AstraZeneca

Clinical Study Report

Drug substance:	Esomeprazole magnesium
Edition No.:	1.41
Study code:	D9612L00082
Date:	25 October 2007

An Open-Label, 2-way Crossover Study of Steady-state Intragastric pH Control Comparing 2 Dosage Regimens of Esomeprazole and Lansoprazole in Barrett's Esophagus Patients

Study dates: First patient enrolled: 26 January 2006
Last patient enrolled: 16 February 2007

Phase of development: Therapeutic use (Phase IV)

This study was performed in compliance with Good Clinical Practice.

Drug product:	NEXIUM®	**SYNOPSIS**	
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An Open-Label, 2-way Crossover Study of Steady-state Intragastric pH Control Comparing 2 Dosage Regimens of Esomeprazole and Lansoprazole in Barrett's Esophagus Patients

Coordinating investigator (Not applicable)

Study center(s)

This study was conducted at 12 centers in the United States (a total of 15 sites were initiated; 15 sites received study drug and 12 sites enrolled patients).

Publications

Spechler SJ, Barker PN, Silberg DG. Intragastric Acid Control In Patients Who Have Barrett's Esophagus: Comparison of Once- and Twice-Daily Regimens of Esomeprazole and Lansoprazole. Proceedings of the American College of Gastroenterology Annual Scientific Meeting 2007: Abstract # 750748 Preview

Study dates

First patient enrolled: 26 January 2006
Last patient completed: 22 April 2007

Phase of development

Therapeutic use (IV)

Objectives

- *Primary*: To compare the pharmacodynamic efficacy of esomeprazole 40 milligrams (mg) once daily (qd) and lansoprazole 30 mg qd in controlling intragastric pH in Barrett's esophagus (BE) patients by evaluation of the percentage of time that intragastric pH is >4.0 over a 24-hour period at steady state

- *Secondary*: To compare the pharmacodynamic efficacy of esomeprazole 40 mg (E40) twice daily (bid) and lansoprazole 30 mg (L30) bid in controlling intragastric pH in BE patients by evaluation of the percentage of time that intragastric pH is >4.0 over a 24-hour period at steady state.

- *Secondary*: To compare the differential increase in pharmacodynamic efficacy of E40 and L30 in controlling pH in BE patients when increasing dosing from qd to bid by evaluation of the difference in the percentage of time with intragastric pH >4.0 over a 24-hour period at steady state between the 2 dosing regimens within each treatment arm (bid minus qd)

- *Secondary*: To compare the extent of intragastric acid control of E40 and L30 in BE patients by evaluation of the percentage of patients achieving intragastric pH >4.0 for >12 hours at steady state (qd to qd and bid to bid)

- *Secondary*: To assess the short-term safety and tolerability of E40 following qd and bid dosing.

Study design

Randomized, open-label, comparative, 2-way crossover, intragastric pH study of esomeprazole and lansoprazole in patients with documented BE

The study consisted of 2 dose-escalating treatment arms, each arm with a 15-day interval of qd dosing (referred to as a "treatment interval") followed by a 10-day treatment interval of bid dosing. The treatment arms were as follows:

- Arm A: E40 qd for 15 days followed by E40 bid for 10 days

- Arm B: L30 qd for 15 days followed by L30 bid for 10 days

Patients were randomized to 1 of 2 treatment sequences: Arm A followed by Arm B, or Arm B followed by Arm A. There was no washout period between treatment intervals or arms.

Target patient population and sample size

The study population was to include *Helicobacter pylori* (*H. pylori*)-negative male and female patients, ages 18 to 70 years inclusive, with histologically proven BE (columnar lined epithelium ≥2 cm) documented within 2 years of enrollment and without evidence of high-grade dysplasia or adenocarcinoma. Approximately 80 patients were to be randomized to obtain at least 60 PP evaluable patients.

