Proportion (%) of nighttimes with no heartburn over 14 days of treatment				
N	861	848		
Mean (95% C.I.)	74.2 (72.2, 76.2)	67.0 (64.9, 69.1)	< 0.0001	< 0.0001
Median	85.7	78.6		
Min – Max	0.0 – 100.0	0.0 – 100.0		

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

[b] Nonparametric p-value is based on a supportive nonparametric ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

Source: Reviewer's Table (the results concur with those from the sponsor)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses on the primary and secondary efficacy variables were conducted by the sponsor for the following factors for each study and the integrated analysis on data pooled over Studies 301, 302, and 305:

1) Age (< 65 years and ≥65 years)
2) Gender (male and female)
3) Race (Caucasian, Hispanic, other races)

The results for the primary endpoint of Studies 301 and 302 and the primary endpoint of Study 305 are discussed in Section 4.1 below. For the other efficacy variables, the results were very similar across the subgroups. Moreover, the results for these variables are not of great clinical interest and so they will not be further discussed in this review.

4.1 Gender, Race and Age

The subgroup results from the primary efficacy analyses on subgroups of gender, race, and age are summarized in Table 4.1 and 4.2 below. All the p-values were generated by a parametric ANCOVA as opposed to nonparametric ANCOVA, which was used by the sponsor on the nighttime heartburn endpoint for Study 305 and the combined data. Although the p-values across the subgroups may look different, the differences were mainly caused by the sample size differences among the subgroups. There were some noticeable treatment effect differences across subgroups that could not be explained by the sample size differences; however, there was no consistent trend across the studies and they might be purely random incidences. In general, the treatment group statistics are similar across the various subgroups.

Table 4.1. Proportion (%) of 24-hour days with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Study 301			
Age (< 65 years)			
N	258	244	
Mean (95% C.I.)	60.0 (56.3, 63.6)	45.2 (41.6, 48.9)	< 0.0001
Median	64.3	50.0	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	24	38	
Mean (95% C.I.)	59.3 (45.2, 73.4)	48.6 (41.0, 56.2)	0.0820
Median	63.2	50.0	
Min – Max	0.0 – 100.0	0.0 – 92.9	
Gender (male)			
N	104	100	
Mean (95% C.I.)	57.1 (51.3, 62.8)	43.9 (37.9, 49.8)	0.0001
Median	62.2	44.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.
Source: Reviewer's Table (the results concur with those from the sponsor)

Table 4.1. (Cont'd) Proportion (%) of 24-hour days with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Gender (female)			
N	178	182	
Mean (95% C.I.)	61.6 (57.1, 66.1)	46.7 (42.7, 50.6)	< 0.0001
Median	69.2	50.0	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	195	195	
Mean (95% C.I.)	63.2 (59.1, 67.3)	45.6 (41.6, 49.5)	< 0.0001
Median	71.4	50.0	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	39	39	
Mean (95% C.I.)	48.3 (37.5, 59.0)	43.5 (34.3, 52.8)	0.5251
Median	50.0	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Other)			
N	48	48	
Mean (95% C.I.)	56.0 (47.7, 64.2)	47.8 (39.2, 56.3)	0.2065
Median	61.5	53.8	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Study 302			
Age (< 65 years)			
N	245	250	
Mean (95% C.I.)	64.8 (61.1, 68.5)	45.3 (41.7, 48.9)	< 0.0001
Median	69.2	50.0	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	43	32	
Mean (95% C.I.)	63.7 (52.6, 74.8)	42.4 (31.0, 53.7)	0.0290
Median	71.4	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (male)			
N	98	92	
Mean (95% C.I.)	72.4 (66.7, 78.2)	40.7 (34.1, 47.2)	< 0.0001
Median	78.6	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (female)			
N	190	190	
Mean (95% C.I.)	60.6 (56.2, 65.1)	47.0 (43.1, 51.0)	< 0.0001
Median	64.3	50.0	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	218	209	
Mean (95% C.I.)	68.0 (64.1, 71.9)	44.6 (40.7, 48.5)	< 0.0001
Median	71.4	50.0	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	34	39	
Mean (95% C.I.)	51.6 (38.8, 64.5)	37.6 (28.7, 46.5)	0.1497
Median	59.3	38.5	
Min – Max	0.0 – 100.0	0.0 – 92.9	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

Source: Reviewer's Table (the results concur with those from the sponsor)

