Clinical Study Report

Drug substance:	Esomeprazole
Study code:	D9612L00106
Date:	7 November 2007

A Randomized, Open-Label, Comparative 3-way Crossover Study of 24-hour Intragastric pH Profile of Once Daily Oral Administration of Esomeprazole 40 mg, Lansoprazole 30 mg, and Pantoprazole 40 mg at Steady State in Hispanic Patients with Symptomatic GERD

Study dates:	First patient enrolled: 20 October 2006 Last patient enrolled: 02 April 2007
Phase of development:	IV

This study was performed in compliance with Good Clinical Practice.

Drug substance(s):	Esomeprazole	**SYNOPSIS**	
Study code:	D9612L00106		
Date:	26 October 2007		

A Randomized, Open-Label, Comparative 3-way Crossover Study of 24-hour Intragastric pH Profile of Once Daily Oral Administration of Esomeprazole 40 mg, Lansoprazole 30 mg, and Pantoprazole 40 mg at Steady State in Hispanic Patients with Symptomatic GERD

Study center(s)

This study was conducted at 8 study sites in the United States and territories.

Publications

There were no publications at the time of this report.

Study dates		**Phase of development**
First patient enrolled	20 October 2006	Therapeutic use (IV)
Last patient completed	21 May 2007	

Objectives

The primary objective of this study was to compare the pharmacodynamic efficacy in controlling intragastric pH following administration of esomeprazole 40 mg (E40), lansoprazole 30 mg (L30) and pantoprazole 40 mg (P40) taken orally, once daily (qd) in Hispanic patients with symptomatic gastroesophageal reflux disease (GERD).

The secondary objectives of this study were:

1. To compare nocturnal intragastric acid control in Hispanic patients with symptomatic GERD taking E40, L30, or P40 qd

2. To compare integrated gastric acidity (IGA) during the 24-hour monitoring period on Day 5 among Hispanic patients with symptomatic GERD taking E40, L30, or P40 qd

3. To assess the short-term safety and tolerability of E40, L30, and P40 qd in Hispanic patients with symptomatic GERD

Study design

This was a randomized, open-label, comparative 3-way crossover study of the 24-hour intragastric pH profiles of once-daily oral administration of E40, L30, and P40 at steady state in Hispanic patients with symptomatic GERD.

Target patient population and sample size

Males and females, ages 18 to 69 inclusive with symptomatic GERD who were of Hispanic origin, defined according to the US Census definition as people who originated from Spanish speaking countries or regions. Hispanics could be of any race.

Approximately 90 patients were to be randomized to obtain at least 78 per-protocol evaluable patients. A total of 123 patients were randomized and 114 completed the study.

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

Esomeprazole 40 mg capsule taken orally 30 minutes prior to breakfast (batch numbers 2000099817 and 2000103444; manufacturing lot F1908).

Lansoprazole 30 mg capsule taken orally 30 minutes prior to breakfast (batch number 2000100270; manufacturing lot 426102E80).

Pantoprazole 40 mg tablet taken orally 30 minutes prior to breakfast (batch number 2000100014; manufacturing lot B54636).

GELUSIL® was provided as a rescue medication (batch numbers 2000099813 and 2000101853; manufacturing lot 06136B).

Duration of treatment

Approximately 6 weeks. The study design consisted of three 5- to 7-day treatment periods. The first and second treatment periods were followed by a 10- to 17-day washout period and cross-over.

Criteria for evaluation (main variables)

Efficacy

Efficacy was studied in terms of pharmacodynamic efficacy outcome variables.

- Primary variable: The percent time intragastric pH >4.0 during the 24-hour intragastric monitoring period on Day 5 for each treatment
- Secondary variable: The percent time with intragastric pH >2.5 and 6.0 during the 24-hour intragastric monitoring period on Day 5 for each treatment

- Secondary variable: The percent time with intragastric pH >2.5, 4.0, and 6.0 during the nocturnal period on Day 5 for each treatment

- Secondary variable: The mean hourly IGA during the 24-hour monitoring period on Day 5

All pharmacodynamic efficacy variables were evaluated using both a distal and a proximal electrode; data collected from the distal electrode was considered the primary analysis set. The primary (distal) electrode was placed 10 cm below the lower esophageal sphincter (LES) during the 1st pH recording using the LES locator and/or by esophageal manometry with the second electrode (proximal) placed 5 cm proximal to the tip.

Safety

Standard safety assessments included physical exam, vital signs, AE reports, and clinical laboratory tests.