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

E40 capsules administered orally approximately 30 minutes prior to breakfast during the qd dosing interval and approximately 30 minutes prior to breakfast and dinner during the bid dosing interval 4 (NDC # 0186-5040-54, lot # R3316 and F6030)

L30 capsules administered orally approximately 30 minutes prior to breakfast during the qd dosing interval and approximately 30 minutes prior to breakfast and dinner during the bid dosing interval (NDC # 0300-3046-13, lot # 305452E21 and 438722E80)

Duration of treatment

For each treatment arm, the minimum protocol-specified treatment schedule was 15 days of qd dosing, followed immediately by 10 days of bid dosing[1]. There was no washout period between the 2 treatment arms.

Criteria for evaluation (main variables)

- ***Primary:*** Percent time intragastric pH >4.0 over a 24-hour period at steady state following qd dosing
- ***Secondary:*** Percent time intragastric pH >4.0 over a 24-hour period at steady state following bid dosing
- ***Secondary:*** Difference (within patient) in the percentage of time with intragastric pH >4.0 over a 24-hour period at steady state between the 2 dosing regimens within each treatment arm (bid – qd)
- ***Secondary:*** Percentage of patients with intragastric pH >4.0 for >12 hours at steady state by treatment interval (ie, by treatment and regimen)
- ***Secondary:*** Standard safety assessments, including adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations.

Statistical methods

Two analysis sets were created for the pH data: the intent-to-treat (ITT) set and the per-protocol (PP) set. The PP set was considered primary, and comprised patients with valid pH data during all treatment intervals for a given endpoint and no major protocol deviations or violations that might affect the pharmacodynamic results.

The primary endpoint (percent time intragastric pH >4.0 following qd dosing) was analyzed using a mixed model with fixed effects for treatment sequence, treatment period, and treatment. Patients nested within a sequence were treated as a random effect. The least square means and their 95% confidence intervals (CIs) were calculated for each treatment. The least square mean, 95% CI, and associated p-value for the difference between treatments (E40 minus L30) are presented.

Patient population

Disposition and demographic data of the study population are shown in Table S1. These healthy volunteers were predominantly male Caucasians, with a mean age of 56 years. All

[1] For the per-protocol population analyses, a treatment schedule of 14 days and 9 days was accepted for qd and bid dosing, respectively.

were *Helicobacter pylori*-negative. Most of the patients in this trial had a high body mass index (BMI) (mean BMI of 30.5).

Thirty patients were discontinued from the study. The primary reasons for premature discontinuation from the study were patient unwillingness to continue study treatment (16 patients) and reasons listed as other (7 patients: 4 patients were withdrawn at the Sponsor's request and technical issues with pH monitoring occurred for 3 patients). Other reasons for discontinuation included adverse events (4 patients), eligibility criterion not fulfilled (2 patients), and development of study specific discontinuation criterion (1 patient).

A total of 83 patients completed the study and 46 of these patients were included in the PP analysis of the primary endpoint. The main reason patients were excluded from the PP analysis population was the lack of valid pH data during all treatment intervals for a given endpoint.

Table S1 Patient disposition, demographics, and baseline characteristics

	Treatment sequence					
	E40/L30 n=57		L30/E40 n=56		Total n=113	
Disposition	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Randomized	57	(100.0)	56	(100.0)	113	(100.0)
Completed protocol	40	(70.2)	43	(76.8)	83	(73.5)
Discontinued	17	(29.8)	13	(23.2)	30	(26.5)
N (%) analyzed for safety[a]	57	(100.0)	55	(98.2)	112	(99.1)
N (%) analyzed for efficacy (ITT)[b]	33	(57.9)	34	(60.7)	67	(59.3)
N (%) analyzed for efficacy (PP)[c]	22	(38.6)	28	(50.0)	50	(44.2)
Eligible for qd analysis	19	(33.3)	27	(48.2)	46	(40.7)
Eligible for bid analysis	20	(35.1)	21	(37.5)	41	(36.3)
Eligible for bid-qd analysis	17	(29.8)	20	(35.7)	37	(32.7)

