

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204655Orig1s000**

**STATISTICAL REVIEW(S)**



## STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

**NDA/Serial Number:** 204655 / 0002  
**Drug Name:** NEXIUM® 24HR (esomeprazole magnesium) Delayed-Release Capsules Over-the-Counter 20 mg  
**Indication(s):** Treatment of frequent heartburn (occurs 2 or more days a week)

**Applicant:** AstraZeneca LP  
**Date(s):** Received: May 30, 2013;  
**Review Priority:** Standard; PDUFA date: March 30, 2014

**Biometrics Division:** Division of Biometrics 3 (DBIII)  
**Statistical Reviewer:** Wen-Jen Chen, Ph.D.  
**Concurring Reviewer:** Mike Welch, PhD, Deputy Director, DBIII

**Medical Division:** Gastroenterology and Inborn Error Products (DGIEP)  
**Clinical Team:** Farrokh Sohrabi, M.D.  
Robert Fiorentino, M.D., Team Leader  
**Project Manager:** Mr. Jeffrey Buchanan

**Statistical Keywords:** Clinical studies; NDA review.

## TABLE OF CONTENTS

<b>1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS</b>	<b>3</b>
1.1 Conclusions and Recommendations	3
1.2 Brief Overview of Clinical Study	3
1.3 Statistical Issues and Findings	3
<b>2.0 INTRODUCTION</b>	<b>4</b>
2.1 Overview	4
2.1.1 D961RC00001	5
2.1.2 D961RC00002	6
2.2 Data Sources	6
<b>3.0 STATISTICAL EVALUATION</b>	<b>6</b>
3.1 Evaluation of Efficacy	6
3.1.1 Study D961RC00001	6
3.1.1.1 Design and Endpoints	6
3.1.1.2 Statistical Methodologies	9
3.1.1.3 Patient Disposition	10
3.1.1.4 Demographics and Baseline Characteristics	12
3.1.1.5 Applicant's Efficacy Analysis Results and Conclusions	14
3.1.1.6 Statistical Reviewer's Analysis and Comments	19
3.1.2 Study D961RC00002	22
3.1.2.1 Design and Endpoints	22
3.1.2.2 Statistical Methodologies	22
3.1.2.3 Patient Disposition	22
3.1.2.4 Demographics and Baseline Characteristics	24
3.1.2.5 Applicant's Efficacy Analysis Results and Conclusions	26
3.1.2.6 Statistical Reviewer's Analysis and Comments	31
3.2 Evaluation of Safety	34
3.2.1 Study D961RC00001	34
3.2.1 Study D961RC00002	34
<b>4.0 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS</b>	<b>35</b>
4.1 Gender, Race, and Age	35
4.1.1 Study D961RC00001	36
4.1.2 Study D961RC00001	37
4.2 Other Special / Subgroup Populations	38
<b>5.0 SUMMARY AND CONCLUSIONS</b>	<b>38</b>
5.1 Statistical Issues and Collective Evidence	38
5.2 Conclusions and Recommendations	<b>40</b>

## 1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

### 1.1 Conclusions and Recommendations

Based upon the analyses performed by this reviewer and the applicant, data from two adequate and well-controlled studies show that, compared to placebo, Nexium 20 mg once daily, demonstrated a statistically significant difference in daily heartburn episodes over a two-week period.

### 1.2 Brief Overview of Clinical Study

The primary objective of the two phase 3, multi-center, randomized, double-blind, placebo controlled studies (D961RC00001 and D961RC00002) were to determine the efficacy of Nexium (esomeprazole) 20 mg once daily (qd) over a 14-day regimen for the treatment of frequent heartburn in subjects likely to self-treat with non-prescription medications without consulting a prescriber.

For each study, the primary endpoint was defined as proportion of days with no heartburn over a 14-day, double-blind treatment period. In study D961RC00001, 168 and 163 subjects were analyzed in the Nexium and placebo groups, respectively; the mean difference between the treatment groups was 13.1% (95% CI 7.44 to 18.68;  $p < 0.0001$ ). In study D961RC00002, 162 and 158 subjects were analyzed in the Nexium and placebo groups, respectively; the mean difference between the treatment groups was 15.3% (95% CI 9.88 to 20.62;  $p < 0.0001$ ).

### 1.3 Statistical Issues and Findings

The comments given below for the two studies (D96RC00001 and D96RC00002) are based upon the applicant's analysis results from the NDA submission (dated May 30, 2013) and the analyses performed by this reviewer using data submitted by the applicant dated September 27, 2013.

The percentage of 24-hour days with no heartburn over 14 days of treatment (the primary endpoint) was analyzed using analysis of covariance (ANCOVA) with treatment and center as factors and frequency of heartburn during the run-in phase as a covariate. The results of the primary endpoint analyzed by ANCOVA for both Studies (D96RC00001 and D96RC00002) showed that the Nexium group was statistically superior compared to placebo.

The reviewer's non-parametric exploratory analysis for the primary endpoint also indicated that the mean percentage of heartburn free 24 days of Nexium was significantly higher than that of placebo ( $p$ -value = 0.0002 for Study D96RC00001 and  $p$ -value  $< 0.0001$  for Study D96RC00002) at the two-sided significance level of 0.05. In addition, from this reviewer's sensitivity analysis based upon the primary endpoint, no study center was considered to

dominate the comparisons of Nexium to placebo. Therefore, the superiority of Nexium to placebo shown by the applicant's primary endpoint analysis can be deemed as statistically convincing.

According to the applicant's and this reviewer's secondary endpoints analyses, the following pre-specified secondary endpoints showed positive results in favor of Nexium:

- 1) Proportion of subjects with heartburn two days or less during the 14-Day randomized period (both Weeks 1 and 2);
- 2) Percentage of 24-hour days with no heartburn during Days 1 through 4 of the the 14-Day treatment period;
- 3) Proportion of subjects with heartburn less than or equal to one day during the last 7 consecutive days of treatment;
- 4) Proportion of subjects with heartburn less than or equal to one day during the second week (days 8 to 14) of treatment;
- 5) Proportion of subjects with heartburn less than or equal to one day during the first week (days 1 to 7) of treatment.

Accordingly, based upon this reviewer's and the applicant's analyses, the data submitted by the applicant support Nexium efficacy as assessed by the secondary endpoints. However, the appropriateness of the secondary endpoints for labeling purposes should be assessed by the clinical team.

## **2.0 INTRODUCTION**

### **2.1 Overview**

NEXIUM® (esomeprazole magnesium) Delayed-Release Capsules (NDA 21-153) was approved by the Agency on February 20, 2001 and is currently indicated for the treatment of gastro-esophageal reflux disease (GERD); risk reduction of NSAID-associated gastric ulcer; H. pylori eradication to reduce the risk of duodenal ulcer recurrence; and pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

On August 13, 2012, AstraZeneca announced that it has entered into an agreement with Pfizer Inc. for the OTC rights for Nexium. Pfizer has exclusive rights to market Nexium OTC in the United States. AstraZeneca will continue to hold the IND and NDA and is filing the NDA on behalf of the alliance.

Accordingly, the purpose of this submission is to support the efficacy of esomeprazole 20 mg once daily (qd) over a 14-day regimen for OTC treatment of subjects with frequent heartburn who are likely to self-treat with non-prescription medications.

During initial review of this NDA submission, several deficiencies were noted. Besides unclear data set definitions and documentation, the following were noted:

- The full analysis set (FAS) defined as all randomized subjects who took at least one dose of randomized treatment, had a valid baseline heartburn assessment and at least one valid post-baseline heartburn assessment was used as primary analysis for the efficacy comparisons. Thus the FAS population may be a biased representation of the target population;
- Regarding the secondary endpoint #2. Instead of comparing percentages of heartburn free days between two treatment groups for Days 1 through 4, the applicant compared the proportions of subjects with heartburn free 24-hour days over Days 1 to 4, as an alternative analysis.
- The reviewer determined that the ANCOVA model used for the primary endpoint analysis may have included unnecessary parameters (e.g., center). In addition, the assumption of the data distribution used for the ANCOVA method may not have been met.

In order to address these issues, in the 74 days letter dated August 06, 2012, the Agency requested AstraZeneca perform the following analyses using a modified intent to treat (MITT) population defined as all randomized patients who took at least one post randomization dose:

- Perform efficacy analysis on the percentage of days with no heartburn on Days 1 through 4 of the 14- day treatment period using the FAS and MITT populations.
- For the primary endpoint, perform a blocked, two-sample Wilcoxon rank sum (WRS) test (i.e., the van Elteren test), stratified by US and non-US if applicable, to assess treatment group differences.

The applicant's response to the 74 days letter and new datasets for the requested efficacy analyses were received by the Agency on September 27, 2013.

Overviews of the design for Studies D961RC00001 and D961RC00002 are presented as follows.

#### 2.1.1 Study D961RC00001

The primary objective of this Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel group study was to determine the efficacy of esomeprazole 20 mg once daily (qd) over a 14-day regimen for the treatment of frequent heartburn in subjects likely to self-treat with non-prescription medications without consulting a prescriber and without a confirmed GERD diagnosis.

The phases of the study consisted of Placebo Run-in (Day-8 to Day-1), Randomization (Day 0), Double-blind treatment period (Day 1 to Day 14), and Placebo Follow-up (Day 15 to Day 22).

The primary endpoint was defined as proportion of days with no heartburn over the 14-day treatment.

The secondary endpoints are listed below:

- Proportion of subjects with heartburn two days or less during the 14-day randomized period (both Weeks 1 and 2);
- Percentage of 24-hour days with no heartburn on Days 1 through 4 of the treatment phase;
- Proportion of subjects with heartburn less than or equal to one day during the last 7 consecutive days of treatment;
- Proportion of subjects with heartburn less than or equal to one day during the second week (days 8 to 14) of treatment;
- Proportion of subjects with heartburn less than or equal to one day during the first week (days 1 to 7) of treatment.

Randomization codes were assigned as subjects became eligible for randomization. Randomization via Interactive Voice Response System (IVRS) was stratified by center. Subjects were randomized to either esomeprazole 20 mg or placebo to examine efficacy as measured by the proportion of days with no heartburn during the 14 day study treatment. Approximately 500 subjects were planned to be enrolled and 300 subjects, 150 to each group, were to be randomized into the study. For further detail, see Section 3.1.1.1.

#### 2.1.2 Study D961RC00002

The primary objective and study design (including primary and secondary endpoints) of this study were the same as that of Study D961RC00001. For further detail, refer to Section 3.1.2.1.

## 2.2 Data Sources

To assess the clinical efficacy of the two Studies (D961RC00001 and D961RC00002) used in support of the labeling indication claim, this reviewer reviewed the original electronic NDA supplement submission, dated 05/30/2013 and located at “\\CDSESUB1\EVSPROD\NDA204655\204655.enx”.

## 3.0 STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

#### 3.1.1 Study D961RC00001

##### 3.1.1.1 Design and Endpoints

The primary objective of this phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel group study was to determine the efficacy of Nexium (esomeprazole) 20 mg Once daily (qd) over a 14-day regimen for the treatment of frequent heartburn in subjects likely to self-treat with non-prescription medications without consulting a prescriber and without a confirmed GERD diagnosis.

