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:	21-957 / (b) (4) & 005
Drug Name:	NEXIUM® (esomeprazole magnesium) Delayed-Release Oral Suspension (2.5 mg, 5 mg, and 10 mg)
Indication(s):	Short Term Treatment of Gastroesophageal Reflux Disease (GERD) in Patients 0-11 Months Old (b) (4)
Applicant:	AstraZeneca LP
Date(s):	Stamp Date: 12/18/2008
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Keywords: Clinical studies, enrichment design, NDA review, pediatric exclusivity, proportional hazards, sample size

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1. EXECUTIVE SUMMARY

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and Section 314 of Title 21 of the Code of Federal Regulations (21 CFR 314), AstraZeneca has submitted this supplement to NDA 21-957 for NEXIUM® (esomeprazole magnesium) delayed-release oral suspension for Pediatric Exclusivity determination. This supplement provides efficacy, safety and pharmacokinetic information on the use of NEXIUM® in patients 0-11 months old, inclusive, for the short-term treatment of gastroesophageal reflux disease (GERD) (b) (4)

1.1 Conclusions and Recommendations

(b) (4)

1.2 Brief Overview of Clinical Studies

The current application is based on three pediatric studies, including one pivotal study (D9614C00096, hereafter called Study 96) and two clinical pharmacology studies (SH-NEC-0001 and SH-NEC-0002, hereafter called Study NEC-1 and NEC-2). The data to support the efficacy of esomeprazole in patients aged 1 to 11 months are provided by the pivotal Study 96 and are supported by clinical outcomes and PD data from Study NEC-1. The data to support the use of esomeprazole in patients aged 0 to 1 month are provided by Study NEC-2.

1.3 Statistical Issues and Findings

This statistical review will only evaluate and discuss the data from the pivotal Study 96 (b) (4)

2. INTRODUCTION

2.1 Overview

Gastroesophageal reflux (GER), the retrograde passage of gastric contents into the esophagus, is presumed to be caused primarily by transient relaxation of the lower esophageal sphincter and is a common occurrence in healthy infants and children. GER is considered to be subclinical or silent if the extent of the reflux is limited to the esophagus, or it can be manifested as regurgitation or vomiting of the gastric contents. This presentation is common in infants and occurs frequently in the first year of life. Regurgitation of at least one episode per day occurs in

50% of infants aged 0 to 3 months and in 67% of infants aged 4 to 6 months. In most infants, the incidence of physiologic regurgitation is significantly reduced or resolves completely by 18 months. Infants with physiologic GER, in the absence of other symptoms, are considered to have uncomplicated GER and may be referred to as "happy spitters." Uncomplicated GER in infants does not typically require medical therapy and may be addressed with lifestyle changes, such as positioning therapy or changes in diet.

GERD is present when the reflux of gastric content is the cause of troublesome symptoms and/or complications. The acidic nature of the refluxate associated with pepsin activation is considered to be the principal irritant causing mucosal inflammation, the resulting symptomatology, and potential long-term sequelae of GERD. In infants, common esophageal manifestations of infantile GERD include irritability, vomiting, dysphagia, and weight loss or poor weight gain. Infants aged 0 to 11 months may present with more severe symptoms such as failure to thrive. Some infants may also experience supraesophageal symptoms and conditions such as coughing, wheezing, apnea, and bradycardia. Additionally, an increase in the frequency of regurgitation or vomiting alone might indicate GERD.

The primary goals of treatment of infantile GERD include symptom relief, mucosal healing, promotion of normal weight gain and growth, and prevention of long-term complications. A variety of treatment modalities are available for the clinical management of infantile GERD, including lifestyle changes, medical management with pharmacological agents, and surgical intervention in cases of failed medical management.

