AstraZeneca

Clinical Study Report

Drug substance:	Esomeprazole magnesium
Edition No.:	
Study code:	D9612L00083
Date:	20 March 2007

An Open-Label Study of Once-Daily Oral Administration of Esomeprazole 40 mg in Patients with Symptoms of Gastroesophageal Reflux Disease (GERD) to Investigate the Relationship between the Presence of Erosive Esophagitis (EE) at Baseline and Heartburn Resolution after 4 Weeks of Treatment

Study dates: First patient enrolled: 21 October 2005
Last patient enrolled: 6 December 2005

Phase of development: Phase IV

This study was performed in compliance with Good Clinical Practice.

Drug product:	NEXIUM®	**SYNOPSIS**	
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An Open-Label Study of Once-Daily Oral Administration of Esomeprazole 40 mg in Patients with Symptoms of Gastroesophageal Reflux Disease (GERD) to Investigate the Relationship between the Presence of Erosive Esophagitis (EE) at Baseline and Heartburn Resolution after 4 Weeks of Treatment

Coordinating investigator (Not applicable)

Study center(s)

Twenty-two study sites in the United States (US) enrolled patients in this study.

Publications

None at the time of writing this report.

Study dates:

First patient enrolled 21 October 2005
Last patient completed 19 January 2006

Phase of development:

Therapeutic use (IV)

Objectives

Primary: To determine whether there is a difference in heartburn resolution rates at the end of the 4-week treatment period in patients with symptoms of GERD between those patients with EE and those without EE at baseline

Secondary: To determine whether there is a difference in acid regurgitation, dysphagia and epigastric pain resolution rates after 2 and 4 weeks of treatment between those patients with EE and those without EE at baseline

Secondary: To determine whether there is a difference in heartburn resolution rates after 2 weeks of treatment between those patients with EE and those without EE at baseline

Secondary: To determine if any of the symptom questions at screening predict either the presence of EE at baseline or resolution of heartburn at the end of the 4-week treatment period

Secondary: To estimate the prevalence of EE in patients with symptoms of GERD

Secondary: To assess the safety and tolerability of esomeprazole 40 mg (E40)

Exploratory: To estimate the prevalence of histologic findings related to acid exposure among all patients with symptoms of GERD, among those patients with EE, and among those without EE

Exploratory: To evaluate heartburn resolution rates at the end of the 4-week treatment period in patients with EE and/or histologic findings as compared to those without EE and/or histologic findings.

Study design

This was an open-label study of once-daily oral administration of E40 in patients with symptoms of GERD to determine whether there is a difference in heartburn resolution rates at the end of the 4-week treatment period between those patients with EE, as defined by LA Classification Grades A-D, and those without EE at baseline.

Target patient population and sample size

Approximately 350 male and female patients with symptoms of GERD, ages 18-70 years inclusive, were to be enrolled to obtain approximately 318 evaluable patients. Enrollment was to be stratified by EE status: approximately 50% of the patients were to have EE at baseline esophagogastroduodenoscopy (EGD).

Investigational product: dosage, mode of administration, and batch number

1 open-label E40 capsule (NDC # 0186-5040-31, batch number P5581) taken orally each morning approximately 30 minutes prior to breakfast.

Duration of treatment

4 weeks (28 to 32 days)

Criteria for evaluation (main variables)

Primary objective: The outcome variable was the resolution of heartburn at the end of the 4-week treatment period, where resolution was defined as a response of 'None' on the final Symptom questionnaire (*Symptom questionnaire–Treatment* [Protocol Appendix E]); and the independent variable was EE status (present/absent) at baseline.

Secondary objective #1: The outcome variables were the resolution of acid regurgitation, dysphagia, and epigastric pain after 2 and 4 weeks of treatment as measured by the patient-reported Symptom questionnaire *(Symptom questionnaire-Treatment*); and the independent variable was baseline EE status.