Approximately 500 subjects were planned to be enrolled and 300 subjects, 150 to each group, were to be randomized into this study. For sample size determination, the applicant indicated that in a previous similar lansoprazole study there was a 14% difference between treatments (active–placebo) in heartburn free days over the 14-day treatment period with a standard deviation of approximately 30%. Based on this data, assuming a similar effect, 120 evaluable subjects per treatment group would provide 95% power at an alpha level=0.05 (2-sided). In order to account for the combined effect of early discontinuation and missing data 150 subjects per treatment group were planned to be randomized into the study.

The phases of the study consisted of the following periods:

- **Placebo Run-in (Day-8 to Day-1):** Subjects, who met all the inclusion criteria, satisfactorily completed the screening assessments and completed the wash-out from any antacid, H2 receptor antagonist (H2RA), or PPI use, entered a single blind, 1-week placebo run-in period as baseline. During the run-in, all the subjects completed a daily diary via interactive voice response system (IVRS) to document heartburn symptoms during the previous 24-hour period. Subjects began taking the placebo run-in medication on Day -7 and began reporting heartburn symptoms on Day -6 and at each subsequent 24-hour period through Day 0.
- **Randomization (Day 0):** At the end of the placebo run-in period, subjects returned to the investigational center for possible randomization in the study. Subjects who reported at least one episode of heartburn during two separate 24-hour periods (two episodes of heartburn in total) in the run-in period were randomized into a double-blind treatment period. Total 300 eligible subjects who met inclusion but not exclusion criteria were randomized into esomeprazole or placebo in 1:1 ratio.

Randomization schedules were generated and kept by AstraZeneca. Randomization codes were assigned as subjects became eligible for randomization. Randomization via IVRS was stratified by center.

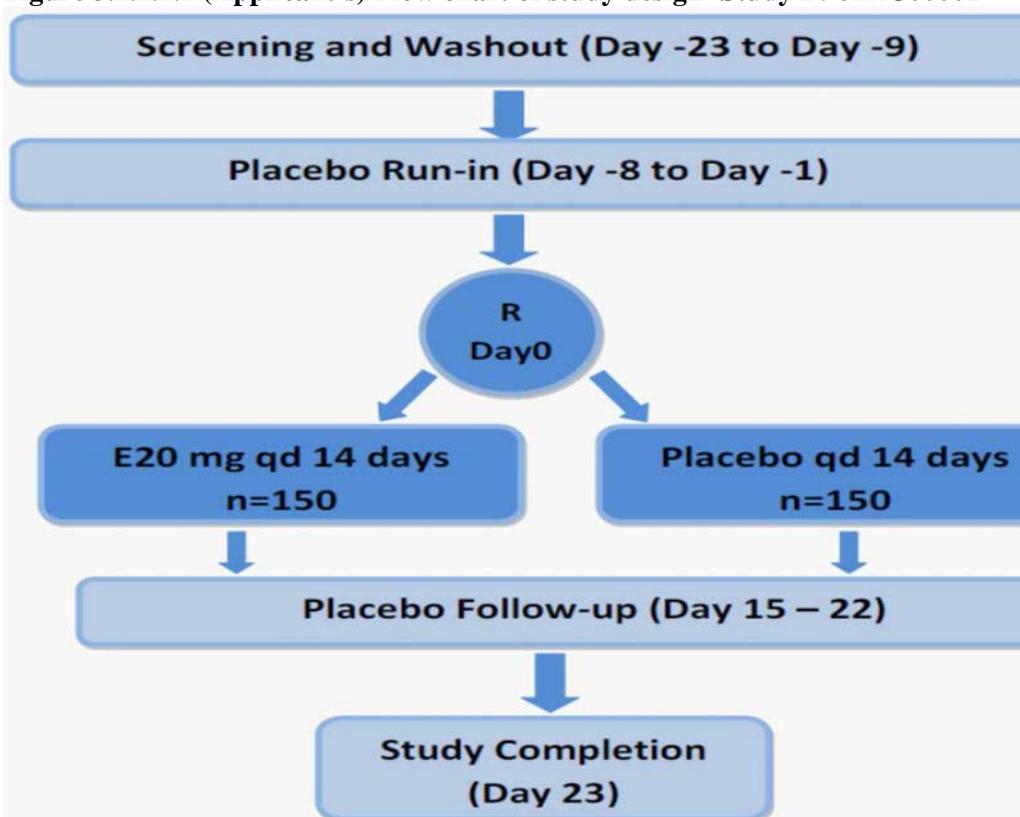
- **Double-blind treatment period (Day 1 to Day 14):** All randomized subjects received a 14-day regimen of esomeprazole 20 mg qd capsule or matching placebo. Subjects continued to record daily heartburn symptoms in IVRS for the previous 24-hour period during the 14-day treatment regimen. Subjects started taking study investigational products (IP) on Day 1 and began reporting symptoms on Day 2 and at each subsequent 24-hour period through Day 15. At the end of the 14-day study treatment regimen, subjects returned to the investigational center for assessments on Day 15.

Also on the same day (Day 15) subjects answered Global Assessment Questions (GASTQ) in order to measure satisfaction with the study IP over the previous 14-days.

- **Placebo Follow-up (Day 15 to Day 22):** Subjects entered a single-blind, 1-week placebo follow-up period from Day 15 to Day 22. Subjects began taking placebo on Day 16 and continued to record heartburn symptoms beginning Day 17 via IVRS during the follow-up period through Day 23. Subjects returned to the investigational center for final assessments (Study Completion) on Day 23.

Figure 3.1.1.1.1 shows the study design and the sequence of treatment periods.

**Figure 3.1.1.1.1 (Applicant's) Flow chart of study design- Study D961RC00001**



Source: Figure 1 at page 19 in Study D961RC00001 Report

The primary endpoint was defined as the proportion of days with no heartburn over the 14-day treatment. For example, if a subject had 5 heartburn free 24-hour days during 14 days then the percentage of heartburn free 24-hour would be  $(5/14) \times 100 = 35.75$ .

The secondary endpoints are listed below:

- Proportion of subjects with heartburn two days or less during the 14-day treatment period (both Weeks 1 and 2);

- Percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase;
- Proportion of subjects with heartburn less than or equal to one day during the last 7 consecutive days of treatment;
- Proportion of subjects with heartburn less than or equal to one day during the second week (days 8 to 14) of treatment.
- Proportion of subjects with heartburn less than or equal to one day during the first week (days 1 to 7) of treatment.

### 3.1.1.2 Statistical Methodologies

The following defines the analysis data sets used in this review:

Full analysis set (FAS): All randomized subjects who took at least one dose of randomized treatment, had a valid baseline heartburn assessment, and at least one valid post-baseline heartburn assessment. Subjects were classified according to randomized treatment. This analysis set was used for all confirmatory efficacy analyses.

Per-protocol (PP) analysis set: A subset of the FAS excluding data from subjects with important protocol deviations.

Safety Population: Subjects who received at least one dose of study medication. This was the primary population for all safety assessments.

The applicant indicated that the null hypothesis for efficacy assessments in this study was that there would be no difference between the placebo and Nexium groups for the assessed variables. The alternative hypothesis was that the two groups would differ for the assessed variables. All analyses were based on a two-sided test at the significance level of 0.05. Nominal P values were reported without any adjustment for multiple endpoints.

For the primary endpoint, missing data were handled as follows:

$Y = [\text{number of 24-hour days with no heartburn} + m \cdot (\text{proportion of 24-hour days with no heartburn during the run-in phase})] / 14$ ; where  $m$  = the number of days with missing data.

A sensitivity analysis was performed where subject missing data were assumed to be days with heartburn. As a result, when calculating the proportion of subjects who were heartburn free for a given day, subjects without data for that day were assumed to have had heartburn.

The percentage of 24-hour days with no heartburn over 14 days of treatment (expressed as percentages and analyzed as a continuous variable) was analyzed using analysis of covariance (ANCOVA) including treatment and center as factors and frequency of

heartburn during the run-in phase as a covariate. Model-based point estimates, 95% confidence intervals and two-sided p-value were reported.

For the secondary endpoints regarding the proportion of subjects with resolution of frequent heartburn, the treatment comparisons were based on a chi-square test. Missing diary days were treated as days with heartburn. For the percentages of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase, the applicant indicated (in the SAP) that the counts of 24-hour days with no heartburn over Days 1 to 4 were to be analyzed using a proportional odds model (i.e., cumulative logit model) for ordinal outcomes (via SAS PROC LOGISTIC) with treatment as factor and the baseline results as a covariate. The results were to be expressed in terms of an odds ratio and its associated CI.

A hierarchical testing procedure was used to control the study-wise type I error rate. The primary and secondary efficacy variables were analyzed sequentially in the following order:

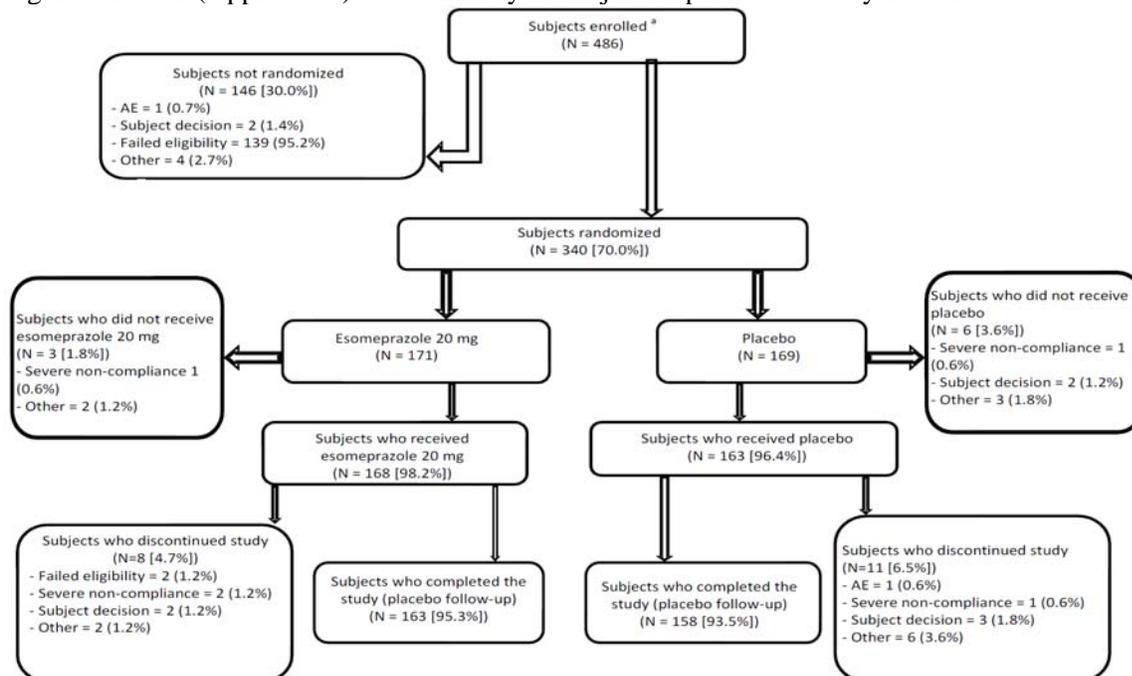
- 1) Percentage of 24-hour days with no heartburn during 14-days of treatment (primary efficacy variable);
- 2) Proportion of subjects with heartburn two days or less during the 14-day randomized period (both Weeks 1 and 2);
- 3) Percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase;
- 4) Proportion of subjects with heartburn less than or equal to one day during the last 7 consecutive days of treatment.
- 5) Proportion of subjects with heartburn less than or equal to one day during the second week (days 8 to 14) of treatment.
- 6) Proportion of subjects with heartburn less than or equal to one day during the first week (days 1 to 7) of treatment.