Proton-pump inhibitors (PPIs) have been established as an effective pharmacologic treatment for GERD in adults and children older than one year. So far, there is no PPI approved for any indication in pediatric patients with less than a year of age. Esomeprazole magnesium (hereafter called esomeprazole) is a PPI that is currently approved for the treatment of GERD and in combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* (*H. pylori*) in peptic ulcer disease. Approval was first obtained on March 10, 2000 in Sweden and subsequently in the rest of the European Union (EU), the United States (US), Canada, Australia, and most countries in South America, Africa, and Asia, except in Japan (no application). Esomeprazole has also been approved in the US for risk reduction of nonsteroidal anti-inflammatory drugs (NSAIDs)-associated gastric ulcer, and in the EU for the treatment and prevention of ulcers associated with the use of NSAIDs. Furthermore, esomeprazole is approved for pathological hypersecretory conditions including Zollinger-Ellison syndrome. As of October 15, 2008, total worldwide exposure for esomeprazole has been estimated to be approximately 740 million patient treatment courses since its launch.

The NEXIUM® pediatric clinical program was designed to investigate the potential of esomeprazole to safely treat GERD in children from birth through age 17 years, inclusive. The first group studied in the program consisted of patients aged 12 to 17 years, inclusive. Label extensions for esomeprazole use in patients 12 years of age or older were approved in the EU on July 25, 2006 and the US on April 28, 2006.

The second age group studied in the NEXIUM® pediatric clinical program consisted of patients aged 1 to 11 years, inclusive. Label extensions for children who require a 10 mg dose of

esomeprazole were approved in EU on April 16, 2008, the US on February 27, 2008, and Canada on October 1, 2007.

The third group studied was children aged 0 to 11 months, inclusive. Data supporting the safe and effective usage of oral esomeprazole 2.5 mg, 5 mg, and 10 mg by this pediatric population were submitted in this application.

The main focus of this statistical review, Study 96, is the single, pivotal, phase 3 clinical trial that AstraZeneca conducted to investigate the efficacy and safety of esomeprazole in patients aged 1 to 11 months, inclusive, with a diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Study 96 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, treatment-withdrawal study. The study consisted of a 10-day screening period (Visit 1 to Visit 2), a 2-week open-label treatment phase (Visit 2 to Visit 3), a 4-week double-blind treatment-withdrawal phase (Visit 3 to Visit 5), and a 2-week safety follow-up period.

Study NEC-1 was a clinical pharmacology study conducted to investigate the PK, PD, and ability of esomeprazole to reduce GERD symptoms in pediatric patients aged 1 to 24 months. The clinical outcomes and PD data for infants 1 to 11 months of age in this study were submitted to support the efficacy of esomeprazole in patients aged 1 to 11 months. Study NEC-2 was a clinical pharmacology study conducted to investigate the PK, PD, and ability of esomeprazole to reduce GERD symptoms in preterm infants and neonates aged 0 to 1 month. The clinical outcomes and PD data from this study were submitted to support the efficacy of esomeprazole in patients aged 0 to 1 month.

2.2 Data Sources

Materials reviewed include the clinical study report, protocol, and statistical analysis plan (SAP) for Study 96. This application was submitted in electronic Common Technical Document (eCTD) format, with SAS datasets and programs provided, to EDR at \\Cdsesub1\evsprod\NDA021957.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Study 96 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, treatment-withdrawal study designed to evaluate the efficacy and safety of esomeprazole for the treatment of GERD in infants aged 1 to 11 months, inclusive. The primary objective of this study was to evaluate the efficacy of once daily esomeprazole for reducing the esophageal and supraesophageal signs and symptoms of infantile GERD. The secondary efficacy objective of this study was to evaluate the safety and tolerability of once daily esomeprazole in infants aged 1

to 11 months, inclusive, with GERD. The study also described the burden of pediatric GERD on the primary caregiver from a psychological, social, and economic perspective on an exploratory basis.

