AstraZeneca

Clinical Study Report

Drug substance:	Esomeprazole magnesium
Edition No.:	FINAL
Study code:	D9612L00062
Date:	6 March 2006

A Multicenter, Double-Blind, Randomized Trial of the Relationship of Intragastric Acid Control and Healing Status of Moderate and Severe Erosive Esophagitis After Treatment with Esomeprazole Magnesium (NEXIUM®) 10 mg and 40 mg Once Daily

Study dates: First patient enrolled: 29 June 2004
Last patient enrolled: 11 July 2005

Phase of development: Phase IV

This study was performed in compliance with Good Clinical Practice.

Drug product:	NEXIUM®	**SYNOPSIS**	
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Coordinating investigator

Not applicable

Study center(s)

This study was conducted at 33 study sites in the United States, 30 of which enrolled patients.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	29 June 2004	Therapeutic use (IV)
Last patient completed	5 August 2005	

Objectives

Primary: To determine the relationship between 24-hour intragastric pH at Day 5 and healing status of moderate to severe erosive esophagitis (EE) patients, defined by LA Classification as Grade C or D, after 4 weeks of treatment with 2 doses of esomeprazole magnesium.

Secondary: To compare the 24-hour intragastric pH at Day 5 of the patients who have resolved their heartburn symptoms (overall treatment effect responders), with those with continued heartburn symptoms (overall treatment effect non-responders) at the end of the 4-week treatment period.

Secondary: To determine the relationship between 24-hour intragastric pH at Day 5 and change of patients' symptoms from baseline to final visits.

Secondary: To determine the relationship between healing status at the end of 4 weeks and the use of rescue medication for GERD-related symptoms throughout the study period.

Study design

This was a 4-week, multicenter, double-blind, randomized study. Approximately 120 randomized male and female patients with moderate to severe EE [LA Grade C or D verified by esophagogastroduodenoscopy (EGD)] were to be randomized to 1 of 2 treatment groups: esomeprazole magnesium 10 mg or 40 mg once daily for 4 weeks (E10 or E40). On Day 14, patients were to return to the site for hematology assessments. Outcome measures included a 24-hour intragastric pH study on Days 5-6 of therapy, a final EGD evaluation on Day 28, investigator assessment of gastroesophageal reflux disease (GERD) symptoms at the baseline and final visits, and investigator assessment of overall treatment effect (based on heartburn resolution) at the final visit.

Target patient population and sample size

Male and female patients aged 18 to 75 years diagnosed with moderate to severe EE (LA Grade C or D). It was estimated that a sample size of 50 evaluable patients per dose group (100 total) would provide approximately 90% power to detect a correlation of 0.32 at an alpha level of 0.050.

Investigational product and comparator(s): dosage, mode of administration, and batch numbers

- E10: esomeprazole magnesium 10 mg capsule taken orally before breakfast (batch number H1221-02-01-06)
- E40: esomeprazole magnesium 40 mg capsule taken orally before breakfast (batch number H1222-04-01-11)

Duration of treatment

4 weeks (26 – 30 days)

Criteria for evaluation (main variables)

The intent of this study was not to evaluate the efficacy of the treatment arms, but to evaluate the relationship between intragastric acid control and EE healing, GERD symptoms, and rescue medication use, based on the following variables:

- *Primary:* EE healing status on Day 28
- *Primary:* Percentage of the 24-hour intragastric pH monitoring period with pH >4.0 on Day 5
- *Secondary:* 24 hour integrated gastric acidity (IGA) on Day 5
- *Secondary:* Overall treatment effect (ie, heartburn symptom resolution)
- *Secondary:* Investigator assessment of GERD-related symptoms

- *Secondary:* Use of rescue medication
- *Secondary:* Standard safety assessments, including adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations.

Statistical methods

The primary analysis was a Spearman rank correlation calculated for the primary endpoints--healing status and the percentage of time the 24-hour intragastric pH >4.0--using the Per-protocol (PP) population. A test was conducted of the null hypothesis of no correlation.

Patient population

The study population was predominantly male, Caucasian, *Helicobacter pylori*-negative, and overweight, and was representative of the target patient population with respect to demographics, baseline characteristics, and medical history. There was good compliance with study treatment and procedures, and the concomitant medications taken were reasonable in a clinical context.

Table S1 Patient population and disposition

		E10	E40	Total
Patient disposition				
N randomized		80 (100%)	89 (100%)	169 (100%)
Completed study: n (%)		66 (83%)	65 (73%)	131 (78%)
Discontinued: n (%)		14 (18%)	24 (27%)	38 (23%)
N analyzed for safety [a]		77 (96%)	88 (99%)	165 (98%)
N analyzed for efficacy (ITT)[b]		80 (100%)	89 (100%)	169 (100%)
N analyzed for efficacy (PP)[c]		53 (66%)	50 (56%)	103 (61%)
Demographic characteristics (PP population)				
Gender: n (%)	Male	32 (60%)	35 (70%)	67 (65%)
	Female	21 (40%)	15 (30%)	36 (35%)
Age in years:	Mean (SD)	50.0 (12.5)	47.4 (11.6)	48.7 (12.1)
	Range	23 - 74	18 - 67	18 - 74
Race: n (%)	Caucasian	47 (89%)	47 (94%)	94 (91%)
	Black	4 (8%)	3 (6%)	7 (7%)
	Oriental	1 (2%)	0	1 (1%)
	Other	1 (2%)	0	1 (1%)
Baseline characteristics (PP population)				
Reflux history (months)	Mean (SD)	125 (111)	105 (106)	115 (108)
	Range	7 - 420	0 - 360	0 - 420
EE history: n (%)	No	43 (81%)	39 (78%)	82 (80%)
	Yes	10 (19%)	11 (22%)	21 (20%)

