AstraZeneca

Clinical Study Report

Drug substance:	Esomeprazole
Edition No.:	FINAL
Study code:	D9612L00064
Date:	24 March 2006

A 4-week Study to Investigate the Relationship between Resolution of Acid-Associated Heartburn Symptoms and Dose of Esomeprazole Magnesium

Study dates: First patient enrolled: 11 November 2004
Last patient enrolled: 3 June 2005

Phase of development: Phase IV

This study was performed in compliance with Good Clinical Practice.

Drug product:	NEXIUM®	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
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A 4-week Study to Investigate the Relationship between Resolution of Acid-Associated Heartburn Symptoms and Dose of Esomeprazole Magnesium

Study center(s)

This study was conducted at 25 study centers in the United States (US).

Publications

None at the time of writing this report.

Study dates

First patient enrolled 11 November 2004
Last patient completed 22 July 2005

Phase of development

Therapeutic use (IV)

Objectives

The objective of this proof-of-concept study was to investigate the relationship between dose of esomeprazole magnesium and acid-associated heartburn symptoms during 4 weeks of treatment. The safety and tolerability of esomeprazole magnesium in doses up to 40 mg BID were also assessed.

Study design

This was a multicenter, double-blind, parallel-group, randomized, proof-of-concept trial. After screening assessments and a 2-week run-in period, patients were randomized to receive 4 weeks of treatment in 1 of the following 3 arms: 20 mg once daily (QD), 40 mg QD, or 40 mg twice daily (BID) of esomeprazole magnesium. A follow-up visit was to occur at Week 4.

Target patient population and sample size

Approximately 330 male and female patients between the ages of 18 and 75 inclusive who reported a history of at least 6 months with heartburn, reported prior symptomatic response to antacid use and/or acid suppressive, had a positive esophageal acid perfusion test, and were *Helicobacter pylori* (*H. pylori*) negative were to be enrolled into this study.

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

- E20 QD regimen: Esomeprazole 20 mg capsule taken orally 30 minutes prior to breakfast (batch number H1189-04-01-09) and placebo capsule taken orally 30 minutes prior to dinner (batch number H0459-06-03-11)
- E40 QD regimen: Esomeprazole 40 mg capsule taken orally 30 minutes prior to breakfast (batch number H1222-04-01-12) and placebo capsule taken orally 30 minutes prior to dinner (batch number H0459-06-03-11)
- E40 BID regimen: Esomeprazole 40 mg capsule taken orally 30 minutes prior to breakfast and 30 minutes prior to dinner (batch number H1222-04-01-12)

GELUSIL® was provided as a rescue medication to be used during the run-in period only.

Duration of treatment

4 weeks (26-32 days)

Criteria for evaluation (main variables)

- Sustained resolution of heartburn during the 4th week of treatment. Sustained resolution was defined as 7 consecutive days with a daily e-diary heartburn assessment of "None"
- Relief of heartburn during the 4th week of treatment. Relief was defined as 6 days with a daily e-diary assessment of 'none', and 1 day of either 'none' or 'mild'
- Cumulative daily sustained resolution rate through 4 weeks of treatment
- Time to the first day of the first 7-day period of sustained resolution of heartburn
- Time to the first day of the first 7-day period of relief of heartburn
- Percentage of heartburn-free days through 4 weeks of treatment
- Percentage of heartburn-free nights through 4 weeks of treatment
- Standard safety assessments, including adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations

Statistical methods

All of the outcome variables are presented descriptively. No inferential statistical methods were used. The efficacy data were summarized using both an Intent-to-treat (ITT) population and a Per-protocol (PP) population: The ITT population comprised all randomized patients who took at least 1 dose of study drug and had at least 1 post-treatment efficacy assessment; and the PP population was determined prior to unblinding the study, using a prospectively

defined set of evaluability guidelines. The safety population comprised all patients who took at least 1 dose of study drug.

Patient population

Disposition, demographic data, and baseline characteristics of the study population are shown in Table S1. The study population was *Helicobacter pylori*-negative with a mean age of 45 years; was predominantly female Caucasian, and overweight; was generally representative of the target patient population with respect to demographics and medical history; and was presumed to have acid-related heartburn, based on previous positive response to antacids or acid-suppressive therapy. A total of 16 patients discontinued before completing the study, due to adverse events (5 patients), loss to follow-up (3 patients), or other reason (8 patients). The most common reasons for exclusion from the PP population were concomitant medications and diseases or conditions that could affect symptomatic response to a PPI.