When a test resulted in statistically insignificant result, the next test in the sequence was not to be carried out.

### 3.1.1.3 Patient Disposition

The first subject was enrolled on August 11, 2011 and the last subject's last visit was on October 19, 2011. Disposition of all the randomized subjects in this study is summarized in Figure 3.1.1.3.1.

Figure 3.1.1.3.1 (Applicant's) Summary of subject disposition – Study D961RC00001



<sup>a</sup>: All subjects who provided informed consent.

Source: Figure 2 at page 42 in the D961RC00001 Report.

From 486 enrolled subjects who signed an informed consent, 340 (70.0%) subjects were randomized in the study (171 and 169 subjects in esomeprazole 20 mg and placebo groups, respectively). In total, 146 (30.0%) of enrolled subjects were not randomized as most of these subjects (139 [95.2%]) did not fulfill the eligibility criteria. Of the 171 subjects randomized to the esomeprazole 20 mg group, 168 (98.2%) subjects received esomeprazole 20 mg and 3 (1.8%) subjects did not receive esomeprazole 20 mg. Of the 169 subjects randomized to the placebo group, 163 (96.4%) subjects received placebo and 6 (3.6%) subjects did not receive placebo.

In total, 163 (95.3%) of the randomized subjects in the esomeprazole 20 mg group and 158 (93.5%) of the randomized subjects in the placebo group completed the study and returned for Visit 5 assessment at Day 23 (i.e., study completion). However, a total of 8 (4.7%) and 11 (6.5%) of the randomized subjects in the esomeprazole 20 mg and placebo groups, respectively discontinued the study. The main reasons for discontinuation from the study in the esomeprazole 20 mg group were subject decision (2 [1.2%] subjects), eligibility criteria not fulfilled (2 [1.2%] subjects), severe non-compliance to the protocol as determined by the investigator (2 [1.2%] subjects), and other reasons (2 [1.2%] subjects). The main reasons for discontinuation from the study in the placebo group were other reasons (6 [3.6%] subjects), subject decision (3 [1.8%] subjects), AE (1 [0.6%] subject), and severe non-compliance to the protocol (1 [0.6%] subject).

Finally, the applicant indicated that the treatment groups were well balanced with regards to subject disposition. Table 3.1.1.3.1 below presents subjects disposition.

**Table 3.1.1.3.1 (Applicant's) Subjects disposition - Study D961RC00001**

	Number (%) of subjects		
	Esomepra zole 20 mg	Placebo	Total
Subjects Enrolled <sup>a</sup>			486
Subjects Who Were Not Randomized			146 (30.0)
Withdrawn From Study Due To Adverse Event			1 (0.7)
Withdrawn From Study Due To Eligibility Criteria Not Fulfilled			139 (95.2)
Withdrawn From Study Due To Subject Decision			2 (1.4)
Withdrawn From Study Due To Other			4 (2.7)
Subjects Randomized	171	169	340 (70.0)
Subjects Who Received Treatment	168 (98.2)	163 (96.4)	331 (97.4)
Subjects Who Did Not Receive Treatment	3 (1.8)	6 (3.6)	9 (2.6)
Withdrawn From Study Due To Severe Non- Compliance To Protocol	1 (0.6)	1 (0.6)	2 (0.6)
Withdrawn From Study Due To Subject Decision	0 (0.0)	2 (1.2)	2 (0.6)
Withdrawn From Study Due To Other	2 (1.2)	3 (1.8)	5 (1.5)
Subjects Who Completed Study	163 (95.3)	158 (93.5)	321 (94.4)
Subjects Who Discontinued Study	8 (4.7)	11 (6.5)	19 (5.6)
Subject Decision	2 (1.2)	3 (1.8)	5 (1.5)
Eligibility criteria not fulfilled	2 (1.2)	0 (0.0)	2 (0.6)
Adverse event	0 (0.0)	1 (0.6)	1 (0.3)
Severe non-compliance to protocol	2 (1.2)	1 (0.6)	3 (0.9)
Other	2 (1.2)	6 (3.6)	8 (2.4)

<sup>a</sup>: All subjects who provided informed consent.

Source: Table 7 at page 43 in Study D961RC00001 Report.

#### 3.1.1.4 Demographics and Baseline Characteristics

The target population for the study was male and female subjects aged  $\geq 18$  years with frequent heartburn occurring  $\geq 2$  days per week, without a confirmed GERD diagnosis. The mean age was 43.6 years (range: 19.0 to 73.0 years) for the esomeprazole 20 mg group and 45.9 years (range: 19.0 to 85.0 years) for the placebo group. The majority of the subjects were White (101 [60.12%] and 108 [66.26%] subjects in the esomeprazole 20 mg and placebo groups, respectively) or Black/African American (64 [38.10%] in the esomeprazole treatment group and 53 [32.52%] in the placebo group).

A higher number of female subjects were randomized in the study as compared to male subjects (104 [61.90%] versus 64 [38.10%] in the esomeprazole 20 mg group and 95 [58.28%] versus 68 [41.72%] in the placebo group, respectively).

The applicant indicated that the treatment groups were well balanced for demographic characteristics with respect to the gender, age, race, and ethnicity and the study population was representative of the intended target population. Table 3.1.1.4.1 summarizes the results.

**Table 3.1.1.4.1 (Applicant's) Key Demographic and Baseline characteristics (Full Analysis Set) - Study D961RC00001**

Demographic characteristic		Esomeprazole 20 mg (N=168)	Placebo (N=163)
Age(years)	n	168	163
	Mean	43.6	45.9
	SD	12.2	12.6
	Median	43.0	46.0
	Min	19.0	19.0
	Max	73.0	85.0
Sex n (%)	F	104 (61.90)	95 (58.28)
	M	64 (38.10)	68 (41.72)
	Total	168 (100.0)	163 (100.0)
Race n (%)	WHITE	101 (60.12)	108 (66.26)
	BLACK OR AFRICAN AMERICAN	64 (38.10)	53 (32.52)
	ASIAN	0 (0.00)	1 (0.61)
	AMERICAN INDIAN/ALASKA NATIVE	1 (0.60)	0 (0.00)
	OTHER	2 (1.19)	1 (0.61)
	Total	168 (100.0)	163 (100.0)
Ethnic Group n (%)	HISPANIC OR LATINO	34 (20.24)	25 (15.34)
	NOT HISPANIC OR LATINO	56 (33.33)	57 (34.97)
	NOT REPORTED	78 (46.43)	81 (49.69)
	Total	168 (100.0)	163 (100.0)

F: Female; M: Male; SD Standard Deviation.

Source: Table 10 at page 47 in Study D961RC00001 Report.

Finally, the summary of medical history for heartburn symptoms at baseline of subjects in the FAS is presented in Table 3.1.1.4.2.

**Table 3.1.1.4.2 (Applicant's) Summary of subjects heartburn medical history at baseline (Full Analysis Set) - Study D961RC00001**

		Number(%) of Subjects	
		Esomeprazole 20 mg (N=168)	Placebo (N=163)
Days with heartburn in the last month	Mean	14.21	15.74
	Median	12.00	15.00
	SD	5.48	5.88
	Min	5.00	8.00
	Max	30.00	30.00
Rating of most intense heartburn	Mild	15(8.93)	12(7.36)
	Moderate	95(56.55)	95(58.28)
	Severe	58(34.52)	56(34.36)
Heartburn caused by food/beverage	Yes	162(96.43)	158(96.93)
Heartburn caused by stress/anxiety	Yes	81(48.21)	83(50.92)
Heartburn caused by lying down	Yes	103(61.31)	89(54.60)
Heartburn caused by physical activity	Yes	26(15.48)	26(15.95)
Heartburn caused by hectic lifestyle	Yes	42(25.00)	38(23.31)
Heartburn caused by medication	Yes	4(2.38)	8(4.91)
Received OTC/prescribed heartburn medication in past 5 years	No	21(12.50)	15(9.20)
	Yes	147(87.50)	148(90.80)

OTC: Over-the-counter; SD Standard Deviation.

Source: Table 11 at page 48 in Study D961RC00001

Based upon Table 3.1.1.4.2, the applicant indicated that the mean frequency of days with heartburn in the last month was 14.21 (equates to 3.26 days/week, range 5 to 30 days) in the esomeprazole 20 mg group and 15.74 (equates to 3.61 days/week, range 8 to 30 days) in the placebo group. In total, 58 (34.52%) subjects in the esomeprazole 20 mg group and 56 (34.36%) subjects in the placebo group rated their most intense heartburn as severe during last month before enrollment. The most common cause of heartburn was food/beverages observed in 162 (96.43%) subjects in the esomeprazole 20 mg group and 158 (96.93%) subjects in the placebo group. In addition, based upon Table 51 at page 251 of the study report, the percentages of heart burn free 24-hour days between Nexium and placebo during the run-in period were numerically similar (means 18% and 19%, respectively for Nexium and placebo).

### 3.1.1.5 Applicant's Efficacy Analysis Results and Conclusions

The applicant indicated that all efficacy analyses were performed using the FAS. The primary and secondary efficacy variables were analyzed sequentially. A hierarchical testing procedure was used to control the type I error for the primary and secondary endpoints based upon the order presented below.

The following efficacy analysis results regarding the primary and secondary endpoints are copied from the NDA study report.

## 1) Primary endpoint analysis

The primary endpoint was the percentage of heartburn free 24-hour days over 14 days of randomized treatment period and was analyzed by ANCOVA with centers and treatment as fixed effects and frequency of heartburn during the run-in phase as a covariate.

Table 3.1.1.5.1 presents the efficacy analysis results.

**Table 3.1.1.5.1 (Applicant's) Percentage of heartburn-free 24-hour days during 14 days of treatment by treatment group using FAS population - Study D961RC00001**

Variable	Esomeprazole 20mg (N=168) LS Mean (SE)		Placebo (N=163) LS Mean (SE)		Difference between groups <sup>a</sup>		
	n		n		LS Mean (SE)	95% CI	p-value
Percentage heartburn free 24 hour day	168	46.13( 2.24)	163	33.07( 2.26)	13.06( 2.86)	(7.44,18.68)	< 0.0001

<sup>a</sup> Obtained from analysis of covariance with centers and treatment as fixed effects and frequency of heartburn during the run-in phase as a covariate.

Missing values were imputed based on the run-in phase data;

ANCOVA Analysis of covariance; CI Confidence interval; LS Least square; SE Standard error;

n- number of subjects included in the analysis.

Source: Table 14 at page 56 in Study D961RC00001 Report

Based upon Table 3.1.1.5.1, the applicant indicated that the percentage of heartburn free 24-hour days over 14 days of randomized treatment period was statistically significantly higher in subjects receiving esomeprazole 20 mg (46.13%) as compared to placebo (33.07%). The least square (LS) mean difference between the treatment groups was 13.06% (95% CI 7.44 to 18.68; p<0.0001).

In addition, based upon the applicant's analysis results using the PP data set, the percentage of heartburn free 24-hour days over 14 days was also statistically significantly higher in subjects receiving esomeprazole 20 mg (47.51%) as compared to placebo (34.36%). The LS mean difference between the treatment groups was 13.15% (95% CI 7.24 to 19.06; p<0.0001).