To be considered for inclusion in the study, patients had to be either a term or post-term infant beyond the neonatal period, but less than 12 months of age, or be a preterm infant with a corrected gestational age of at least 44 weeks, but less than 12 months, and weigh between 3 kg and 12 kg, inclusive. Prior to consideration for enrollment in the study, each patient was diagnosed with suspected GERD, symptomatic GERD, or endoscopically proven GERD, documented according to accepted medical standards. Patients were to be symptomatic at study entry, with a minimum frequency and duration of symptoms stipulated by the inclusion criteria.

The study used the Interactive Voice Response System (IVRS) to capture the patient's daily symptoms and usage of rescue medications. The IVRS was a telephone-based system, accessible 24 hours a day, 7 days a week. The IVRS allowed the parent/guardian to report the previous 24-hour up to two days.

The study consisted of a 10-day screening period (Visit 1 to Visit 2), a 2-week open-label treatment phase (Visit 2 to Visit 3), a 4-week double-blind treatment-withdrawal phase (Visit 3 to Visit 5), and a 2-week safety follow-up period.

During the open-label phase, patients were treated once daily with esomeprazole according to body weight obtained at enrollment (Visit 2), approximately 30 to 60 minutes before breakfast or a morning feed. Patients weighing 3 kg to 5 kg received 2.5 mg, patients weighing more than 5 kg to 7.5 kg received 5 mg, and patients weighing more than 7.5 kg to 12 kg received 10 mg.

Patients must have demonstrated response to therapy in the open-label phase to be eligible to enter the randomized treatment-withdrawal phase. In particular, for a patient to be potentially eligible for inclusion in the double-blind treatment-withdrawal phase, there must have been an improvement in the Physician's Global Assessment (PGA) of a patient's GERD symptoms of at least one category compared with the baseline assessment, and the investigator must have considered that there were no indications of severe symptoms of any duration that might require medical intervention and might, at the discretion of the investigator, have disqualified the patient from being on placebo. Since the PGA is a scoring (0 = none, 1 = Mild, 2 = Moderate, 3 = severe) that the investigator uses to provide the overall clinical impression of the patient's GERD-related symptoms over the last seven days based on the severity of symptoms reported by the parent/guardian in IVRS, one category improvement in the PGA score here means one point less. However, the patient symptom assessment reported by the parent/guardian in IVRS is a scoring system with four categories: vomiting/regurgitation; irritability; supraesophageal and respiratory disturbances; and feeding difficulties.

Ineligible patients were to be discontinued from the study at Visit 3. Eligible patients were to be randomly assigned in a 1:1 ratio to continue to receive their original (open-label phase) dose of esomeprazole or placebo for up to four weeks. Those patients were to have a follow-up visit (Visit 4) and a final visit (Visit 5) in two weeks and four weeks, respectively, after the randomization.

Following administration of the final dose of the study drug, all patients (discontinued or completed) received a safety follow-up phone call from study personnel at the investigational site. The safety follow-up assessment was to occur two weeks after the final dose.

The primary efficacy variable for this study was the time from randomization to discontinuation due to symptom worsening in the randomized treatment-withdrawal phase. As noted earlier, parents were to complete IVRS assessments of symptoms on a daily basis. The symptoms evaluated in the IVRS assessment were based upon the validated Orenstein's Infant Gastroesophageal Reflux Questionnaire (I-GERQ). Before every contact the investigator had with parents/guardians, the investigator used all previously collected IVRS data as diary card information to aid in making their assessment of treatment response. Patients who discontinued for reasons other than symptom worsening were to have their times right censored at the point of discontinuation, or at the last contact date, if they were lost to follow-up.

The secondary efficacy variables were: 1) the time from randomization into the double-blind phase of the study to discontinuation due to any cause; 2) the proportion of treatment responders randomized into the double-blind phase who were classified as treatment successes at the end of the 4-week, double-blind phase; 3) daily patient symptom assessment as reported by the parent/guardian; and 4) symptom severity recorded on the PGA.