Table 4.1. (Cont'd) Proportion (%) of 24-hour days with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Race (Other)			
N	36	34	
Mean (95% C.I.)	56.6 (47.1, 66.1)	55.6 (44.6, 66.6)	0.0800
Median	58.6	64.3	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Study 305			
Age (< 65 years)			
N	253	250	
Mean (95% C.I.)	49.7 (45.5, 53.9)	31.5 (28.0, 35.0)	< 0.0001
Median	57.1	28.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	38	34	
Mean (95% C.I.)	49.8 (38.7, 60.9)	14.5 (6.6, 22.4)	0.0023
Median	51.7	0.0	
Min – Max	0.0 – 100.0	0.0 – 78.6	
Gender (male)			
N	118	103	
Mean (95% C.I.)	53.8 (47.8, 59.9)	29.3 (23.6, 35.1)	< 0.0001
Median	57.1	23.1	
Min – Max	0.0 – 100.0	0.0 – 92.9	
Gender (female)			
N	173	181	
Mean (95% C.I.)	46.9 (41.7, 52.0)	29.5 (25.5, 33.6)	< 0.0001
Median	50.0	28.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	196	183	
Mean (95% C.I.)	56.0 (51.5, 60.4)	31.7 (27.7, 35.8)	< 0.0001
Median	64.0	28.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	44	45	
Mean (95% C.I.)	32.3 (22.2, 42.4)	17.1 (10.0, 24.2)	0.1141
Median	25.0	7.1	
Min – Max	0.0 – 100.0	0.0 – 92.9	
Race (Other)			
N	51	56	
Mean (95% C.I.)	40.7 (30.4, 51.0)	31.9 (23.7, 40.1)	0.6505
Median	35.7	28.6	
Min – Max	0.0 – 100.0	0.0 – 92.9	
Combined data			
Age (< 65 years)			
N	756	744	
Mean (95% C.I.)	58.1 (55.8, 60.4)	40.6 (38.5, 42.7)	< 0.0001
Median	64.3	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	105	104	
Mean (95% C.I.)	57.7 (51.0, 64.5)	35.4 (29.7, 41.2)	< 0.0001
Median	64.3	35.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.

Source: Reviewer's Table (the results concur with those from the sponsor)

Table 4.1. (Cont'd) Proportion (%) of 24-hour days with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Gender (male)			
N	320	295	
Mean (95% C.I.)	60.6 (57.1, 64.0)	37.8 (34.2, 41.3)	< 0.0001
Median	64.3	35.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (female)			
N	541	553	
Mean (95% C.I.)	56.5 (53.8, 59.3)	41.2 (38.8, 43.6)	< 0.0001
Median	64.3	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	609	587	
Mean (95% C.I.)	62.6 (60.2, 65.0)	40.9 (38.6, 43.2)	< 0.0001
Median	69.2	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	117	123	
Mean (95% C.I.)	43.2 (36.8, 49.6)	31.9 (26.8, 37.1)	0.0312
Median	42.9	28.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Other)			
N	135	138	
Mean (95% C.I.)	50.4 (44.8, 55.9)	43.3 (38.0, 48.6)	0.0999
Median	57.1	42.9	
Min – Max	0.0 – 100.0	0.0 – 100.0	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of 24-hour days with heartburn during the Run-in phase as a covariate.
Source: Reviewer's Table (the results concur with those from the sponsor)

Table 4.2. Proportion (%) of nighttimes with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Study 301			
Age (< 65 years)			
N	258	244	
Mean (95% C.I.)	79.8 (76.7, 82.8)	75.9 (72.6, 79.3)	0.0614
Median	89.3	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	24	38	
Mean (95% C.I.)	76.5 (63.0, 90.1)	78.9 (72.1, 85.8)	0.4114
Median	92.9	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (male)			
N	104	100	
Mean (95% C.I.)	77.7 (72.7, 82.7)	73.7 (68.2, 79.2)	0.0173
Median	85.2	84.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of nighttimes with heartburn during the Run-in phase as a covariate.
Source: Reviewer's Table (the results concur with those from the sponsor)