Finally, for the sensitivity analysis (imputing missing data for a given day as a heartburn event) using the FAS population, the percentage of heartburn free 24-hour days during 14 days of treatment period for esomeprazole 20 mg was statistically significantly higher than that for placebo. The LS mean difference between the treatment groups was 12.50% (43.47% versus 30.97%; p<0.0001).

## 2) Secondary endpoint analysis

- Proportion of subjects with heartburn two days or less during the 14 days randomized treatment period (both weeks 1 and 2)

Table 3.1.1.5.2 presents the result of comparing proportions of patients with resolution of frequent heartburn defined as heartburn two days or less for the 14 days of treatment period of the study between esomeprazole 20 mg and placebo groups in subjects from FAS population.

**Table 3.1.1.5.2 (Applicant's) Percentage of subjects with two or less days of heartburn during 14 days of treatment phase using the FAS population - Study D961RC00001**

Group	N	Number (%) of subjects with resolution of frequent heartburn	Comparison between groups <sup>a</sup> --		
			Relative Risk	95% CI	p-value
Esomeprazole 20mg	168	27(16.07)	3.74	( 1.68, 8.35)	0.0004
Placebo	163	7( 4.29)			

<sup>a</sup> The treatment group proportions compared using a chi-square test.

Missing values were handled as stated in the protocol, i.e., missing days assumed as days with heartburn.

A relative risk > 1 shows esomeprazole 20 mg has a favorable outcome compared to placebo.

N-Number of subjects.

Source: Table 18 at page 57 in Study D961RC00001 Report

The applicant indicated that the proportion of subjects with resolution of frequent heartburn (defined as  $\leq$  2 days with heartburn) during 14 days treatment period was statistically significantly higher in subjects receiving esomeprazole 20 mg (16.07%) compared to placebo (4.29%) (RR=3.74, 95% CI 1.68 to 8.35; p=0.0004).

- Percentage of heartburn free 24-hour days over Days 1 to 4

In Sub-section 7.1.2.2 of the Clinical Study Report, titled "Percentage of heartburn free 24-hour days over days one to four", instead of comparing the percentages of heartburn free days over Days 1 to 4 during the 14 day treatment period, the applicant used a proportional odds model to compare the counts of subjects with heartburn free 24-hour days over Days 1 to 4 of the 14 day treatment period.

In addition, since the proportional odds assumption for the proportional odds model was not met (Score test for the Proportional Odds Assumption;  $p < 0.001$ ), by the method specified in the SAP, the applicant performed the logistic regression analysis on the binary data by dichotomizing patients into two categories: patients with zero or one day heartburn free versus two, three, or four days heartburn free.

The results of the binary data analysis are presented below.

**Table 3.1.1.5.3 (Applicant's) Percentage of subjects without heartburn - one day or more during Days 1 to 4 between esomeprazole 20 mg and placebo using the FAS population. - Study D961RC00001**

Groups	N	Number (%) of subjects		Comparison between groups <sup>a</sup>	
		(0 or 1 Day)	(2, 3 or 4 Days)	Odds ratio (95% CI)	p-value
Esomeprazole 20mg	168	89(52.98)	79(47.02)	2.76( 1.60, 4.75)	0.0003
Placebo	163	112(68.71)	51(31.29)		

a: Logistic regression with treatment as a factor; the baseline results as a covariate.

Note: Since the proportional odds assumption not met, the analysis was performed by categorizing the data in (0,1) and (2,3,4).

Source: Table 52 at page 251 in Study D961RC00001

Based upon Table 3.1.1.5.3, the applicant indicated that the results showed a statistically significant in favor of esomeprazole 20 mg (OR =2.76, 95% CI 1.60 to 4.75; p=0.0003).

In addition, based upon the applicant's document dated September 27, 2013, in response to our request for an ANCOVA analysis of the percentage of days with no heartburn over Days 1-4 of the treatment period, the percentage of days with no heartburn for esomeprazole 20 mg was significantly higher than that of placebo (LS Mean difference 8.2%, 95%, CI (1.89%, 14.52%), p=0.011).

- Resolution of frequent heartburn for a given week

#### Analysis on the final week of treatment

A comparison of the proportion of subjects with heartburn less than or equal to one day during the final week of treatment is presented in Table 3.1.1.5.4. The final week of treatment was defined as the last 7 consecutive days when subjects were on randomized investigational products.

**Table 3.1.1.5.4 (Applicant's) Percentage of subjects with heartburn one day or less during the final week of treatment using the FAS population - Study D961RC00001**

Group	N	Number (%) of subjects with resolution of frequent heartburn	Comparison between groups <sup>a</sup> --		
			Relative Risk	95% CI	p-value
Esomeprazole 20mg	168	43(25.60)	2.45	( 1.46, 4.12)	0.0003
Placebo	163	17(10.43)			

<sup>a</sup> The treatment group proportions compared by using a chi-square test.

Missing values were handled as stated in the protocol, i.e., missing days assumed as days with heartburn.

A relative risk >1 shows esomeprazole 20 mg has a favorable outcome compared to placebo.

N-Number of subjects.

Source: Table 20 at page 60 in Study D961RC00001 Report

Based upon Table 3.1.1.5.4, the applicant indicated that there was a statistically significant difference in the proportion of subjects who experienced resolution of frequent heartburn in the last 7 calendar days of the treatment period of the study between the esomeprazole 20 mg (25.60%) and placebo (10.43%) treatment groups (RR=2.45, 95% CI 1.46 to 4.12; p=0.0003).

#### Analysis on the second week of treatment

A comparison of the proportion of subjects with heartburn less than or equal to one day during the second week of treatment is presented in Table 3.1.1.5.5. The second week of treatment was defined as Days 8 to 14 of the two-week treatment period.

**Table 3.1.1.5.5 (Applicant's) Percentage of subjects with heartburn one day or less during the second week of treatment using the FAS population - Study D961RC00001**

Group	N	Number (%) of subjects with resolution of frequent heartburn	Comparison between groups <sup>a</sup> ---		
			Relative Risk	95% CI	p-value
Esomeprazole 20mg	168	43( 25.60)	2.61	( 1.53, 4.44)	0.0002
Placebo	163	16( 9.82)			

<sup>a</sup> The treatment group proportion compared by using a chi-square test.

Missing values were handled as stated in the protocol, i.e., missing days assumed as days with heartburn.

A relative risk > 1 shows Esomeprazole 20 mg has a favorable outcome compared to placebo.

N-Number of subjects.

Source: Table 21 at page 61 in Study D961RC00001 Report.

Based upon Table 3.1.1.5.5, the applicant indicated that there was a statistically significant difference in the proportion of subjects who experienced resolution of frequent heartburn in the second week of the treatment phase of the study between the esomeprazole 20 mg (25.60%) and placebo (9.82%) treatment groups (RR=2.61, 95% CI 1.53 to 4.44; p=0.0002).

### Analysis on the first week of treatment

A comparison of the proportion of subjects with heartburn less than or equal to one day during the first week of treatment is presented in Table 3.1.1.5.6. The first week of treatment was defined as the first 7 calendar days of the treatment phase of the study (between Visit 3 and Visit 4; Days 1 through 7).

**Table 3.1.1.5.6 (Applicant's) Percentage of subjects with heartburn one day or less during the first week of treatment using the FAS population - Study D961RC00001**

Group	N	Number (%) of subjects with resolution of frequent heartburn	Comparison between groups <sup>a</sup> -----		
			Relative Risk	95% CI	p-value
Esomeprazole 20mg	168	26(15.48)	2.52	( 1.26, 5.06)	0.0064
Placebo	163	10( 6.13)			

a The treatment group proportions compared by using a chi-square test.

Missing values were handled as stated in the protocol, i.e., missing days assumed as days with heartburn.

A relative risk > 1 shows esomeprazole 20 mg has a favorable outcome compared to placebo.

Source: Table 22 at page 61 in Study D961RC00001 Report.

Based upon Table 3.1.1.5.6, the applicant indicated that there was a statistically significant difference in the proportion of subjects who experienced resolution of frequent heartburn in the first 7 calendar days of treatment phase of the study between the esomeprazole 20 mg (15.48%) and placebo (6.13%) treatment groups (RR=2.52, 95% CI 1.26 to 5.06; p=0.0064).

#### 3.1.1.6 Statistical Reviewer's Analysis and Comments

In order to validate the applicant's claim on the superiority of Nexium to placebo, this reviewer performs the following analyses: i) non-parametric analysis for the primary endpoint, ii) efficacy comparison by center, and iii) analysis for the percentage of 24-hour days with no heartburn during Days 1 through 4 of the 14 days treatment period (one of the secondary endpoints). Then, this reviewer will give a comment on the overall strength of efficacy of Nexium according to the evidence provided by the study.

Based upon the applicant's response (dated September, 27, 2014) to the Agency information request, the MITT and FAS populations are the same (i.e., there were no randomized subjects who took study drug and did not have post-baseline data). Accordingly, for this study, the FAS population is used by this reviewer to perform the efficacy analyses.

#### Statistical Reviewer's Analysis

##### i) Non-parametric analysis - Primary endpoint

The ANCOVA model used for the primary endpoint (percentage of heartburn free days during the 14 days treatment period) analysis may include unnecessary parameters and the

assumption of the data distribution used for the ANCOVA model-based method may not be met. In order to validate the ANCOVA analysis results assessed by the primary endpoint, this reviewer applies a non-parametric method (Wilcoxon rank sum test) to compare the efficacy between Nexium and placebo. The non-parametric analysis result performed by this reviewer is the same as that of performed by the applicant and reported in the response documents to the 74 days letter. Table 3.1.1.6.1 presents the result of non-parametric analysis using FAS population.

**Table 3.1.1.6.1 (Reviewer's) Efficacy comparison by a non-parametric method using the FAS population - Study D961RC00001**

Endpoint	Treatment	N	Mean %	P-value <sup>a</sup>
Percentage of heartburn free days during treatment period	Nexium	168	46.13%	0.0002
	Placebo	163	33.07%	

a: Wilcoxon rank sum test.

Table 3.1.1.6.1 indicates that the mean percentage for Nexium is significantly higher than that for placebo (p-value = 0.0002) at a two-sided significance level of 0.05.

ii) Efficacy comparison by center – Primary endpoint

In the efficacy comparison by center, this reviewer compares the efficacy of Nexium versus placebo based upon the percentage of heartburn free 24-hour days over 14 days of randomized treatment period by center. Table 3.1.1.6.2 presents the analysis results. Data used in this analysis was submitted on 09/27/2013.

**Table 3.1.1.6.2 (Reviewer's) Mean percentage of heartburn free 24-hour days in the treatment period by center using the FAS population - Study D961RC00001**

CENTER NUMBER	NEXIUM (N) % FREE DAY	PLACEBO (P) % FREE DAY	% DIF. N - P	CENTER NUMBER	NEXIUM (N) % FREE DAY	PLACEBO (P) % FREE DAY	DIF. N - P
Center 7801	67.0%	50.0%	7.0%	Center 7807	22.0%	22.2%	-0.2%
Center 7802	34.3%	28.4%	5.9%	Center 7808	18.6%	20.5%	-1.9%
Center 7803	31.3%	31.3%	0.0%	Center 7809	42.8%	33.7%	9.1%
Center 7804	43.7%	19.5%	24.2%	Center 7810	29.0%	39.5%	-10.5%
Center 7805	76.4%	33.5%	42.9%				
Center 7806	55.7%	31.5%	24.2%	Total	46.1%	33.1%	13.0%

Note: twenty subjects enrolled in center 7805.