Additionally, the economic impact of pediatric GERD was evaluated by gathering information on employment impact (absenteeism and presenteeism) and household expenses specifically related to managing the child's symptoms and care. The sponsor indicated that the data collected from the Pediatric GERD Caregiver Impact Questionnaire (PGCIQ) would be provided in a separate report.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

The pivotal Study 96 was conducted at a total of 33 sites, 16 sites in the US, 4 sites in France, 9 sites in Germany, and 4 sites in Poland. A total of 98 pediatric patients were enrolled to start the open-label phase, and 80 patients were subsequently randomized into the double-blind, treatment-withdrawal phase. The first patient was enrolled on April 12, 2007, and the last patient completed the study on June 4, 2008.

The intent-to-treat (ITT) population was considered the primary analysis population for this study. For all summaries and formal statistical analyses conducted on data collected from the double-blind treatment withdrawal phase of the study, the ITT analysis set included all randomized patients with available data for a particular endpoint and who took at least one dose of the study medication in the double-blind phase. For summaries of data collected from the open-label phase, the ITT population included all patients who were enrolled in the open label phase with available data for a particular endpoint and took at lease one dose of study medication in the open-label phase.

The sponsor claimed that a per-protocol (PP) analysis was not appropriate because the treatment withdrawal design and the relatively small sample size of the study. However, this reviewer

noticed large gaps between the planned visit dates and actual visit dates for some patients and so a PP analysis on that regard will be evaluated.

Patients who were given at least one dose of the study medication were included in the safety analyses. For this study, the safety and ITT populations coincide.

Of 103 patients screened for this study, five patients failed to be eligible and were not enrolled into the open-label phase. Reasons for screen failure included voluntary discontinuation by the parent/guardian and non-compliance with the protocol.

As summarized in Table 1 below, 98 patients in total were entered into the open-label phase from 33 study sites and were evaluable in both the safety and ITT populations. Of these, 80 were randomized into the double-blind randomized phase and were evaluable in both the safety and ITT populations (39 patients were randomized to the esomeprazole group and 41 patients the placebo group). Of the 80 patients randomized, 53 (66.3%) patients completed the study with 29 (74.4%) patients in the esomeprazole group and 24 (58.5%) patients in the placebo group.

Eighteen (18.4%) patients were discontinued from the open-label phase. Reasons for discontinuing the study during the open-label phase included lack of therapeutic response (9 [9.2%] patients), adverse event (5 [5.1%] patients), and voluntary discontinuation by the parent/guardian (4 [4.1%] patients).

Twenty-seven (33.8%) patients were discontinued from the double-blind randomized phase with 10 (25.6%) patients in the esomeprazole group and 17 (41.5%) patients in the placebo group. The most common reason for discontinuation during the double-blind randomized phase was lack of therapeutic response (8 [20.5%] patients in the esomeprazole group and 17 [41.5%] in the placebo group). Two (5.1%) patients in the esomeprazole group discontinued during the double-blind randomized phase due to adverse events.

Table 1. Patient disposition

Disposition	N (%) of patients in each category		
		Double-blind randomized treatment	
	Open-label	Esomeprazole	Placebo
Enrolled/randomized			
Enrolled in the open label phase	98 (100.0)		
Evaluable for safety and ITT in the open label phase	98 (100.0)		
Randomized in the double-blind phase	80 (81.6)	39 (100.0)	41 (100.0)
Evaluable for safety and ITT in the double-blind phase	80 (81.6)	39 (100.0)	41 (100.0)
Completed the study		29 (74.4)	24 (58.5)
Discontinued	18 (18.4)	10 (25.6)	17 (41.5)
Adverse event	5 (5.1)	2 (5.1)	0
Lack of therapeutic response	9 (9.2)	8 (20.5)	17 (41.5)
Voluntary discontinuation by the parent/guardian	4 (4.1)	0	0

Source: Study 96 Clinical Study Report, Table 11.1.4 (Module 5.3.5.1).