		Analysis population				
Demographic characteristics		**All Randomized (n=113)**	**Safety (n=112)**	**ITT (n=67)**	**PP qd dosing (n=46)**	**PP bid dosing (n=41)**
Gender, n (%):	Male	82 (72.6)	81 (72.3)	47 (70.1)	31 (67.4)	27 (65.9)
	Female	31 (27.4)	31 (27.7)	20 (29.9)	15 (32.6)	14 (34.1)
Age (years):	Mean (SD)	56.0 (9.1)	55.9 (9.1)	57.3 (8.1)	58.1 (7.2)	58.9 (6.6)
	Range	31.0 - 70.0	31.0 - 70.0	31.0 - 70.0	41.0 - 70.0	43.0 – 69.0
Race, n (%):	Caucasian	109 (96.5)	108 (96.4)	65 (97.0)	44 (95.7)	40 (97.6)
	Black	0	0	0	0	0
	Oriental	0	0	0	0	0
	Other	4 (3.5)	4 (3.6)	2 (3.0)	2 (4.3)	1 (2.4)
Height (in)	Mean (SD)	68.9 (3.6)	68.9 (3.6)	68.3 (3.6)	68.2 (3.8)	67.6 (3.7)
	Range	59.0 – 76.0	59.0 – 76.0	59.0 – 74.0	59.0 – 74.0	59.0 – 74.0
Weight (lb)	Mean (SD)	206.2 (41.5)	205.7 (41.3)	203.0 (41.6)	200.2 (39.2)	199.5 (44.7)
	Range	122.0 – 308.0	122.0 – 308.0	123.0 – 308.0	123.0 – 290.0	123.0 – 308.0
BMI (kg/m^2)	Mean (SD)	30.5 (5.7)	30.5 (5.7)	30.6 (5.9)	30.2 (5.5)	30.6 (6.1)
	Range	19.7 – 47.4	19.7 – 47.4	20.5 – 47.4	20.5 – 47.4	20.5 – 47.4
Baseline characteristics						
H. pylori status, n (%)	Negative	113 (100.0)	112 (100.0)	67 (100.0)	46 (100.0)	41 (100.0)

[a] Number of patients who took ≥1 dose of study treatment and had ≥1 post-screening safety data point.
[b] Patients with at least 1 valid qd or bid pH measurement.
[c] Patients in either the PP qd or bid population (without major protocol violations or deviations).
E40 = esomeprazole 40 mg; L30 = lansoprazole 30 mg; qd = once daily; bid = twice daily,
ITT = Intention-to-treat; PP = Per-protocol.

Pharmacodynamic efficacy results

The primary variable in this study was steady-state gastric acid suppression, as determined by the total percentage of time (of 24 hours) that intragastric pH was above 4.0 at steady state after treatment with E40 qd or L30 qd.

As shown in Table S2, E40 qd displayed greater steady-state acid suppression than L30 qd as measured by LS mean percent time with pH above 4.0. After E40 qd administration, the pH was above 4.0 for 67.06% of the 24-hour period, or 16.1 hours, which was significantly longer ($p<0.0001$) than the percent time above pH 4.0 for L30 (50.81% or 12.2 hours).

Table S2 Summary of percent time (of 24 hours) intragastric pH was above 4.0 at steady state following qd dosing (PP population, n=46)

PPI and regimen	% time pH >4.0		LS mean (SEM) difference	p-value [a]
	Mean (SEM)	LS Mean (SEM)		
E40 qd	67.08 (2.16)	67.06 (2.59)	16.25 (2.74)	<0.0001
L30 qd	50.38 (2.86)	50.81 (2.59)		

[a] Analysis via mixed model with fixed effects for sequence, period, and treatment (with patients random).
E40 = esomeprazole 40 mg; L30 = lansoprazole 30 mg; qd = once daily; SEM = standard error of the mean; LS = least squares.