Based upon the results from Table 3.1.1.6.2, except for center 7805, no center demonstrates that the percentage of heartburn free for Nexium is around 40% higher than that of placebo. However, after removing data from center 7805, the mean percentage of heartburn free 24 hour days during treatment period for the Nexium group remained significantly higher than that of placebo group (p=0.0012) using non-parametric (Wilcoxon rank sum test) method.

- iii) Analysis on the percentage of heartburn free days on Days 1 through 4 of the treatment period

In the initial submission the applicant compared the counts (instead of the percentages) of heartburn-free days during Days 1 through 4 of the 14-day treatment period. In order to ensure that Nexium is adequately assessed by this endpoint, this reviewer applied a non-parametric method (Wilcoxon rank sum test) to compare the efficacy of Nexium and placebo as assessed by this endpoint. The result of the non-parametric method is presented in Table 3.1.1.6.3.

**Table 3.1.1.6.3 (Reviewer's) Efficacy comparison by a non-parametric method using the FAS population- Study D961RC00001**

Endpoint	Treatment	N	Mean %	P-value <sup>a</sup>
Percentage of heartburn free 24-hour days on Days 1 through 4 of the treatment period	Nexium	168	38.64%	0.022
	Placebo	163	29.54%	

a: Two-sided Wilcoxon rank sum test.

Table 3.1.1.6.3 indicates that the mean percentage of Nexium is significantly higher than that of placebo (p-value = 0.022) at two-sided significance level of 0.05.

#### Statistical Reviewer's Comments on the Strength of Nexium Efficacy

This reviewer's non-parametric analysis for the primary endpoint indicates that the mean percentage of heartburn free 24 days of Nexium is significantly higher than that of placebo (p-value = 0.0002) at a two-sided significance level of 0.05. In addition, from this reviewer's sensitivity analysis based upon the primary endpoint, no center is considered to dominate the superiority of Nexium to placebo. Therefore, the applicant's analysis results for the superiority of Nexium to placebo assessed by the primary endpoint can be deemed as statistically convincing.

According to the applicant's and this reviewer's secondary endpoint analyses, the following pre-specified secondary endpoints were positive in favor of Nexium:

- 1) Proportion of subjects with heartburn two days or less during the 14-Day randomized period (both Weeks 1 and 2);
- 2) Percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase;
- 3) Proportion of subjects with heartburn on one day or less during the last 7 consecutive days of treatment.
- 4) Proportion of subjects with heartburn on one day or less during the second week (days 8 to 14) of treatment.

- 5) Proportion of subjects with heartburn on one day or less during the first week (days 1 to 7) of treatment.

Accordingly, this reviewer's and the applicant's analysis results on the pre-specified secondary endpoints support the efficacy of Nexium compared to placebo.

### 3.1.2 Study D961RC00002

The study design (including primary and secondary endpoints) of this study were the same as that of Study D961RC00001. For detail, please refer to Sub-section 3.1.1.1.

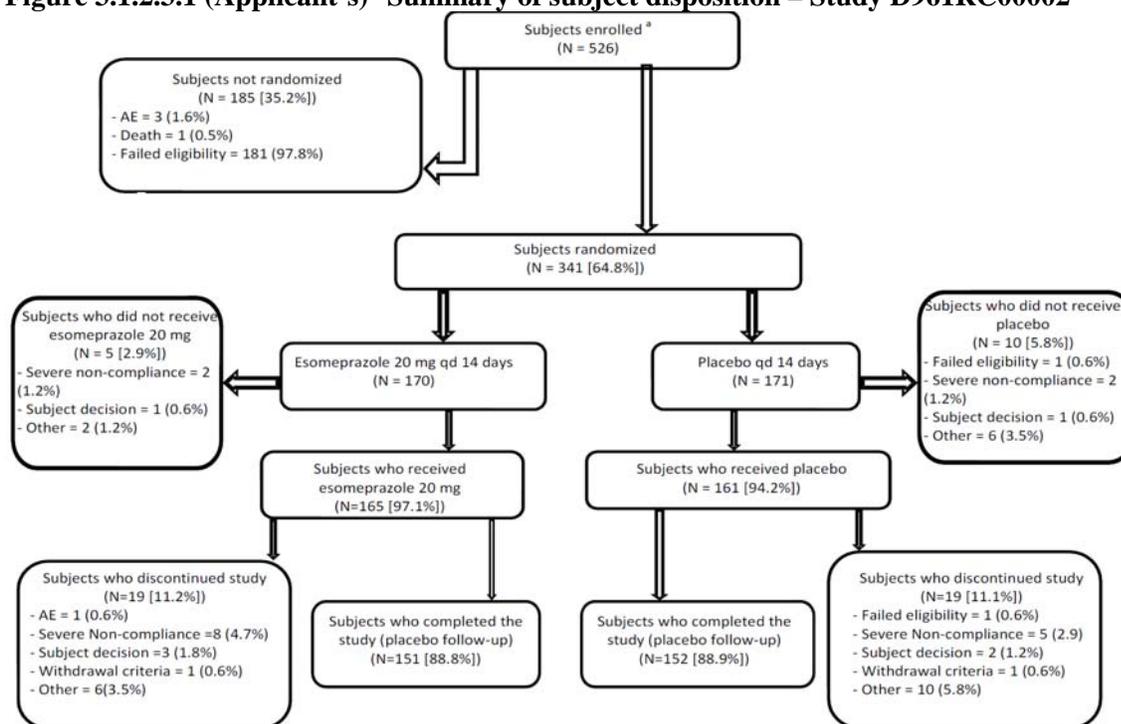
#### 3.1.2.2 Statistical Methodologies

The statistical analysis methods (including analysis data sets) of this study were the same as that for D961RC00001. For detail, please refer to Sub-section 3.1.1.2.

#### 3.1.2.3 Patient Disposition

The first subject was enrolled on August 11, 2011, and the last subject completed the study on October 24, 2011. Disposition of all the randomized subjects in this study is summarized in Figure 3.1.2.3.1.

**Figure 3.1.2.3.1 (Applicant's) Summary of subject disposition – Study D961RC00002**



<sup>a</sup>: All subjects who provided informed consent.

Source: Figure 2 at page 41 in Study D961RC00002 Report

The applicant indicated that a total of 526 subjects signed an informed consent and were enrolled into the study. Of the enrolled subjects, 341 (64.8%) subjects (who completed the placebo run-in period) were randomized to the 14-days treatment period (170 and 171 subjects in the esomeprazole 20 mg and the placebo groups, respectively). In total, 185 (35.2%) subjects were enrolled but not randomized, primarily due to the eligibility criteria not fulfilled (181 [97.8%]). There were 3 subjects who were not randomized due to AEs (3 [1.6%]), and 1 subject died after being enrolled, but before starting the placebo run-in period (1 [0.5%] subject).

Of the 170 subjects randomized to the esomeprazole 20 mg group, 165 (97.1%) received esomeprazole 20 mg and 5 (2.9%) did not receive esomeprazole 20 mg. Of the 171 subjects randomized to the placebo group, 161 (94.2%) received placebo and 10 (5.8%) did not receive placebo.

Of those subjects who were randomized to esomeprazole 20 mg, 151 (88.8%) completed the study (i.e., returned for Visit 5 assessment at Day 23) and 19 (11.2%) discontinued the study, the main reasons being severe non-compliance to protocol (8 [4.7%]) and 'other' reasons (6 [3.5%]). Of those subjects who were randomized to placebo, 152 (88.9%) completed the study (i.e., returned for Visit 5 assessment at Day 23) and 19 (11.1%) discontinued the study, the main reasons being severe non-compliance to protocol (5 [2.9%]) and 'other' reasons (10 [5.8%]).

Finally, the applicant indicated that the treatment groups were well balanced with regards to subject disposition. Table 3.1.2.3.1 below presents subjects disposition.

**Table 3.1.2.3.1 (Applicant's) Subjects disposition – Study D961RC00002**

	Number (%) of subjects		
	Esomeprazole 20 mg	Placebo	Total
<b>Subjects Enrolled<sup>a</sup></b>			526
<b>Subjects Who Were Not Randomized</b>			185 (35.2)
Withdrawn From Study Due To Adverse Event			3 (1.6)
Withdrawn From Study Due To Death			1 (0.5)
Withdrawn From Study Due To Eligibility Criteria Not Fulfilled			181 (97.8)
<b>Subjects Randomized</b>	170	171	341 (64.8)
Subjects Who Received Treatment	165 (97.1)	161 (94.2)	326 (95.6)
Subjects Who Did Not Receive Treatment	5 (2.9)	10 (5.8)	15 (4.4)
Withdrawn From Study Due To Eligibility Criteria Not Fulfilled	0 (0.0)	1 (0.6)	1 (0.3)
Withdrawn From Study Due To Severe Non-Compliance To Protocol	2 (1.2)	2 (1.2)	4 (1.2)
Withdrawn From Study Due To Subject Decision	1 (0.6)	1 (0.6)	2 (0.6)
Withdrawn From Study Due To Other	2 (1.2)	6 (3.5)	8 (2.3)
<b>Subjects Who Completed Study</b>	151 (88.8)	152 (88.9)	303 (88.9)
<b>Subjects Who Discontinued Study</b>	19 (11.2)	19 (11.1)	38 (11.1)
Subject Decision	3 (1.8)	2 (1.2)	5 (1.5)
Eligibility criteria not fulfilled	0 (0.0)	1 (0.6)	1 (0.3)
Adverse event	1 (0.6)	0 (0.0)	1 (0.3)
Severe non-compliance to protocol	8 (4.7)	5 (2.9)	13 (3.8)
Development of study-specific withdrawal criteria	1 (0.6)	1 (0.6)	2 (0.6)
Other	6 (3.5)	10 (5.8)	16 (4.7)

<sup>a</sup>: All subjects who provided informed consent.

Source: Table 7 at page 42 in Study D961RC00002 Report.

### 3.1.2.4 Demographics and Baseline Characteristics

The target population for the study was male and female subjects aged greater than or equal to 18 years with frequent heartburn occurring greater than or equal to two days per week, without a confirmed GERD diagnosis. The mean age was 41.6 years and 42.8 years for esomeprazole 20 mg and placebo groups, respectively. The majority of the subjects were White (107 [66%] in the esomeprazole 20 mg group and 111 [70.3%] in the placebo group) or Black/African American (48 [29.6%] in the esomeprazole 20 mg group and 46 [29.1%] in the placebo group). The proportion of female subjects randomized into the study were comparable to males subjects (86 [53.1%] versus 76 [46.9%] for esomeprazole 20 mg group and 82 [51.9%] versus 76 [48.1%] for placebo group, respectively).

The applicant indicated that there was no difference between treatment groups in baseline body mass index (BMI). The treatment groups were well balanced for demographic characteristics with respect to the gender, age, race, and ethnicity and the study population was representative of the intended target population. Table 3.1.2.4.1 summarizes the results.