There were three patients in this study who had major deviations, which were defined after the study by the sponsor, during the double-blind phase. One patient was randomized to a weight group according to the weight obtained at randomization instead of that obtained at the beginning of the open-label phase and so potentially would receive the wrong study drug dose during the double-blind treatment phase. However, since this patient was randomized to placebo there is minimal impact on the double-blind phase data. One patient was randomized to placebo when there was no improvement in their PGA score compared to baseline at randomization. This patient reached the end of the study without showing symptom worsening. The other major deviation in the double-blind phase was due to study treatment compliance: a patient randomized to esomeprazole, who completed the study without showing symptom worsening, had study drug compliance less than 80% during the double-blind phase.

There were more males than females enrolled in both treatment phases. In particular, of the 98 patients enrolled, 63 (64.3%) were male and 35 (35.7%) were female. Of the 80 randomized patients, 57 (71.3%) were male and 23 (28.8%) were female. Most patients were Caucasian (86 [87.8%] in the open-label phase and 72 [90%] in the double-blind phase), with fewer than 12% who were non-Caucasian. The mean age of all patients enrolled into the study was 4.9 months, with patients distributed throughout the age range (1-11 months). Mean dose per body weight at the start of the open-label period was 0.88 mg/kg for all patients in open-label phase, 0.86 mg/kg for patients subsequently randomized to esomeprazole in the double-blind phase, and 0.92 mg/kg for patients randomized to placebo. Twenty (20.4%) patients had endoscopies performed at baseline, of which only six patients (four eventually randomized to esomeprazole and two to placebo) had erosive esophagitis. Baseline demographic factors were similar between the two randomized treatment groups.

3.1.3 Statistical Methodologies

The Statistical Analysis Plan (SAP) was prepared before database lock. All formal statistical analyses were conducted at a 2-sided 5% significance level.

For the double-blind treatment phase, the time from randomization to discontinuation due to symptom worsening was analyzed using the Cox proportional hazards model, adjusting for treatment. The time from randomization to discontinuation due to any reason was analyzed in the same manner. The proportion of treatment successes following the double-blind phase was compared between the two treatment groups using a Chi-square test. The PGA at the final/early termination visit was analyzed using the Cochran-Mantel-Haenszel (CMH) statistic, stratified by baseline score (with baseline taken as the score at the end of the open-label phase, prior to randomization).

The sponsor did not provide any missing data handling or multiplicity adjustment strategies. There was no formal statistical analysis for daily patient symptom or safety assessments. The corresponding results were only summarized descriptively and will not be discussed in this statistical review.

In the SAP, the sponsor indicated that there were patients met the discontinuation criteria (worsening of PGA) during the double-blind phase but were not discontinued from the study for that reason (but for adverse events instead), and some patients demonstrated worsening of symptoms at the final visit. Those patients would be counted toward the primary endpoint. Although the sponsor should have prespecified this strategy in the protocol, the proposal seems reasonable for the efficacy assessment.

The SAP also proposed the strategy of dealing with discontinuation time greater than 28 days. In particular, any patients experiencing an event, with time to discontinuation greater than 28 days, will have their uncensored time to discontinuation truncated to 28 days. Meanwhile, any patients completing the double-blind phase without experiencing an event (i.e., censored individuals with right censored time to discontinuation of 26 days or longer) will have their right-censored time to discontinuation set to be 28 days in the analysis. This reviewer found the truncation method rather arbitrary.

Furthermore, the sponsor proposed some post-hoc additional exploratory endpoint summary statistics and subgroup analyses. Because these analyses were performed after unblinding the data and these endpoints were of limited clinical interest, the results will not be discussed in this statistical review.