Table 4.2. (Cont'd) Proportion (%) of nighttimes with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Gender (female)			
N	178	182	
Mean (95% C.I.)	80.5 (76.7, 84.3)	77.8 (74.1, 81.4)	0.6650
Median	92.3	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	195	195	
Mean (95% C.I.)	82.6 (79.3, 86.0)	78.5 (75.0, 81.9)	0.0105
Median	92.9	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	39	39	
Mean (95% C.I.)	67.4 (56.7, 78.0)	70.5 (60.5, 80.4)	0.3021
Median	76.9	83.3	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Other)			
N	48	48	
Mean (95% C.I.)	76.6 (69.5, 83.7)	72.5 (64.4, 80.5)	0.9355
Median	83.3	78.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Study 302			
Age (< 65 years)			
N	245	250	
Mean (95% C.I.)	81.9 (78.9, 85.0)	77.3 (74.2, 80.5)	0.0007
Median	92.3	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	43	32	
Mean (95% C.I.)	79.9 (71.7, 88.1)	74.5 (65.3, 83.7)	0.3450
Median	85.7	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (male)			
N	98	92	
Mean (95% C.I.)	86.6 (82.3, 90.9)	73.2 (67.3, 79.0)	0.0001
Median	100.0	85.2	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (female)			
N	190	190	
Mean (95% C.I.)	79.1 (75.4, 82.7)	78.9 (75.5, 82.2)	0.1174
Median	85.7	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	218	209	
Mean (95% C.I.)	84.5 (81.6, 87.3)	79.1 (75.9, 82.2)	< 0.0001
Median	92.9	85.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	34	39	
Mean (95% C.I.)	70.2 (58.2, 82.2)	64.3 (53.5, 75.1)	0.7678
Median	82.1	78.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of nighttimes with heartburn during the Run-in phase as a covariate.

Source: Reviewer's Table (the results concur with those from the sponsor)

Table 4.2. (Cont'd) Proportion (%) of nighttimes with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Race (Other)			
N	36	34	
Mean (95% C.I.)	75.2 (66.0, 84.3)	78.9 (70.6, 87.2)	0.7387
Median	82.9	85.7	
Min – Max	0.0 – 100.0	14.3 – 100.0	
Study 305			
Age (< 65 years)			
N	253	250	
Mean (95% C.I.)	61.4 (57.2, 65.6)	49.0 (45.1, 53.0)	< 0.0001
Median	71.4	57.1	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	38	34	
Mean (95% C.I.)	63.3 (51.8, 74.8)	38.7 (27.7, 49.6)	0.0224
Median	75.0	40.7	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (male)			
N	118	103	
Mean (95% C.I.)	65.2 (59.5, 70.9)	48.2 (41.7, 54.7)	0.0001
Median	71.4	54.5	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (female)			
N	173	181	
Mean (95% C.I.)	59.3 (53.9, 64.6)	47.5 (43.0, 52.1)	0.0004
Median	71.4	50.0	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	196	183	
Mean (95% C.I.)	68.3 (63.9, 72.8)	54.2 (49.8, 58.5)	< 0.0001
Median	78.6	58.3	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	44	45	
Mean (95% C.I.)	41.6 (30.8, 52.4)	27.7 (19.3, 36.1)	0.5275
Median	42.9	27.3	
Min – Max	0.0 – 100.0	0.0 – 92.9	
Race (Other)			
N	51	56	
Mean (95% C.I.)	53.3 (43.4, 63.3)	43.1 (33.9, 52.2)	0.4069
Median	57.1	42.9	
Min – Max	0.0 – 100.0	0.0 – 92.9	
Combined data			
Age (< 65 years)			
N	756	744	
Mean (95% C.I.)	74.3 (72.2, 76.4)	67.4 (65.1, 69.6)	< 0.0001
Median	85.7	78.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Age (≥ 65 years)			
N	105	104	
Mean (95% C.I.)	73.2 (67.1, 79.4)	64.2 (58.1, 70.4)	0.0106
Median	85.7	71.4	
Min – Max	0.0 – 100.0	0.0 – 100.0	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of nighttimes with heartburn during the Run-in phase as a covariate.

Source: Reviewer's Table (the results concur with those from the sponsor)

Table 4.2. (Cont'd) Proportion (%) of nighttimes with no heartburn over 14 days of treatment by subgroups (ITT population)

Statistic	Lansoprazole 15 mg	Placebo	p-value[a]
Gender (male)			
N	320	295	
Mean (95% C.I.)	75.8 (72.7, 78.9)	64.6 (60.9, 68.3)	< 0.0001
Median	85.7	71.4	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Gender (female)			
N	541	553	
Mean (95% C.I.)	73.2 (70.6, 75.8)	68.2 (65.7, 70.8)	0.0003
Median	85.7	78.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Caucasian)			
N	609	587	
Mean (95% C.I.)	78.7 (76.6, 80.8)	71.1 (68.8, 73.3)	< 0.0001
Median	85.7	78.6	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Hispanic)			
N	117	123	
Mean (95% C.I.)	58.4 (51.8, 65.1)	52.8 (46.3, 59.2)	0.9764
Median	71.4	57.1	
Min – Max	0.0 – 100.0	0.0 – 100.0	
Race (Other)			
N	135	138	
Mean (95% C.I.)	67.4 (62.1, 72.8)	62.2 (56.6, 67.8)	0.5340
Median	75.0	71.4	
Min – Max	0.0 – 100.0	0.0 – 100.0	