**Table 3.1.2.4.1 (Applicant's) Key Demographic and Baseline characteristics (Full Analysis Set) – Study D961RC00002**

Demographic characteristic		Esomeprazole 20 mg (N=162)	Placebo (N=158)
Age(years)	N	162	158
	Mean	41.6	42.8
	SD	14.0	13.2
	Median	41.0	42.5
	Min	19.0	18.0
	Max	90.0	84.0
Sex n (%)	F	86 ( 53.1)	82 ( 51.9)
	M	76 ( 46.9)	76 ( 48.1)
	Total	162 (100.0)	158 (100.0)
Race n (%)	WHITE	107 ( 66.0)	111 ( 70.3)
	BLACK OR AFRICAN AMERICAN	48 ( 29.6)	46 ( 29.1)
	NATIVE HAWAIIAN/PACIFIC ISLANDER	1 ( 0.6)	0 ( 0.0)
	AMERICAN INDIAN/ALASKA NATIVE	3 ( 1.9)	0 ( 0.0)
	OTHER	3 ( 1.9)	1 ( 0.6)
	TOTAL	162 (100.0)	158 (100.0)
	Ethnic Group n (%)	HISPANIC OR LATINO	24 ( 14.8)
NOT HISPANIC OR LATINO		51 ( 31.5)	42 ( 26.6)
NOT REPORTED		87 ( 53.7)	95 ( 60.1)
TOTAL		162 (100.0)	158 (100.0)

F: Female; M: Male; SD Standard Deviation.

Source: Table 10 at page 46 in Study D961RC00002 Report

The summary of medical history for heartburn symptoms at baseline of subjects in the FAS population is presented in Table 3.1.2.4.2.

**Table 3.1.2.4.2 (Applicant's) Summary of subject heartburn medical history at baseline (Full Analysis Set) - Study D961RC00002**

		Number(%) of Subjects	
		Esomeprazole 20 mg (N=162)	Placebo (N=158)
Days with heartburn in the last month	Mean	14.02	13.58
	Median	12.00	12.00
	SD	7.07	6.90
	Min	2.00	2.00
	Max	30.00	30.00
Rating of most intense heartburn	Mild	13(8.02)	11(6.96)
	Moderate	93(57.41)	97(61.39)
	Severe	56(34.57)	50(31.65)
Heartburn caused by food/beverage	Yes	154(95.06)	153(96.84)
Heartburn caused by stress/anxiety	Yes	68(41.98)	73(46.20)
Heartburn caused by lying down	Yes	84(51.85)	95(60.13)
Heartburn caused by physical activity	Yes	20(12.35)	24(15.19)
Heartburn caused by hectic lifestyle	Yes	22(13.58)	31(19.62)
Heartburn caused by medication	Yes	6(3.70)	14(8.86)
Received OTC/prescribed heartburn medication in past 5 years	No	11(6.79)	12(7.59)
	Yes	151(93.21)	146(92.41)

OTC: Over-the-counter; SD Standard Deviation.

Source: Table 11 at page 47 in Study D961RC00002

Based upon Table 3.1.2.4.2, the applicant indicated that the mean frequency of days with heartburn in the last month was 14.02 days (equates to 3.22 days/week; range 2 to 30 days) in the esomeprazole 20 mg group and 13.58 days (equates to 3.12 days/week; range 2 to 30 days) in the placebo group. In total, 56 (34.57%) subjects in the esomeprazole 20 mg group and 50 (31.65%) subjects in the placebo group rated their most intense heartburn as severe during the last month before enrollment. The most common cause of heartburn was intake of food/beverage with 154 (95.06%) subjects in the esomeprazole 20 mg group and 153 (96.84%) subjects in the placebo group. In addition, based upon Table 51 at page 232 of the study report, the percentages of heart burn free 24-hour days between Nexium and placebo during the run-in period were numerically similar (means 22.3% and 21.4%, respectively for Nexium and placebo).

### 3.1.2.5 Applicant's Efficacy Analysis Results and Conclusions

The applicant indicated that all efficacy analyses were performed using the FAS. The primary and secondary efficacy variables were analyzed sequentially. A hierarchical testing procedure was used to control the type I error for the primary and secondary endpoints based upon the order presented below.

The following efficacy analysis results regarding the primary and secondary endpoints are copied from the NDA clinical study report.

1) Primary endpoint analysis

The primary endpoint was the percentage of heartburn free 24-hour days over 14 days of randomized treatment period and was analyzed by ANCOVA with centers and treatment as fixed effects and frequency of heartburn during the run-in phase as a covariate.

Table 3.1.2.5.1 presents the efficacy analysis results.

**Table 3.1.2.5.1 (Applicant's) Percentage of heartburn-free 24-hour days during 14 days of treatment by treatment group using the FAS population - Study D961RC00002**

Variable	Esomeprazole 20 mg (N=162) LS Mean (SE)		Placebo (N=158) LS Mean (SE)		Difference between groups <sup>a</sup>		
	n		n		LS Mean (SE)	95% CI	p-value
Percentage heartburn free 24-hour day	162	48.00( 1.96)	158	32.75( 1.99)	15.25( 2.73)	( 9.88,20.62)	<0.0001

a Obtained from analysis of covariance with centers and treatment as fixed effects and frequency of heartburn during the run-in phase as a covariate.

Missing values were imputed based on the run-in phase data;

ANCOVA Analysis of covariance; CI Confidence interval; LS Least square; SE Standard error;

n- number of subjects included in the analysis.

Source: Table 14 at page 53 in Study D961RC00002 Report

Based upon Table 3.1.2.5.1, the applicant indicated that the percentage of heartburn free 24-hour days over 14-days of randomized treatment period was statistically significantly higher in subjects receiving esomeprazole 20 mg (48.00%) as compared to placebo (32.75%). The least square (LS) mean difference between the treatment groups was 15.25% (95% CI 9.88 to 20.62;  $p < 0.0001$ )

In addition, based upon the applicant's analysis results using the PP data set, the percentage of heartburn free 24-hour days over 14-days of randomized treatment period was statistically significantly higher in subjects receiving esomeprazole 20 mg (48.87%) as compared to placebo (33.34%). The LS mean difference between the treatment groups was 15.52% (95% CI 9.70 to 21.35;  $p < 0.0001$ )

Finally, for the sensitivity analysis (imputing missing data for a given day to heartburn) using FAS population, the percentage of heartburn free 24-hour days during 14 days of treatment period for esomeprazole 20 mg remained statistically significantly higher than that for placebo. The LS mean difference between the treatment groups was 14.55% (95% CI 9.00 to 20.09;  $p < 0.0001$ ).

## 2) Secondary endpoint analysis

- Proportion of subjects with heartburn two days or less during the 14-day randomized treatment period (both weeks 1 and 2)

Table 3.1.2.5.2 presents the result of comparing proportions of patients with resolution of frequent heartburn defined as heartburn two days or less for the 14 days of treatment period of the study between esomeprazole 20 mg and placebo groups in subjects from FAS population.

**Table 3.1.2.5.2 (Applicant’s) Percentage of subjects with two or less days of heartburn during 14 days of treatment phase using the FAS population - Study D961RC00002**

Group	N	Number (%) of subjects with Resolution of frequent heartburn	Comparison between groups <sup>a</sup>		
			Relative Risk	95% CI	p-value
Esomeprazole 20 mg	162	27(16.67)	13.17	( 3.18,54.44)	<0.0001
Placebo	158	2( 1.27)			

a The treatment group proportion compared by using a chi-square test.

Missing values are handled as stated in the protocol, i.e., missing days assumed as days with heartburn.

A relative risk >1 shows esomeprazole 20 mg has a favorable outcome compared to placebo.

N - Number of subjects.

Source: Table 18 at page 56 in Study D961RC00002 Report

Based upon Table 3.12..5.2, the applicant indicated that the proportion of subjects with resolution of frequent heartburn (defined as  $\leq 2$  days with heartburn) during 14-days treatment period was statistically significantly higher in subjects receiving esomeprazole 20 mg (16.67%) compared to placebo (1.27%) (RR=13.17; 95% CI 3.18 to 54.44;  $p<0.0001$ ).

- Percentage of heartburn free 24-hour days on Days 1 to 4

Similar to Study D961RC00001, in Sub-section 7.1.2.2 of the Clinical Study Report, titled “Percentage of heartburn free 24-hour days over days one to four”, instead of comparing the percentages of heartburn free days over Days 1 to 4 during the 14 day treatment period, the applicant used a proportional odds model to compare the counts of subjects with heartburn free 24-hour days over Days 1 to 4 of the 14 day treatment period.

In addition, since the proportional odds assumption for the proportional odds model was not met (Score test for the Proportional Odds Assumption;  $p<0.001$ ), by the method specified in the SAP, the applicant performed the logistic regression analysis on the binary data by dichotomizing patients into two categories: patients with zero or one day heart-burn free versus two, three, or four days heartburn free.

These results are presented below.

**Table 3.1.2.5.3 (Applicant's) Percentage of subjects without heartburn - one day or more during Days 1 to 4 between esomeprazole 20 mg and placebo using the FAS population. - Study D961RC00002**

Groups	N	Number (%) of subjects		Comparison between groups <sup>a</sup>	
		(0 or 1 Day)	(2, 3 or 4 Days)	Odds ratio (95% CI)	p-value
Esomeprazole 20mg	162	87(53.70)	75(46.30)	2.28( 1.37, 3.80)	0.0015
Placebo	158	111(70.25)	47(29.75)		

a Logistic regression model with treatment as a factor; the baseline results as a covariate.

Note: Since the proportional odds assumption not met, the analysis was performed by categorizing the data in (0,1) and (2,3,4).

Source: Table 52 at page 232 in Study D961RC00002

Based upon Table 3.1.2.5.3, the applicant indicated that the results showed a statistically significant in favor of esomeprazole 20 mg (OR =2.28, 95% CI 1.37 to 3.80; p=0.0015).

In addition, based upon the applicant's document dated September 27, 2013, in response to our request for an ANCOVA analysis of the percentage of days with no heartburn over Days 1-4 of the treatment period, the percentage of days with no heartburn for esomeprazole 20 mg was significantly higher than that of placebo (LS Mean difference 14.85%, 95%, CI (8.78%, 20.92%), p < 0.0001).

- Resolution of frequent heartburn for a given week

#### Analysis on the final week of treatment

A comparison of the proportion of subjects with heartburn less than or equal to one day during the final week of treatment is presented in Table 3.1.2.5.4. The final week of treatment was defined as the last 7 consecutive days when subjects were on randomized investigational products.

**Table 3.1.2.5.4 (Applicant's) Percentage of subjects with heartburn one day or less during the final week of treatment using the FAS population - Study D961RC00002**

Group	N	Number (%) of subjects with resolution of frequent heartburn	Comparison between groups a		
			Relative Risk	95% CI	p-value
Esomeprazole 20 mg	162	40(24.69)	2.29	( 1.36, 3.87)	0.0011
Placebo	158	17(10.76)			

a The treatment group proportions compared by using a chi-square test.

Missing values were handled as stated in the protocol, i.e., missing days assumed days with heartburn.

A relative risk >1 shows esomeprazole 20 mg has a favorable outcome compared to placebo.

N-Number of subjects.

Source: Table 20 at page 59 in Study D961RC00002 Report.

Based upon Table 3.1.2.5.4, the applicant indicated that there was a statistically significant difference in the proportion of subjects who experienced resolution of frequent heartburn in the last 7 calendar days of the treatment period of the study between the esomeprazole 20 mg (24.69%) and placebo (10.76%) treatment groups (RR=2.29; 95% CI 1.36 to 3.87; p=0.0011).

#### Analysis on the second week of treatment

A comparison of the proportion of subjects with heartburn less than or equal to one day during the second week of treatment is presented in Table 3.1.2.5.5. The second week of treatment was defined as Days 8 to 14 of the two week treatment period.