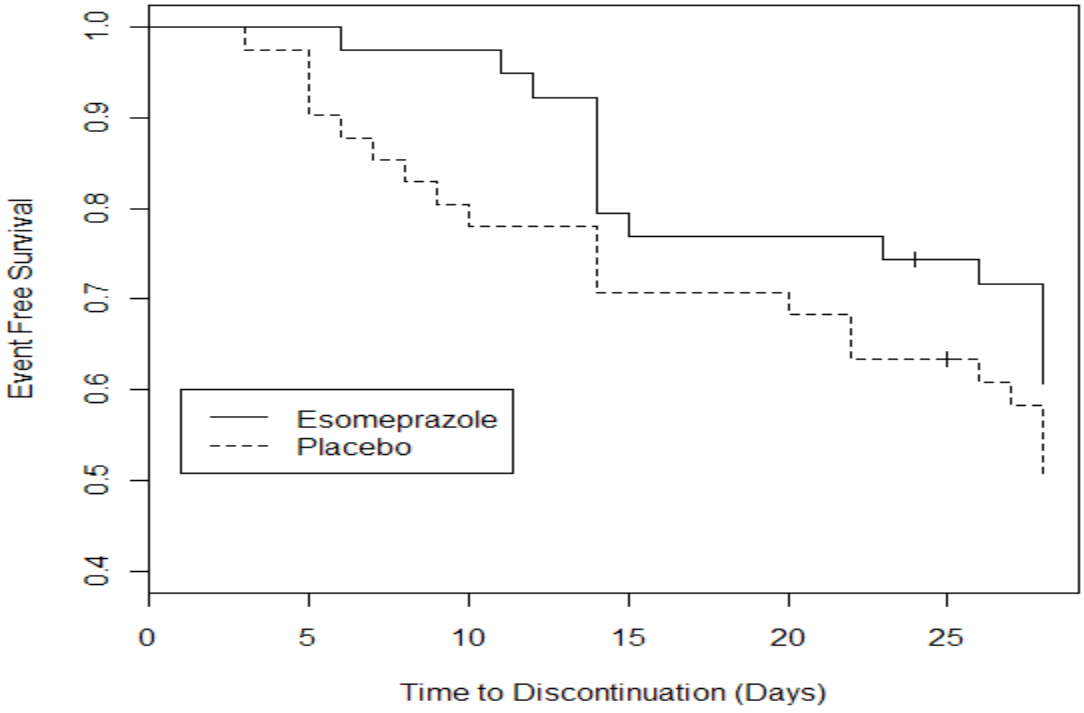
The sample size was determined based on the assumptions of 80% active-treatment and 40% placebo success rates. To provide at least 90% power to detect this difference at a 2-sided significance level of 5% using Fisher's exact test, 38 patients per treatment group were to be randomized to double-blind treatment phase. It was planned to enroll approximately 100 patients in order to get 76 responders eligible for randomization at the end of the open-label phase.

3.1.4 Results and Conclusions

A smaller percentage of patients, who were given esomeprazole, experienced the event of discontinuation due to symptom worsening, compared with those who were given placebo (38.5% [15/39] and 48.8% [20/41], respectively). In addition to the 27 randomized patients who prematurely discontinued from the study, five patients who were given esomeprazole and three patients who were given placebo that did complete the study were included as having discontinuation events in the primary analysis because they demonstrated worsening in their PGA scores at the study completion visit. The hazard ratio of 0.69 (esomeprazole/placebo) indicated a 31% lower risk of discontinuing due to symptom worsening with esomeprazole as compared with placebo. The difference was not statistically significant with a p-value of 0.275 and 95% CI of (0.35, 1.35).

The figure below (Figure 1) shows the Kaplan-Meier curves of time to discontinuation due to symptom worsening. The esomeprazole group had better performance throughout the double-blind treatment phase. During the first two weeks a larger percentage of patients who were given placebo had discontinuation events compared with those given esomeprazole. For the final two weeks of the double-blind phase, the two treatment groups had similar discontinuation rates.