[a] Parametric p-value is based on an ANCOVA with treatment and center as factors and the proportion of nighttimes with heartburn during the Run-in phase as a covariate.
Source: Reviewer's Table (the results concur with those from the sponsor)

4.2 Other Special/Subgroup Populations

The sponsor also conducted some subgroup analyses on disease factors and the treatment effect was found to be larger for patients who experienced more heartburn 24-hour days or nighttimes during the run-in period. The efficacy results based on a subgroup of subjects from Studies 301 and 302 who met the inclusion/exclusion criteria of Study 305 were compared to those from Study 305 by the sponsor. Those results were very consistent across the studies.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Statistical issues arose mainly from the post-hoc nature of the analysis plan. The sponsor had changed crucial components of the analysis plan, including efficacy endpoints, primary analyses, and missing data handling, during the courses of the trials without adequate communication with the Agency.

The primary efficacy variables specified in the protocols for Studies 301 and 302 were the proportions of subjects in each treatment group with no heartburn on each day of the two-week

double-blind treatment period. Accordingly, the primary analysis was the CMH test stratified by center and all 14 p-values with no multiplicity adjustment were to be presented. The SAPs for these two studies later identified the additional efficacy variable, the proportion of 24-hour days with no heartburn over the 14 days treatment period, as a more reasonable primary efficacy variable. The primary analysis corresponding to this endpoint was specified as an ANCOVA of the percent of days using treatment and center as factors and the proportion of baseline heartburn days as a covariate.

For all three studies, all the comparisons on the primary, secondary and tertiary efficacy variables were planned to be analyzed independently of one another in the protocols. The sponsor later added a sequential testing procedure in the SAPs. This also entailed a newly specified testing order. In addition, for Studies 301 and 302 the sponsor changed the tertiary secondary efficacy variable of the proportion of 24-hour days with no heartburn during Days 1 through 2 of the 14-day treatment period to a secondary efficacy variable, and added a new secondary efficacy variable of the time to confirmed response. In general, the whole secondary efficacy variable set was revised from the original one.

The most important change, which occurred after unblinding the data for Studies 301 and 302, was the primary analysis on the secondary efficacy variable, the proportion of nighttimes with no heartburn over the 14 days treatment period. The original primary analysis was an ANCOVA based on the percent of days; this was the same model used for the primary efficacy variable for Studies 301 and 302. The sponsor retrospectively changed the analysis of this secondary variable in Studies 301 and 302 to a nonparametric ANCOVA, which was initially only identified as a supportive analysis.

There were also other minor changes, including modifications to the missing data handling strategies. They are minor only in the sense that for this review the results and conclusions were not greatly affected. All the post-hoc modifications on the statistical analysis plan have caused difficulties on the evaluation of the efficacy and the interpretation of the results.

5.2 Conclusions and Recommendations

PREVACID® (lansoprazole) has been on the market since 1995 and its safety profile has been established. The efficacy of lansoprazole 15 mg QD on the endpoint of proportion of 24-hour days with no heartburn over 14 days of treatment has been demonstrated by three randomized, placebo-controlled, phase 3 studies. [redacted]

b(4)

[redacted] In conclusion, despite the planning flaws, the data support the efficacy on the frequent 24-hour heartburn treatment indication for lansoprazole delayed-release capsules, 15 mg, QD, 14-day treatment.

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/s/

Freda Cooner
4/6/2009 04:07:44 PM
BIOMETRICS

Mike Welch
4/6/2009 04:40:19 PM
BIOMETRICS
Concur with review.