Table S1 Patient population and disposition

		Treatment group							
		20 mg QD		40 mg QD		40 mg BID		Total	
Patient disposition: n (%)									
Randomized		122	(100.0%)	121	(100.0%)	126	(100.0%)	369	(100.0%)
Completed study		119	(97.5%)	113	(93.4%)	121	(96.0%)	353	(95.7%)
Discontinued		3	(2.5%)	8	(6.6%)	5	(4.0%)	16	(4.3%)
Analyzed for safety [a]		122	(100.0%)	121	(100.0%)	126	(100.0%)	369	(100.0%)
Analyzed for efficacy (ITT)[b]		121	(99.2%)	121	(100.0%)	126	(100.0%)	368	(99.7%)
Analyzed for efficacy (PP)[c]		104	(85.3%)	100	(82.6%)	111	(88.1%)	315	(85.4%)
Demographic characteristics (ITT population):									
Gender: n (%)	Male	56	(46.3%)	51	(42.1%)	48	(38.1%)	155	(42.1%)
	Female	65	(53.7%)	70	(57.9%)	78	(61.9%)	213	(57.9%)
Age in years:	Mean (SD)	43.7	(13.5)	43.9	(12.1)	46.9	(13.2)	44.9	(13.0)
	Range	19	- 72	21	- 71	20	- 74	19	- 74
Race: n (%)	Caucasian	71	(58.7%)	72	(59.5%)	73	(57.9%)	216	(58.7%)
	Black	7	(5.8%)	10	(8.3%)	13	(10.3%)	30	(8.2%)
	Oriental	6	(5.0%)	4	(3.3%)	1	(0.8%)	11	(3.0%)
	Other	37	(30.6%)	35	(28.9%)	39	(31.0%)	111[d]	(30.2%)
BMI	Mean (SD)	29.2	(5.8)	29.8	(6.3)	30.5	(6.6)	29.8	(6.3)
	Range	18	- 57	18	- 52	19	- 64	18	- 64
Baseline characteristics (ITT population): n (%)									
Heartburn history:	0.5-5 years	7	(5.8%)	11	(9.1%)	8	(6.3%)	26	(7.1%)
	>5 years	114	(94.2%)	110	(90.9%)	118	(93.7%)	342	(92.9%)
EE history:	No	105	(86.8%)	106	(87.6%)	111	(88.1%)	322	(87.5%)
	Yes	16	(13.2%)	15	(12.4%)	15	(11.9%)	46	(12.5%)

[a] Number of patients who took ≥1 dose of study treatment.
[b] Number of patients who took ≥1 dose of study treatment and had ≥1 efficacy data point after dosing.
[c] Number of ITT patients who met predefined guidelines for evaluability.
[d] Approximately 90% of the patients of 'Other' race identified themselves as Hispanic.

E20 QD = esomeprazole 20 mg once daily; E40 QD = esomeprazole 40 mg once daily; E40 BID = esomeprazole 40 mg twice daily; N=Number; ITT=Intent to treat; PP=Per-protocol

Efficacy results

No clear dose-response relationship was apparent for any of the heartburn variables assessed.

Table S2 Efficacy summary by treatment group (ITT population)

Heartburn outcome variable	E20 QD		E40 QD		E40 BID	
	N	Result	N	Result	N	Result
Mean % of patients with sustained resolution during Week 4 (ie, no heartburn on any of the 7 days)	98	48.0%	91	44.0%	99	41.4%
Mean % of patients with relief during Week 4 (ie, 6 days with no heartburn, and 1 day of either no or mild heartburn)	98	59.2%	91	51.7%	99	53.5%
Cumulative daily sustained resolution rate through 4 weeks of treatment	43	62.8%	50	52.0%	50	62.0%
Mean number of days to the first day of the first 7-day period of sustained resolution	121	14.7	121	14.0	126	15.5
Mean number of days to the first day of the first 7-day period of relief	121	12.1	121	12.5	126	12.9
Mean % of heartburn-free days during Week 4	120	66.5%	112	62.4%	121	67.8%
Mean % of heartburn-free nights during Week 4	120	80.8%	112	78.0%	121	88.2%

E20 QD = esomeprazole 20 mg once daily; E40 QD = esomeprazole 40 mg once daily; E40 BID = esomeprazole 40 mg twice daily; SE = standard error; SD = standard deviation.

Safety results

The safety results of this study raised no concerns about esomeprazole. All 3 dose regimens were well tolerated. Adverse events (AEs) are summarized in Table S3 and Table S4. There were 3 serious AEs (SAEs), 1 prior to study treatment, none attributed by the investigator to esomeprazole. Five patients discontinued due to AEs.

With respect to clinical laboratory tests and vital signs, there were isolated changes but no notable within-or between-treatment trends.

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

Category of adverse event (AE)	20 mg QD (n=122)	40 mg QD (n=121)	40 mg BID (n=126)
Any AE	21 (17.2%)	22 (18.2%)	27 (21.4%)
Serious AE[a]	0	0	2 (1.6%)
Discontinuations of study treatment due to AEs	0	3 (2.5%)	2 (1.6%)
Treatment-related AEs	6 (4.9%)	12 (9.9%)	10 (7.9%)

[a] One additional serious AE occurred before study drug was started.
E20 QD = esomeprazole 20 mg once daily; E40 QD = esomeprazole 40 mg once daily; E40 BID = esomeprazole 40 mg twice daily.

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

	Number (%) of patients who had an AE			
AE preferred term	E20 QD (n=122)	E40 QD (n=121)	E40 BID (n=126)	Total (N=369)
Diarrhea	4 (3.3%)	7 (5.8%)	6 (4.8%)	17 (4.6%)
Headache	4 (3.3%)	5 (4.1%)	6 (4.8%)	15 (4.1%)
Nausea	3 (2.5%)	4 (3.3%)	1 (0.8%)	8 (2.2%)
Constipation	0	1 (0.8%)	4 (3.2%)	5 (1.4%)
Fatigue	0	4 (3.3%)	1 (0.8%)	5 (1.4%)
Nasopharyngitis	2 (1.6%)	2 (1.7%)	0	4 (1.1%)
URI	3 (2.5%)	0	1 (0.8%)	4 (1.1%)

[a] Events with a total frequency of ≥1% across all treatment groups are included in this table.
E20 QD = esomeprazole 20 mg once daily; E40 QD = esomeprazole 40 mg once daily; E40 BID = esomeprazole 40 mg twice daily.

Date of the report

24 March 2006