Figure 1. Kaplan-Meier plot of time to discontinuation due to symptom worsening



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

The sponsor performed an additional pre-specified Cox proportional hazard analysis of the primary endpoint adjusted for treatment and weight group. The results were similar to the primary analysis with a p-value of 0.296. This reviewer also performed several additional analyses, including using the original visit/discontinuation date without 28-day truncation, excluding the patients with major protocol deviations or out-of-window visits (PP population analysis). The results were fairly consistent across the analyses with p-values ranging roughly from 0.2 to 0.4.

The results for the secondary variable of time to discontinuation due to any cause were identical to those for the primary variable because the only two patients discontinued due to adverse events also had worsening in their GERD symptoms at discontinuation according to the PGA scores. For the secondary variable of proportion of treatment responders with treatment successes at the end of the double-blind phase, numerically more patients who continued to receive esomeprazole were considered treatment successes than those who received placebo (61.5% [24/39] and 51.2% [21/41], respectively). However, the effect was not statistically significant with a Chi-square test p-value of 0.352. For the secondary variable of PGA scores, at the worst post-randomization assessment, 15 (38.5%) patients who were given esomeprazole had moderate to severe PGAs compared with 19 (46.3%) patients who were given placebo. Using a CMH test stratified by PGA at Visit 3, there was no statistically significant difference found between the treatment groups with a p-value of 0.327.

In conclusion, there were no statistically significant differences found between treatment groups on the efficacy variables. As summarized in Figure 2 and Table 2 in the Appendix, the results were also fairly consistent in the male gender and Caucasian race subgroups; however, not in the female or non-Caucasian subgroups. Due to the small sample size of this study, the subgroup analyses were uninformative.