E40 also showed significantly greater acid suppression than L30, as assessed by percent time pH >4.0 following bid dosing. Following both qd and bid dosing, the percentage of patients with pH >4.0 for >12 hours was significantly higher with E40 compared to L30 (87.0% vs 52.2%, respectively; p=0.0004 following qd dosing, and 97.6% vs 80.5%, respectively; p=0.0156 following bid dosing). There was no evidence of a differential increase in the amount of acid suppression between treatment groups when dosing increased from a once daily to a twice daily treatment regimen.

Safety results

As shown in Table S3 and Table S4, E40 and L30 were well tolerated, during both qd and bid dosing. AEs were reported most frequently during E40 bid and L30 qd treatments. Diarrhea, anxiety, headache, and nausea were the most frequently reported AEs during the study. Diarrhea, anxiety, and nausea were most often reported during the L30 qd treatment period. Two patients had AEs that were attributed to study treatment by the investigators; these events were diarrhea (2 patients) and abdominal pain (1 patient) and all were reported during the L30 qd treatment period.

One patient reported 2 SAEs during the study and 1 patient, who discontinued due to an AE, experienced a worsening of that AE following study completion that met the criteria for an SAE. No SAEs or discontinuations were attributed to study drug. No deaths occurred during the study.

Table S3 Number (%) of patients who had an adverse event in each category by treatment and regimen (safety population)

Category of AE	E40 qd (n=102)	E40 bid (n=92)	L30 qd (n=98)	L30 bid (n=91)	Total (n=112)
Any AE	12 (11.8)	16 (17.4)	17 (17.3)	10 (11.0)	38 (33.9)
SAE leading to death	0	0	0	0	0
SAE not leading to death[a]	0	0	0	1 (1.1)	1 (0.9)
DAE	0	0	3 (3.1)	1 (1.1)	4 (3.6)
Treatment-related AE	0	0	2 (2.0)	0	2 (1.8)

[a] One event is not included in the clinical database. The event met the criteria for an SAE; however, the event occurred after the patient was discontinued from the study due to an AE. The SAE was a worsening of an AE that occurred during L30 bid dosing.

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. An AE that started in a given treatment interval and continued into ≥1 other treatment interval was counted under all relevant treatments.

E40 = esomeprazole 40 mg; L30 = lansoprazole 30 mg; qd = once daily; bid = twice daily; AE = adverse event; SAE = serious AE; DAE = AE leading to discontinuation of study treatment.

Table S4 Number (%) of patients with the most commonly reported[a] AEs (Safety population, n=112)

AE (preferred term)	E40 qd (n=102)	E40 bid (n=92)	L30 qd (n=98)	L30 bid (n=91)
Diarrhea	0	1 (1.1)	5 (5.1)	2 (2.2)
Anxiety	1 (1.0)	1 (1.1)	4 (4.1)	0
Headache	1 (1.0)	2 (2.2)	2 (2.0)	1 (1.1)
Nausea	0	0	5 (5.1)	1 (1.1)
Pharyngolaryngeal pain	1 (1.0)	3 (3.3)	0	1 (1.1)
Sinusitis	3 (2.9)	0	0	0
Fatigue	0	0	2 (2.0)	0
Flatulence	2 (2.0)	0	0	0
Hypertension	0	2 (2.2)	0	0
Pain in extremity	1 (1.0)	0	2 (2.0)	0

[a] This table includes only those events that occurred in at least 2 patients during the study.

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. AEs are associated with the last treatment taken prior to the time of onset, or worsening.

AE = adverse event; E40 = esomeprazole 40 mg; L30 = lansoprazole 30 mg; qd = once daily; bid = twice daily.

Review of the clinical laboratory, physical examination, and vital sign data did not reveal any unexpected trends within or between treatments. The safety data for this study were consistent with the known safety profile of esomeprazole.

Date of the report

25 October 2007