Secondary objective #2: The outcome variable was the resolution of heartburn after 2 weeks of treatment as measured by the patient-reported Symptom questionnaire *(Symptom questionnaire-Treatment)*, and the independent variable was baseline EE status.

Secondary objective #3: The outcome variables were the resolution of heartburn after 4 weeks of treatment and baseline EE status, and the independent variables were the responses to the symptom questions asked at screening (*Symptom questionnaire-Screening* [Appendix D]*)*.

Secondary objective #4: The outcome variable was baseline EE status.

Secondary objective #5: The outcome variables were adverse events, clinical laboratory test results, physical examination findings, and vital signs.

The first exploratory outcome variable was baseline histologic findings related to acid exposure (from esophageal biopsy specimens), both overall and stratified by the presence or absence of EE. The second exploratory outcome variable was heartburn resolution at the end of the 4-week treatment period, stratified by the presence or absence of EE and/or histologic findings related to acid exposure at baseline.

Statistical methods

The primary statistical analysis was the Chi-square test for association between the presence of EE (LA Classification Grades A-D) at baseline and the resolution of heartburn at the end of the 4-week treatment period, using an Intent-to-treat (ITT) population (ie, patients with EGD results who received a 'randomization' number, took ≥1 dose of study medication, and had ≥1 post-screening symptom assessment).

Patient population

The study population was generally representative of the target patient population with respect to demographics, baseline characteristics, and medical history, although there were slightly more females than males. The concomitant medications taken were reasonable in a clinical context. Protocol compliance was adequate for an assessment of safety and efficacy. Of the 55 patients who were discontinued, 41 were discontinued prior to receiving study treatment (26 of these 41 were discontinued because the EE stratum was filled).

Disposition and demographic data of the study population are shown in Table S1.

Table S1 Patient population and disposition

Disposition:			
N enrolled		399	(100.0%)
N (%) of patients who:	Were admitted to treatment	357	(89.5%)
	Completed treatment	344	(86.2%)
	Discontinued treatment	14	(3.5%)
N (%) in endoscopy population[a]		399	(100.0%)
N (%) analyzed for safety[b]		358	(89.7%)
N (%) analyzed for efficacy (ITT)[c]		356	(89.2%)
N (%) analyzed for efficacy (PP)[d]		312	(78.2%)
Demographic and baseline characteristics (ITT population):			
Gender, n (%):	Male	148	(41.6%)
	Female	208	(58.4%)
Age (years):	Mean (SD)	44.2	(13.3)
	Range	19	to 70
Race/ethnic group, n (%):	Caucasian	289	(81.2%)
	Hispanic	30	(8.4%)
	Black	26	(7.3%)
	Oriental	8	(2.2%)
	Other	3	(0.8%)
BMI (kg/m^2)	Mean (SD)	30.1	(6.7)
	Range	17.8	to 53.5
H. pylori status, n (%)	Positive	32	(9.0%)
	Negative	323	(90.7%)
History of reflux symptoms (months)	Mean (SD)	96.2	(90.3)
	Range	3	to 540
EE history, n (%)	Yes	104	(29.2%)
	No	252	(70.8%)
Baseline EE status, n (%)	Absent	177	(49.7%)
	Present	179	(50.3%)

[a] Number of patients who completed the endoscopy.
[b] Number of patients who took ≥1 dose of study medication (includes 1 patient without a 'randomization' number).
[c] Number of patients who completed the endoscopy, received a 'randomization' number, took ≥1 dose of study medication, and had ≥1 post-screening symptom assessment (*Symptom questionnaire-Treatment*).
[d] Number of ITT patients who met predefined guidelines for evaluability.
N is Number; SD is standard deviation; ITT is Intent-to-treat; PP is Per-protocol; BMI is body mass index; EE is erosive esophagitis.

Efficacy results

As shown in Table S2, Week 4 heartburn resolution rates were higher among patients who had EE at baseline than among the non-EE patients.