3.2 Evaluation of Safety

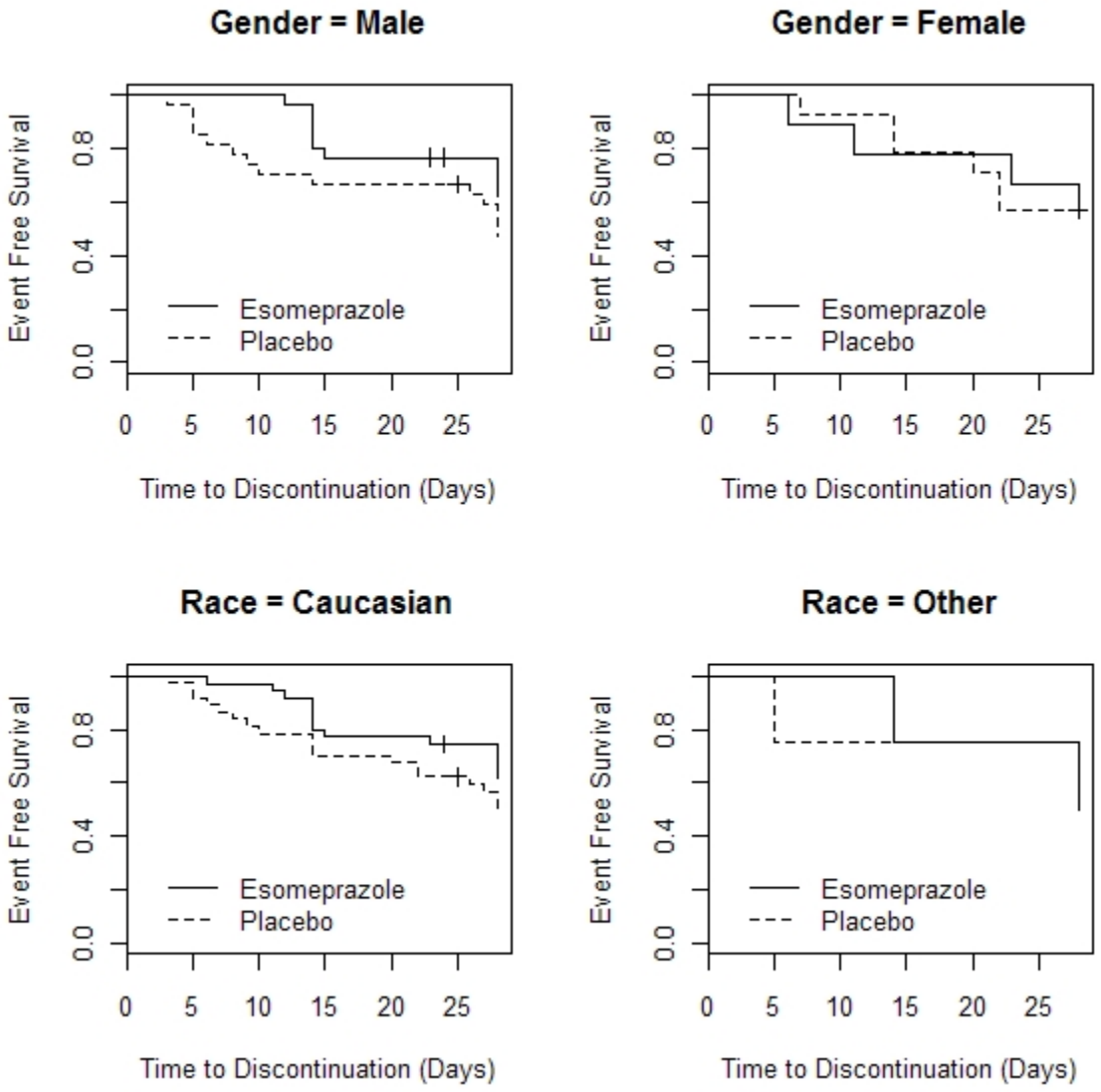
There were no deaths in this clinical development program. The sponsor reported that in Study 96, 47 of the 98 patients in the open-label phase experienced 68 adverse events and 50 of the 80 patients in the double-blind phase (23 patients who received esomeprazole and 27 patients who received placebo) experienced 135 adverse events (79 in the esomeprazole and 56 in the placebo group), regardless of causality. Seven patients had serious adverse events and seven patients discontinued due to adverse events during the study, none of which were considered related to the study treatment. There were four patients had adverse events considered to be treatment related (abdominal pain, regurgitation, tachypnea, and ALT increased). The most common adverse events reported were from the System Organ Class of infections and infestations.

4. SUMMARY AND CONCLUSIONS

Based on the data from the pivotal Study 96, (b) (4) the results were not statistically significant. In addition, the study failed to show any statistical significance on the comparisons of the secondary variables. (b) (4)

APPENDIX

Figure 2. Kaplan-Meier plot of time to discontinuation due to symptom worsening by subgroups



Source: Reviewer's Figure

Table 2. Analysis of time to discontinuation due to symptom worsening (double-blind phase) by subgroups (ITT population)

Treatment	Number of patients with event[a]	% of patients with event[a]	Comparison between groups		
			Hazard ratio	95% CI	p-value[b]
Gender = Male					
Esomeprazole (N=30)	11	36.7	0.57	(0.26, 1.27)	0.169
Placebo (N=27)	14	51.9			
Gender = Female					
Esomeprazole (N=9)	4	44.4	1.00	(0.28, 3.57)	0.994
Placebo (N=14)	6	42.9			
Race = Caucasian					
Esomeprazole (N=35)	13	37.1	0.66	(0.32, 1.35)	0.254
Placebo (N=37)	18	48.6			
Race = Other					
Esomeprazole (N=4)	2	50.0	0.93	(0.13, 6.63)	0.943
Placebo (N=4)	2	50.0			

[a] Patients classified as discontinuing due to symptom worsening
[b] Analysis via Cox proportional hazards model
Source: Reviewer's Table

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/s/

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