Statistical methods

The primary endpoint (percent time pH >4.0 from distal probe) was summarized by treatment group and 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 2-sided 95% confidence intervals for the difference between E40 and L30 and the difference between E40 and P40 were calculated. The difference between E40 and L30 and the difference between E40 and P40 was tested using a significance level of 0.05. No adjustments were made for multiplicity.

The percent time with intragastric pH >2.5, 4.0, and 6.0 during the nocturnal period and the percent time with intragastric pH >2.5 and 6.0 during the 24-hour intragastric pH monitoring period was summarized and analyzed in the same manner as the primary endpoint. An additional secondary analysis of the primary endpoint compared the percentage of patients with pH >4.0 for at least 12 hours and at least 16 hours between the treatments. The pH analyses were repeated using measurements from the proximal probe (at 5 cm proximal to the tip) as the secondary analyses.

The mean hourly IGA during the 24-hour monitoring period on Day 5 was also summarized and analyzed in the same manner as the primary endpoint for each hour.

Short-term safety and tolerability data were summarized by treatment group.

Patient population

Disposition and demographic data of the study population are shown in Table S1. The Hispanic patients in this study were predominantly female and Caucasian with a BMI over 25, and generally representative of the target patient population with respect to demographics and medical history. The mean age was 39 years. Approximately half (46.3%) of the patients were born in the USA. The majority of patients had a mother or father from Mexico. Less than 30% of the randomized patients tested were *Helicobacter pylori* (*H. pylori*) positive.

A total of 9 patients were prematurely discontinued from the study. The reasons for withdrawal from the study were voluntary discontinuation by patient (5 patients), adverse event (3 patients), and severe non-compliance to protocol (1 patient). The remaining 114 patients completed the study and 83 of these patients were included in the PP analysis of the primary endpoint. Reasons for exclusion from the PP population included <3 valid pH studies, not receiving dose 25 to 60 minutes prior to breakfast, inclusive, and treatment compliance <75% or >125%.

Table S1 Patient population and disposition

		N (%) or mean (SD)	
Disposition			
N randomized		123	(100.0%)
N (%) of patients who:	Completed	114	(92.7%)
	Discontinued	9	(7.3%)
N (%) analyzed for safety[a]		123	(100.0%)
N (%) analyzed for efficacy (ITT)[b]		116	(94.3%)
N (%) analyzed for efficacy (PP)[c]		83	(67.5%)
Demographic characteristics (PP population[d])			
Sex, n (%)	Male	31	(37.3%)
	Female	52	(62.7%)
Age (years)	Mean (SD)	38.7	(13.2)
	Range	19 to 69	
Race, n (%)	White	72	(86.7%)
	Black or African American	5	(6.0%)
	American Indian or Alaska Native	4	(4.8%)
	Asian	1	(1.2%)
	Native Hawaiian or Other Pacific Islander	1	(1.2%)
Ethnic group, n (%)	Hispanic or Latino	83	(100.0%)
Height (in)	Mean (SD)	64.8	(4.0)
	Range	57.0 to 75.0	
Weight (lbs)	Mean (SD)	176.6	(43.7)
	Range	90.0 to 300.0	
Body Mass Index (kg/m^2)	Mean (SD)	29.4	(5.9)

		N (%) or mean (SD)
	Range	18.2 to 39.6
Baseline characteristics (PP population[d])		
H. pylori status (n and % of patients)	Yes	20 (24.1%)
	No	63 (75.9%)

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.
[b] Number of patients who were randomized and had valid intragastric pH data during at least 1 treatment interval for a given endpoint.
[c] Number of patients who were included in the ITT set, had valid intragastric pH data from the distal electrode during all treatment intervals for a given endpoint, and had no major protocol deviations or violations.
[d] Demography data presented for PP population (distal probe).
ITT intent-to-treat. PP per protocol. SD standard deviation.

Pharmacodynamic efficacy results

Analysis results derived from data collected from the distal electrode are summarized below. As shown in Table S2, E40 provided a significantly longer time with intragastric pH >4.0 over the 24-hour monitoring period. The LS mean percent time with intragastric pH above 4.0 was 10.5 percentage points higher with E40 than with L30, or 2.6 more hours over a 24-hour period. The difference versus P40 was greater: 18.4 percentage points or 4.4 hours.

Consistent with the results of the primary variable, E40 provided a significantly higher percentage of the 24-hour monitoring period with intragastric pH >2.5 and 6.0 compared to L30 and P40.