**Table 3.1.2.5.5 (Applicant's) Percentage of subjects with heartburn one day or less during the second week of treatment using the FAS population - Study D961RC00002**

Group	N	Number (%) of subjects with Resolution of frequent heartburn	Comparison between groups		
			Relative Risk	95% CI	p-value
Esomeprazole 20 mg	162	38(23.46)	2.85	( 1.58, 5.15)	0.0002
Placebo	158	13 ( 8.23)			

a The treatment group proportions compared by using a chi-square test.

Missing values were handled as stated in the protocol, i.e., missing days assumed days with heartburn.

A relative risk > 1 shows Esomeprazole 20 mg has a favorable outcome compared to placebo.

N-Number of subjects.

Source: Table 21 at page 60 in Study D961RC00002 Report.

Based upon Table 3.1.2.5.5, the applicant indicated that there was a statistically significant difference in the proportion of subjects who experienced resolution of frequent heartburn in the second week of the treatment phase of the study between the esomeprazole 20 mg (23.46%) and placebo (8.23%) treatment groups (RR=2.85; 95% CI 1.58 to 5.15; p=0.0002).

#### Analysis on the first week of treatment

A comparison of the proportion of subjects with heartburn less than or equal to one day during the first week of treatment is presented in Table 3.1.2.5.6. The first week of treatment was defined as the first 7 calendar days of the treatment phase of the study (between visit 3 and visit 4; Days 1 through 7).

**Table 3.1.2.5.6 (Applicant's) Percentage of subjects with heartburn one day or less during the first week of treatment using the FAS population - Study D961RC00002**

Group	N	Number (%) of subjects with Resolution of frequent heartburn	Comparison between groups		
			Relative Risk	95% CI	p-value
Esomeprazole 20 mg	162	32(19.75)	4.46	( 2.03, 9.80)	< 0.0001
Placebo	158	7( 4.43)			

a The treatment group proportions compared by using a chi-square test.

Missing values were handled as stated in the protocol, i.e., missing days assumed days with heartburn.

A relative risk > 1 shows esomeprazole 20 mg has a favorable outcome compared to placebo.

N-Number of subjects.

Source: Table 22 at page 60 in Study D961RC00002 Report.

Based upon Table 3.1.2.5.6, the applicant indicated that there was a statistically significant difference in the proportion of subjects who experienced resolution of frequent heartburn in the first 7 calendar days of treatment phase of the study between the esomeprazole 20 mg (19.75%) and placebo (4.43%) treatment groups (RR=4.46; 95% CI 2.03 to 9.80; p<0.0001).

### 3.1.2.6 Statistical Reviewer's Analysis and Comments

In order to validate the applicant's claim on the superiority of Nexium to placebo, this reviewer performs the following analyses: i) non-parametric analysis for the primary endpoint, ii) efficacy comparison by center, and iii) analysis for the percentage of heartburn free 24-hour days over Days one to four during the 14 day treatment period (one of the secondary endpoints). Then, this reviewer gives a comment on the overall strength of Nexium efficacy according to the evidence provided by the study.

Based upon the applicant's response to the Agency request information, for Study D961RC00002, there were 6 subjects in total who were randomized, treated but did not have post-baseline data (FAS=320 subjects, MITT=326 subject). Since the MITT population defined as all randomized patients who took a post randomization dose is normally used for the primary efficacy analysis, for this study, the MITT population is used by this reviewer to perform the efficacy analyses.

### Statistical Reviewer's Analysis

#### i) Non-parametric analysis - Primary endpoint

The ANCOVA model used for the primary endpoint (percentage of heartburn free days during the 14 days treatment period) analysis may include un-necessary parameters and the assumption of the data distribution used for the ANCOVA model-based method may not be met. In order to validate the ANCOVA analysis results assessed by the primary endpoint,

this reviewer applies a non-parametric method (Wilcoxon rank sum test) to compare the efficacy between Nexium and placebo using the MITT population. The result of non-parametric analysis using MITT population is presented in Table 3.1.2.6.1.

**Table 3.1.2.6.1 (Reviewer's) Efficacy comparison by non-parametric method using MITT population - Study D961RC00002**

<b>Endpoint</b>	<b>Treatment</b>	<b>N</b>	<b>Mean %</b>	<b>P-value<sup>a</sup></b>
Percentage of heartburn free days during treatment period	Nexium	165	46.23%	< 0.0001
	Placebo	161	30.73%	

<sup>a</sup>: Two-sided Wilcoxon rank sum test.

Similar to the results using FAS population reported by the applicant's response document dated 09/27/2013, Table 3.1.2.6.1 also indicates that the mean percentage for Nexium is significantly higher than that of placebo (p-value < 0.0001) at two-sided significance level of 0.05.

ii) Efficacy comparison by center – Primary endpoint

In the efficacy comparison by center, this reviewer compares the efficacy of Nexium versus placebo based upon the percentage of heartburn free 24-hour days over 14 days treatment period by center using MITT population. Table 3.1.2.6.1 presents the analysis results. Data used in this analysis was submitted on 09/27/2013.

**Table 3.1.2.6.2 (Reviewer's) Mean percentage of heartburn free 24-hour days in the treatment period by center using MITT population - Study D961RC00002**

<b>CENTER NUMBER</b>	<b>NEXIUM (N) % FREE DAY</b>	<b>PLACEBO (P) % FREE DAY</b>	<b>% DIF. N - P</b>	<b>CENTER NUMBER</b>	<b>NEXIUM (N) % FREE DAY</b>	<b>PLACEBO (P) % FREE DAY</b>	<b>DIF. N - P</b>
<b>Center 7801</b>	27.3%	15.9%	11.4%	<b>Center 7807</b>	44.5%	45.3%	-0.8%
<b>Center 7802</b>	38.5%	26.4%	12.1%	<b>Center 7808</b>	61.5%	33.6%	27.9%
<b>Center 7803</b>	51.9%	23.3%	28.6%	<b>Center 7809</b>	56.4%	45.2%	11.2%
<b>Center 7804</b>	26.7%	7.7%	19.0%	<b>Center 7810</b>	69.3%	59.5%	9.8%
<b>Center 7805</b>	50.2%	43.8%	6.4%				
<b>Center 7806</b>	54.8%	35.0%	19.8%	<b>Total</b>	48.0%	32.8%	15.2%

Based upon Table 3.1.2.6.2, the percentages of differences are ranged from -0.8% to 28.6% across ten centers. In addition, the sizes of percentage differences are appeared to be evenly distributed. Accordingly, no center is identified to have abnormally large effect size to dominate the superiority of Nexium to placebo assessed by the primary endpoint.

- iii) Analysis on the percentage of heartburn free days over Days 1 to 4 of the treatment period

In the initial submission the applicant compared the counts (instead of the percentages) of heartburn-free days during Days 1 through 4 of the 14 day treatment period. In order to ensure that Nexium was adequately assessed by this endpoint, this reviewer applies a non-parametric method (Wilcoxon rank sum statistic) to compare the efficacy of Nexium and placebo assessed by this endpoint using MITT population. The result of the non-parametric method is presented in Table 3.1.2.6.3.

**Table 3.1.2.6.3 (Reviewer's) Efficacy comparison by a non-parametric method using the MITT population- Study D961RC00002**

Endpoint	Treatment	N	Mean %	P-value <sup>a</sup>
Percentage of subjects with heartburn free 24-hour days over one to four days during the treatment period	Nexium	165	41.52%	< 0.0001
	Placebo	161	26.48%	

<sup>a</sup>: Two-sided Wilcoxon rank sum test.

Table 3.1.2.6.3 indicates that the mean percentage of Nexium is significantly higher than that of placebo (p-value < 0.0001) at two-sided significance level of 0.05.

### Statistical Reviewer's Comments on the Strength of Nexium Efficacy

This reviewer's non-parametric analysis for the primary endpoint indicates that mean percentage of heartburn free 24 days of Nexium is significantly higher than that of placebo (p-value < 0.0001) at two-sided significance level of 0.05. In addition, from this reviewer's sensitivity analysis based upon the primary endpoint, no center is considered to dominate the superiority of Nexium to placebo. Therefore, the applicant's analysis results for the superiority of Nexium compared to placebo as assessed by the primary endpoint can be deemed as statistically convincing.

According to the applicant's and this reviewer's secondary endpoint analyses, the following pre-specified secondary endpoints were positive in favor of Nexium:

- 1) Proportion of subjects with heartburn two days or less during the 14-Day randomized period (both Weeks 1 and 2);
- 2) Percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase;
- 3) Proportion of subjects with heartburn on one day or less during the last 7 consecutive days of treatment.
- 4) Proportion of subjects with heartburn on one day or less during the second week (days 8 to 14) of treatment.

- 5) Proportion of subjects with heartburn on one day or less during the first week (days 1 to 7) of treatment.

Accordingly, this reviewer's and the applicant's analysis results on the pre-specified secondary endpoints support the efficacy of Nexium compared to placebo

### 3.2 Evaluation of Safety

#### 3.2.1 Study D961RC00001

The applicant indicated that of the a total of 15 (8.93%) subjects in the esomeprazole 20 mg group and 15 (9.20%) subjects in the placebo group experienced at least one AE during the randomized treatment period. However, both treatment groups were balanced with respect to the number of subjects who experienced at least one AE.

There was no fatal AE or any SAE during the randomized treatment period and there were two AEs leading to discontinuation of treatment (cholelithiasis and nasopharyngitis), both occurring in the placebo group. During placebo run-in period in total, 12 (3.63%) subjects (7 [4.17%] subjects in the esomeprazole 20 mg group and 5 [3.07%] subjects in the placebo group) experienced at least one AE.

There was one SAE reported during placebo run-in period. During the placebo follow-up period, a total of 13 (7.74%) subjects in the esomeprazole 20 mg and 10 (6.13%) subjects in the placebo group experienced at least one AE. However, there were no deaths reported in the study.

The applicant made the following conclusions for the safety evaluation for this study:

- Esomeprazole 20 mg qd over a 14-day regimen was generally well tolerated in subjects with heartburn who are likely to self-treat with non-prescription medications without consulting a prescriber;
- The safety pattern was consistent with the known safety profile of esomeprazole and no safety concerns were raised.

#### 3.2.2 Study D961RC00002

The applicant indicated that in total, 165 subjects received esomeprazole 20 mg and 161 subjects received placebo. The applicant indicated that a total of 25 (15.15%) subjects in the esomeprazole 20 mg group and 16 (9.94%) subjects in the placebo group experienced at least one AE during the randomized treatment period. There were no deaths, SAEs, or other significant AEs reported during the treatment period. One subject discontinued study drug due to an AE (sinusitis) while on esomeprazole 20 mg.

A total of 26 (7.98%) subjects (17 [10.30%] and 9 [5.59%] subjects in the esomeprazole 20 mg and placebo groups, respectively) experienced at least one AE during the placebo run-in

period. At the start of the placebo run-in period, before administration of study drug, one death was reported (Section 8.3.1). One SAE was reported during the screening (and wash-out) phase prior to placebo run-in period before the subject was exposed to the study drug.

Eleven (11) subjects each in the esomeprazole 20 mg and placebo groups experienced at least one AE during the placebo follow-up period. There were no deaths, SAEs during the follow-up period. There was one subject who discontinued the study drug due to an AE during the placebo follow-up period.