		E10	E40	Total
H. pylori serology: n (%)	Negative	46 (87%)	49 (98%)	95 (92%)
	Positive	7 (13%)	0	7 (7%)
	Unknown	0	1 (2%)	1 (1%)
BMI (kg/mm)	Mean (SD)	30.4 (5.5)	30.4 (6.5)	30.4 (6.0)
	Range	19 - 50	21 - 51	19 - 51

[a] Number of patients who took at least 1 dose of study drug.
[b] Number of patients who were randomized.
[c] Number of patients who met predefined criteria for evaluability (primary analysis population).
E10 = esomeprazole 10 mg qd; E40 = esomeprazole 40 mg qd.
N = number; ITT = Intention to treat; PP = Per-protocol.

Clinical and pharmacodynamic efficacy results

All analyses indicated a significant, positive relationship between intragastric acid control and EE healing; ie, healing was associated with increased acid control. There was a significant, negative relationship between EE healing and use of rescue medication; ie, healed patients used less rescue medication over the study period than unhealed patients. The negative relationship between intragastric acid control and change in GERD symptom severity did not reach statistical significance, but there was a significant, negative relationship between intragastric acid control and final severity of daytime heartburn, nocturnal heartburn, and acid regurgitation: increased acid control was associated with decreased final symptom severity.

Table S2 Summary of the results on intragastric pH control, EE healing, GERD symptom control, and use of rescue medication (PP population)

Relationship tested	Variables	Test	Result
Intragastric acid control and EE healing[a]	% time with intragastric pH >4.0 on Day 5 and EE healing status (healed/not healed) on Day 28	Spearman rank correlation	Correlation=34.2%; p=0.0004
		Logistic regression	Odds ratio=1.035; p=0.0002
		T-test on means	61.3% for healed vs 42.1% for not healed; p=0.0002
	24-hour IGA on Day 5 and EE healing status on Day 28	Spearman rank correlation	Correlation=-20.9%; p=0.034
Intragastric acid control and GERD symptom control	% time with intragastric pH >4.0 on Day 5 and overall treatment effect (heartburn resolved/not resolved) during Week 4	T-test on means	60.3% for resolved vs 51.6% for not resolved; p=0.0778

Relationship tested	Variables	Test	Result
	% time with intragastric pH >4.0 on Day 5 and GERD symptom severity[b] on Day 28:	Spearman rank correlation	
	Daytime heartburn		Correlation=-29.0%; p=0.003
	Nighttime heartburn		Correlation=-28.6%; p=0.003
	Acid regurgitation		Correlation=-21.1%; p=0.032
	Dysphagia		Correlation= -7.6%; p=0.446
	Epigastric pain		Correlation=-11.6%; p=0.242
	% time with intragastric pH >4.0 on Day 5 and change in GERD symptom severity[b] from baseline to Day 28:	Spearman rank correlation	
	Daytime heartburn		Correlation=-16.7%; p=0.092
	Nighttime heartburn		Correlation=-18.8%; p=0.057
	Acid regurgitation		Correlation= -9.2%; p=0.356
	Dysphagia		Correlation= -0.4%; p=0.972
	Epigastric pain		Correlation= 8.1%; p=0.417
EE healing and rescue medication use	EE healing status (healed/not healed) on Day 28 and mean daily use of GELUSIL®	T-test on means	0.45 tablets/day for healed vs 0.91 tablets/day for not healed; p=0.0098

[a] Healed = EE not present.
[b] Severity scale: 0=None, 1=Mild, 2=Moderate, 3=Severe.
EE = erosive esophagitis; GERD = gastroesophageal reflux disease; PP = Per-protocol; IGA = Integrated gastric acidity.

Safety results

Both treatment regimens were well tolerated and were similar with respect to the type, frequency, and severity of adverse events. There were no deaths or serious adverse events. None of the events leading to discontinuation was attributed to study treatment.

Table S3 Number (%) of patients who had at least 1 adverse event in any category[a] (safety population)

Category of adverse event (AE)	E10 (N=77)	E40 (N=88)	Overall (N=165)
Any AE	25 (33%)	26 (30%)	51 (31%)
Serious AE	0	0	0
Discontinuations of study treatment due to AE	0	3 (3%)	3 (2%)
Treatment-related AE	4 (5%)	4 (5%)	8 (5%)

[a] 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.
E10 = esomeprazole 10 mg qd; E40 = esomeprazole 40 mg qd.

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

Adverse event (preferred term)	Number (%) of patients who had an adverse event[a]		
	E10 (N=77)	E40 (N=88)	Overall (N=165)
Gastritis erosive	4 (5%)	0	4 (2%)
Nasopharyngitis	1 (1%)	3 (3%)	4 (2%)
ALT increased	3 (4%)	0	3 (2%)
Vomiting	2 (3%)	1 (1%)	3 (2%)
AST increased	2 (3%)	0	2 (1%)
Barrett's esophagus	0	2 (2%)	2 (1%)
Edema peripheral	2 (3%)	0	2 (1%)
Herpes simplex	2 (3%)	0	2 (1%)

[a] Events with a total frequency of ≥2% in either treatment group are included in this table.

E10 = esomeprazole 10 mg qd; E40 = esomeprazole 40 mg qd; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

There were no notable trends for any laboratory parameter or vital sign. The mean changes in vital signs were minor and were not clinically significant.

Date of the report

6 March 2006