Table S2 Summary of percent time (of 24 hours) intragastric pH was above 2.5, 4.0, and 6.0 (PP population, distal electrode; n=83)

PPI	Mean (SEM)	LS mean (SEM)	LS mean (SEM) difference: E40 minus other PPI	p-value
Primary				
% time pH >4.0				
E40	74.18 (1.90)	74.41 (2.39)	NA	NA
L30	63.72 (2.44)	63.93 (2.39)	10.48 (1.98)	<0.0001
P40	55.81 (2.70)	55.97 (2.39)	18.44 (1.98)	<0.0001
Secondary				
% time pH >2.5				
E40	84.64 (1.56)	84.76 (1.92)	NA	NA
L30	78.81 (1.78)	78.90 (1.92)	5.85 (1.70)	0.0007
P40	71.95 (2.33)	72.01 (1.92)	12.75 (1.70)	<0.0001
% time pH >6.0				
E40	36.11 (2.38)	36.46 (2.36)	NA	NA
L30	28.16 (2.35)	28.45 (2.36)	8.00 (1.78)	<0.0001
P40	24.69 (2.18)	24.97 (2.36)	11.49 (1.78)	<0.0001

E40 esomeprazole 40 mg qd. L30 lansoprazole 30 mg qd. NA not applicable. P40 pantoprazole 40 mg qd.

E40 also provided a significantly higher percentage of the nocturnal monitoring period with intragastric pH >2.5 and 4.0 compared to L30 and P40. E40 provided a significantly higher percentage of the nocturnal monitoring period with intragastric pH >6.0 compared to P40, and a numerically higher percentage of the nocturnal monitoring period with intragastric pH >6.0 compared to L30 (p=0.0643).

E40 provided significantly lower IGA than P40 from Hour 1 through Hour 24 (ie, for 24/24 hours). Although E40 showed numerically lower IGA than L30 from Hour 1 through Hour 24, the difference did not reach statistical significance.

When analyses were repeated based on data collected from the proximal electrode, results were broadly supportive of those discussed above.

Safety results

All 3 PPIs were well tolerated. Adverse events were comparable among treatments with respect to type, frequency, and severity. There were no deaths, serious adverse events, or other significant adverse events. Three patients discontinued study medication as a result of an adverse event, none of which were considered treatment-related. Adverse events are

summarized by category in Table S3, and the incidences of the more common events are shown in Table S4.

No clinically important trends within or between treatments were observed for clinical laboratory or vital signs results.

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of patients who had an adverse event in each category[a]					
	E40 (n=118)		L30 (n=119)		P40 (n=121)	
Any adverse events	22	(18.6%)	15	(12.6%)	15	(12.4%)
Serious adverse events leading to death	0		0		0	
Serious adverse events not leading to death	0		0		0	
Discontinuations of study treatment due to adverse events	1	(0.8%)	0		2	(1.7%)
Treatment-related adverse events	3	(2.5%)	5	(4.2%)	3	(2.5%)
	Total number of adverse events[b]					
Adverse events	32		23		18	
Serious adverse events	0		0		0	
Discontinuations of study treatment due to adverse events	1		0		2	
Treatment-related adverse events	5		8		4	

[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.

[b] Events counted by preferred term, ie for patients with multiple events falling under the same preferred term, only 1 occurrence of the event is combined. Therefore, number of events recorded can exceed number of patients.

E40 esomeprazole 40 mg qd. L30 lansoprazole 30 mg qd. P40 pantoprazole 40 mg qd.

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

Adverse event (preferred term)	Number (%) of patients who had an adverse event[a]			
	E40 (n=118)	L30 (n=119)	P40 (n=121)	Total (n=123)
Headache	4 (3.4%)	4 (3.4%)	5 (4.1%)	10 (8.1%)
Pharyngolaryngeal Pain	3 (2.5%)	4 (3.4%)	1 (0.8%)	8 (6.5%)
Nasopharyngitis	4 (3.4%)	0	3 (2.5%)	7 (5.7%)
Diarrhea	1 (0.8%)	2 (1.7%)	3 (2.5%)	6 (4.9%)
Abdominal Distension	2 (1.7%)	2 (1.7%)	0	3 (2.4%)
Dry Mouth	1 (0.8%)	1 (0.8%)	1 (0.8%)	3 (2.4%)
Joint Sprain	2 (1.7%)	1 (0.8%)	0	3 (2.4%)

[a] Events with a total frequency of ≥2% (ie, 3 patients) across all treatment groups are included in this table.
E40 esomeprazole 40 mg qd. L30 lansoprazole 30 mg qd. P40 pantoprazole 40 mg qd.

Date of the report

26 October 2007