Numerically there was a higher number of subjects that experienced at least one AE in the esomeprazole 20 mg group than in the placebo group during the randomized treatment period (25 [15.15%] versus 16 [9.94%] subjects). The AEs reported were isolated events spread over different System organ class (SOCs) with no specific pattern identified

Finally, the applicant concluded that numerically, there were a higher number of subjects that experienced at least one AE in the esomeprazole 20 mg group than in the placebo group during the randomized treatment period. The AEs reported were isolated events spread over different SOC with no specific pattern identified. This numerical difference did not raise any safety concern. In addition, there were no fatal AEs, SAEs, and events qualifying as 'other significant AEs' during the randomized treatment period for this study. There was one death (cardiac arrest) during the placebo run-in period and one additional SAE (myocardial infarction) reported during the screening period. There were no clinically relevant changes in mean values over time with regard to laboratory parameters and vital signs.

The applicant indicated that overall, the safety profile of esomeprazole was consistent with the findings of previous clinical studies, and there were no new safety concerns with esomeprazole in the subject population of this study.

The reader should refer to the Medical Officer's review for further assessment of product safety relating to both studies.

## **4.0 SUBGROUP ANALYSIS**

### **4.1 Gender, Race, and Age**

In order to assess the consistency of the treatment effect for Nexium relative to placebo across subgroups (identified by gender, age group, and race group), this reviewer performs subgroup analysis applying analysis of covariance method to compare the effect of Nexium to placebo assessed by the primary endpoint (percentage of heartburn free 24-hour days over the 14-day randomized treatment period).

#### 4.1.1 Study D96RC00001

For Study D96RC00001, about 95% of the patient population was less than or equal to 65 years of age. Consequently, the only subgroup analyses performed in this section are based on gender and race (Caucasian versus Non-Caucasian) .

#### Gender group (Male versus Female)

Table 4.1.1.1 presents the results of treatment efficacy comparisons by gender using MITT population.

**Table 4.1.1.1 (Reviewer's) Efficacy comparison by analysis of covariate method using MITT population**

##### Female

	Nexium (N) (N= 104)		Placebo (P) (N= 95)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=199)</i>	45.4%	2.86	33.4%	2.92	12.0%	3.73	(4.7%, 19.4%)	0.0015

##### Male

	Nexium (N) (N= 64)		Placebo (P) (N= 68)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=132)</i>	46.7%	4.02	33.9 %	3.79	12.8%	4.75	(3.4%, 22.2%)	0.008

<sup>†</sup>: Least Square Mean.

Table 4.1.1.1 shows that for both gender (Female and Male), the percentages of heartburn free days in the Nexium group are significantly higher than that in the placebo group (p-value = 0.0015 for female group and p-value = 0.008 for male group).

#### Race group (Caucasian versus Non-Caucasian)

Table 4.1.1.2 presents the results of treatment efficacy comparisons by gender using MITT population.

**Table 4.1.1.2 (Reviewer's) Efficacy comparison by analysis of covariate method using the MITT population**

**Caucasian**

	Nexium (N) (N= 101)		Placebo (P) (N= 108)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=209)</i>	51.4%	2.91	33.3%	2.75	18.1%	3.62	(10.9%, 25.2%)	< 0.0001

**Non-Caucasian**

	Nexium (N) (N= 67)		Placebo (P) (N= 55)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=122)</i>	39.6%	4.36	34.1%	4.35	5.5%	4.56	(-3.6%, 14.5%)	0.24

<sup>†</sup>: Least Square Mean.

Table 4.1.1.2 shows that only for Caucasian, the percentage of heartburn free days in the Nexium group is significantly higher than that in the placebo group ( $p$ -value < 0.0001). However, for Non-Caucasian, the percentage of heartburn free days in the Nexium group is numerically higher than that in the placebo group.

4.1.2 Study D96RC00002

For Study D96RC00002 about 95% of the patient population was less than or equal to 65 years of age. Consequently, the only subgroup analyses performed in this section are based on gender and race (Caucasian versus Non-Caucasian)

**Gender group (Male versus Female)**

Table 4.1.2.1 presents the results of treatment efficacy comparisons by gender using MITT population.

**Table 4.1.2.1 (Reviewer's) Efficacy comparison by analysis of covariate method using MITT population****Female**

	Nexium (N) (N= 97)		Placebo (P) (N= 84)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=171)</i>	48.5%	2.68	32.2%	2.81	16.3%	3.69	(9.0%, 23.6%)	< 0.0001

**Male**

	Nexium (N) (N= 78)		Placebo (P) (N= 77)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=155)</i>	47.9%	2.93	34.5 %	3.03	13.4%	4.12	(5.2%, 21.5%)	0.0015

<sup>†</sup>: Least Square Mean.

Table 4.1.2.1 shows that for both gender (Female and Male), the percentages of heartburn free days in the Nexium group are significantly higher than that in the placebo group (p-value < 0.0001 for female group and p-value = 0.0015 for male group).

**Race group (Caucasian versus Non-Caucasian)**

Table 4.1.2.2 presents the results of treatment efficacy comparisons by gender using MITT population.

**Table 4.1.2.2 (Reviewer's) Efficacy comparison by analysis of covariate method using MITT population****Caucasian**

	Nexium (N) (N= 109)		Placebo (P) (N= 112)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=221)</i>	54.0%	2.51	34.6%	2.47	19.4%	3.35	(12.8%, 26.0%)	< 0.0001

**Non-Caucasian**

	Nexium (N) (N= 56)		Placebo (P) (N= 49)		<i>Difference (N- P)</i>			
	LS Mean <sup>†</sup>	SE	LS Mean	SE	LS Mean	SE	95%CI	<i>p-value</i>
<i>All Subjects (N=105)</i>	33.2%	4.15	27.1%	4.53	6.1%	4.54	(-3.0%, 15.1%)	0.185

<sup>†</sup>: Least Square Mean.

Table 4.1.2.2 shows that only for Caucasian, the percentage of heartburn free days in the Nexium group is significantly higher than that in the placebo group (p-value < 0.0001). However, for Non-Caucasian, the percentage of heartburn free days in the Nexium group is numerically higher than that in the placebo group.

## 4.2 Other Special / Subgroup Populations

No other subgroups were analyzed.

## 5.0 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The comments given below for the two studies (D96RC00001 and D96RC00002) are based upon the applicant's analysis results from the NDA submission (dated May 30, 2013) and the analyses performed by this reviewer using data submitted by the applicant dated September 27, 2013.

The percentage of 24-hour days with no heartburn over 14 days of treatment (the primary efficacy endpoint) was analyzed using analysis of covariance (ANCOVA) with treatment and center as factors and frequency of heartburn during the run-in phase as a covariate. The results of the primary endpoint analyzed by ANCOVA for both Studies (D96RC00001 and D96RC00002) showed that Nexium results were superior to those for placebo.

The reviewer's non-parametric exploratory analysis for the primary endpoint also indicated that the mean percentage of heartburn free 24 days of Nexium was significantly higher than that of placebo (p-value = 0.0002 for Study D96RC00001 and p-value < 0.0001 for Study D96RC00002) at two-sided significance level of 0.05. In addition, from this reviewer's exploratory analysis based upon the primary endpoint, no study center was considered to dominate the comparisons of Nexium to placebo, and sensitivity analyses indicated that the efficacy results were not affected by the small percentage of subjects with missing data. Therefore, the superiority of Nexium to placebo as shown by the applicant's primary endpoint analysis can be deemed as statistically convincing.

According to the applicant's and this reviewer's secondary endpoint analyses, the following pre-specified secondary endpoints showed positive results in favor of Nexium:

- 1) Proportion of subjects with frequent heartburn 2 days or less during the 14-Day randomized period (both Weeks 1 and 2);
- 2) Percentage of 24-hour days with no heartburn during Days 1 through 4 of the treatment phase;
- 3) Proportion of subjects with heartburn less than or equal to one day during the last 7 consecutive days of treatment.
- 4) Proportion of subjects with heartburn less than or equal to one day during the second week (days 8 to 14) of treatment;
- 5) Proportion of subjects with heartburn less than or equal to one day during the first week (days 1 to 7) of treatment.

Accordingly, based upon this reviewer's and the applicant's analyses, the data submitted by the applicant support Nexium efficacy as assessed by the secondary endpoint. However, the appropriateness of the secondary endpoint claims and terminology for labeling purposes should be carefully assessed by the clinical team.

## 5.2 Conclusions and Recommendations

Based upon the analyses performed by this reviewer and the applicant, data from two adequate and well-controlled studies show that, compared to placebo, Nexium 20 mg once daily, demonstrated a statistically significant difference in daily heartburn episodes over a two-week period.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WEN JEN CHEN  
03/21/2014

MICHAEL E WELCH  
03/21/2014  
Concur with review.

**STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA** 1

**NDA Number:** 20-4655

**Applicant:** AstraZeneca LP

**Stamp Date:** : 05/30/2013

**Drug Name:** Entereg

**NDA Type:** S0002

**Indication:** Treat frequent heartburn (occurs 2 or more days a week)

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter for RTF</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			X	No paper submission
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			Sample size might be inadequate for gender and racial subgroup analyses
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			Data definition file did not provide enough information for this reviewer to locate the primary and secondary endpoints. In addition, SAS programs written by Macro codes are difficult to understand.

**IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ?** **Yes**

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		Review Issue
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

### Background

In the cover letter of this NDA submission, AstraZeneca LP indicates that the NEXIUM® (esomeprazole magnesium) Delayed-Release Capsules NDA 21-153 was approved by the Division of Gastrointestinal and Coagulation Drug Products on February 20, 2001 and is indicated for the treatment of gastroesophageal reflux disease (GERD); risk reduction of NSAID-associated gastric ulcer, H. pylori eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions, including Zollinger- Ellison syndrome.

On August 13, 2012, AstraZeneca announced that it has entered into an agreement with Pfizer Inc. for the OTC rights for Nexium. Pfizer has exclusive rights to market Nexium OTC in the United States. AstraZeneca will continue to hold the IND and NDA and is filing the NDA on behalf of the alliance.

Accordingly, the purpose of this submission was to support the efficacy of esomeprazole 20 mg once daily (qd) over a 14-day regimen for the treatment of frequent heartburn in subjects who are likely to self-treat with non-prescription medications.

### Review Issues/Concerns

The two issues listed below are the concerns of this NDA review:

- The full analysis set (FAS) defined as all randomized subjects who took at least one dose of randomized treatment, had a valid baseline heartburn assessment and at least one valid post-baseline heartburn assessment was used as primary analysis for the efficacy comparisons. Since the “valid” requirement may not be assessed in impartiality and FAS population complied with too many restrictions, the FAS population may be biased representation of the target population.

Accordingly, the modified intent treat (MITT) dataset, defined as all randomized subjects who took at least one dose of randomized treatment will be used as a benchmark checking.

- The sponsor applied an analysis of covariance (ANCOVA) model with treatment and center as factors and frequency of heartburn during the run-in phase as a covariate to analyze the primary endpoint (percentage of 24-hour days with no heartburn over 14 days of treatment).

It is noted that the ANCOVA model may include un-necessary parameters. In addition, the assumption of the data distribution used for the ANCOVA model-based method may not be met. Accordingly, in order to simplify the analysis, we will apply non-parametric (Wilcoxon rank sum statistics) method to compare the efficacy between study drug and placebo.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
-----

/s/  
-----

WEN JEN CHEN  
07/12/2013

STEPHEN E WILSON  
07/12/2013