STATISTICS FILING REVIEW

NDA Number: 22-327 **Applicant: Novartis Consumer Health, Inc. (NCH)** **Stamp Date: 16-Jul-08**

Drug Name: PREVACID® 24HR (15 mg lansoprazole delayed-release capsule) **NDA/BLA Type: NDA**

On initial review of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Protocol status for studies PRSW-GN-301 and PRSW-GN-302 is *Amendment 3* while for study PRSW-GN-305 is *Final*
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	**Yes**	**No**	**NA**	**Comment**
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			

STATISTICS FILING REVIEW

Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		Such an investigation cannot be located

Background

Prevacid® (lansoprazole) delayed-release capsules are already marketed with a prescription in two dosage strengths (15 mg and 30 mg) for multiple indications. This NDA is for the over-the-counter (OTC) marketing of lansoprazole delayed-release capsules, 15 mg for the treatment of frequent heartburn (occurs two or more days a week), which has been the approval OTC condition for the current OTC PPI, Prilosec OTC® (NDA 21-229). This application is submitted under the provisions of 505(b)(1) of the Food, Drug and Cosmetic Act due to an agreement with TAP Pharmaceutical Products, Inc. (TAP), the holder of NDA 20-406 and IND 30,159 [PREVACID® (lansoprazole) Delayed-Release Capsules], granting NCH full right of reference to the NDA and IND data in support of all applications related to OTC use.

Data sets and study reports have been submitted in electronic Common Technical Document (eCTD) format to the EDR at: \\Cdsesub1\evsprod\NDA022327\0000.

Overview of studies

Three clinical placebo-controlled phase 3 efficacy studies have been submitted for review. The protocols for two identical clinical studies, PRSW-GN-301 and PRSW-GN-302, were submitted on May 5, 2006 under IND 74,256 (Serial No. 000) and then on November 15, 2006 the Statistical Analysis Plans (SAPs) for these two studies were submitted (Serial No. 008). The primary objective of these studies was to demonstrate that repeated daily doses of 15 mg of lansoprazole once a day are effective in increasing the proportion of days with no heartburn during 14 days (24-hour days) of treatment as compared to placebo. On July 26, 2006 a Special Protocol Assessment (SPA) was filed for study PRSW-GN-305 to focus on frequent *nighttime* heartburn (Serial No. 003) and on July 30, 2007 the SAP for this study was filed (Serial No. 020). In this study only, the initial assessment of the 30 mg dose was conducted as part of the Rx-to-OTC development program and allegedly was not intended to support efficacy of 30 mg for the current NDA.

The table below (Table 1-2 in Section 2.7.3 Summary of Clinical Efficacy of the submission) summarizes these studies.

Study No. / # of Sites	**Study objective, population**	**Planned patients**	**Treatment duration**	**Dosage**	**Efficacy endpoints**
PRSW-GN-301/ 35 study sites	efficacy/ safety in target population	576, randomized 1:1 to Lansoprazole 15 mg or placebo	7 day placebo Run-in period, 14 day placebo-controlled Treatment period, 7 day placebo Follow-up period	Treatment period: Lansoprazole 15 mg/day or matching placebo	Primary: proportion of 24-hour days with no heartburn over 14 days. Secondary: proportion of nighttimes with no heartburn over 14 days; proportion of days with no heartburn over Days 1-2; proportion of patients with no heartburn on Day 1.

STATISTICS FILING REVIEW

Study No. / # of Sites	Study objective, population	Planned patients	Treatment duration	Dosage	Efficacy endpoints
PRSW-GN-302/ 37 study sites	efficacy/ safety in target population	576, randomized 1:1 to Lansoprazole 15 mg or placebo	7 day placebo Run-in period, 14 day placebo-controlled Treatment period, 7 day placebo Follow-up period	Treatment period: Lansoprazole 15 mg/day or matching placebo	Primary: proportion of 24-hour days with no heartburn over 14 days. Secondary: proportion of nighttimes with no heartburn over 14 days; proportion of days with no heartburn over Days 1-2; proportion of patients with no heartburn on Day 1.
PRSW-GN-305/ 53 study sites	efficacy/ safety in target population	864, randomized 1:1:1 to Lansoprazole 15 mg, Lansoprazole 30 mg or placebo	7 day placebo Run-in period, 14 day placebo-controlled Treatment period, 7 day placebo Follow-up period	Treatment period: Lansoprazole 15 mg/day, Lansoprazole 30 mg/day or matching placebo	Primary: proportion of nighttimes with no heartburn over 14 days. Secondary: proportion of 24-hour days with no heartburn over 14 days; proportion of patients with no heartburn on Day 1.

Review issues

1. The latest protocols submitted for studies PRSW-GN-301 and PRSW-GN-302 have status labeled as 'Amendment 3' while the latest protocol for study PRSW-GN-305 have status 'Final'. During the review process, we need to clarify whether or not the protocols for the first two studies are the final version and if not, the final protocols should be submitted.
2. The sponsor has submitted the analysis datasets for this NDA in accordance with current eCTD guidance. We should recommend that the sponsor provide electronic analysis programs as well.

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/s/

Freda Cooner
8/28/2008 01:44:29 PM
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Mike Welch
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