Table S2 Heartburn resolution at Week 4/LOCF by baseline EE status (ITT population)

EE status	Number of patients	Number resolved	Percent resolved	p-value[a]
EE	179	124	69.3%	<0.0001
Non-EE	177	85	48.0%	

[a] From Chi-square test.
LOCF is Last observation carried forward.

These results were confirmed in a secondary analysis in which the Week 4 resolution rate was adjusted for baseline heartburn severity (CMH p=0.0001). The mean decrease in heartburn severity score from baseline to Week 4 was also shown to be greater among EE patients than among non-EE patients (ANCOVA p=0.0007).

These significant effects on Week 4 heartburn resolution rates were also present at Week 2.

Resolution rates were numerically higher among EE patients than among non-EE patients for acid regurgitation, dysphagia, and epigastric pain at both Week 2 and Week 4, and all differences were significant except for dysphagia at Week 4. The presence of EE was associated with higher Week 2 and Week 4 resolution rates for acid regurgitation and epigastric pain, but not for dysphagia, when adjusted for baseline symptom severity. EE patients had numerically greater decreases in severity for each symptom at each timepoint, and this was significant for acid regurgitation and epigastric pain at Weeks 2 and 4, and was not significant for dysphagia at either timepoint.

The following were found to be associated with EE: higher age, male gender, higher BMI, higher heartburn frequency, and relief (especially faster relief) with antacids. No association was found with the following: frequency of acid regurgitation, dysphagia, or epigastric pain; severity of any of the 4 symptoms, or relief from H_2-receptor antagonists (H_2RAs).

The following were found to be associated with heartburn resolution at Week 4: male gender, lower dysphagia severity, and relief (especially faster relief) with antacids.

The prevalence of EE was found to be 51.4% (CI 46.5% - 56.3%).

Biopsy results showed that significantly more EE patients had histological changes consistent with acid exposure than those patients without EE (proximal esophagus: p=0.0010; distal esophagus: p=0.0134). Additionally, the distribution of histology results was more shifted towards moderate/severe in the EE patients than in the non-EE patients. This trend was observed in both proximal (3 cm above Z-line) (p=0.0002) and distal (1 cm above Z-line) (p<0.0001) biopsy locations. Additionally, it was observed that 6.7% (25/375) of all assessable patients with GERD had eosinophilic esophagitis. The numbers and percentages of these patients appeared to be closely distributed among both patients with EE (14/188 assessable, 7.4%) and patients without EE (11/187 assessable, 5.9%).

Biopsy results from the proximal region of the esophagus showed a trend towards greater heartburn resolution with more severe histological changes consistent with acid exposure. This trend was statistically significant (p=0.027) for the combined EE and non-EE patient group. Biopsy results from the distal region did not show the same effect of histologic findings.

Safety results

As shown in Table S3 and Table S4, E40 qd was well tolerated over 4 weeks of treatment. There were no deaths or discontinuations due to adverse events. There were 3 serious adverse events in 2 patients, none of which was attributed to study treatment.

Table S3 N (%) of patients with adverse events by category (safety population)

Category of adverse event (AE)	E40 (N=358)
Any AE	77 (21.5%)
Serious AE (SAE)	2 (0.6%)
AE leading to discontinuation of study treatment (DAE)	0
Treatment-related AE	17 (4.7%)

Note: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
E40 is esomeprazole 40 mg qd.

Table S4 Number (%) of patients with the most commonly reported post-treatment adverse events (safety population)

Most commonly reported post-treatment AEs[a]	
Adverse event (preferred term)	**E40 (N=358)**
Headache	14 (3.9%)
Diarrhea	11 (3.1%)
Abdominal pain	5 (1.4%)
Flatulence	4 (1.1%)
Nausea	4 (1.1%)
Bronchitis	4 (1.1%)
Sinusitis	4 (1.1%)
Urinary tract infection	4 (1.1%)

[a] Events with a frequency >1% (ie, ≥4 patients) are included in this table.
E40 is esomeprazole 40 mg qd.

There were isolated changes, but no notable trends, in the laboratory test results and vital signs data.

Date of the report

20 March 2007