AstraZeneca

Drug product:	NEXIUM®	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
Edition No.:			
Study code:	D9612L00063		
Date:	4 April 2005		

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 NSAID-using Patients

Study centers

This study was conducted at 7 study sites in the United States.

Publications

None at the time of writing this report.

Study dates:

First patient enrolled 23 June 2004

Last patient completed 3 November 2004

Phase of development:

Therapeutic use (IV)

Objectives

- ***Primary****:* To compare the pharmacodynamic efficacy in controlling intragastric pH (percent time pH> 4.0) following administration of esomeprazole 40 mg, lansoprazole 30 mg and pantoprazole 40 mg taken orally, once daily in patients taking either nonselective or cyclooxygenase-2 (COX-2) selective nonsteroidal anti-inflammatory drugs (NSAIDs)

- To compare nocturnal intragastric acid control in NSAID-using patients taking esomeprazole 40 mg, lansoprazole 30 mg or pantoprazole 40 mg once daily

- To compare intragastric acid control utilizing thresholds other than pH 4.0 among NSAID-using patients taking esomeprazole 40 mg, lansoprazole 30 mg and pantoprazole 40 mg once daily

- To compare integrated gastric acidity during the 24-hour monitoring period on Day 5 among NSAID-using patients taking esomeprazole 40 mg, lansoprazole 30mg and pantoprazole 40 mg once daily

- To assess the short-term safety and tolerability of esomeprazole 40 mg, lansoprazole 30 mg and pantoprazole 40 mg once daily in NSAID-using patients

Study design

Multicenter, randomized, open-label, comparative, 3-way crossover study of the 24-hour intragastric pH profiles of once daily oral administration of esomeprazole 40 mg (E40), lansoprazole 30 mg (L30), and pantoprazole 40 mg (P40) at steady state (Day 5) in NSAID-using patients

Target patient population and sample size

Males and females, ages 18 to 70 years inclusive, with a medical condition that had required NSAID treatment for at least 5 days per week for 1 month prior to enrollment. The NSAID treatment was to remain at the minimum required daily dose. It was estimated that a total of 66 completed patients would provide 95% power to detect a difference of 7% between the treatment groups in the number of hours/24 where pH >4.0 with a significance level of 0.05.

Investigational product and comparators: dosage, mode of administration, and batch numbers

- Esomeprazole 40 mg capsule taken orally 30 minutes prior to breakfast (batch number H1222-04-01-11)

- Lansoprazole 30 mg capsule taken orally 30 minutes prior to breakfast (batch numbers 100132E21 and 166642E21)

- Pantoprazole 40 mg tablet taken orally 30 minutes prior to breakfast (batch numbers A55623 and A68777)

GELUSIL® was provided as a rescue medication.

Duration of treatment

Three 5-day treatment periods, with 10-17 days of washout between Periods 1 and 2, and between Periods 2 and 3

Criteria for evaluation (main variables)

- ***Primary***: The percentage of time with intragastric pH >4.0 during the 24-hour monitoring period on Day 5

- The percentage of time with intragastric pH >2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, and 6.0 during the nocturnal period on Day 5

- The percentage of time with intragastric pH >2.5, 3.0, 3.5, 4.5, 5.0, 5.5, and 6.0 during the 24-hour monitoring period on Day 5
- The mean hourly integrated gastric acidity (IGA) during the 24-hour monitoring period on Day 5
- Standard safety assessments, including adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations

Statistical methods

All pharmacodynamic efficacy variables were 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 for the difference between E40 and L30 and the difference between E40 and P40 were calculated. These differences were tested using a significance level of 0.05. The primary analysis used a Per-protocol (PP) population.

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

Patient population

The study population was predominantly female, Caucasian, and overweight, and was generally representative of the target patient population with respect to demographics and medical history (Table S1). About half of the patients were on nonselective NSAIDs, and about half had a history of GERD symptoms.

A total of 13 patients discontinued before completing the study, for the following reasons: unwilling to continue (6 patients), development of study-specific discontinuation criteria (lack of valid pH data; 4 patients), lost to follow-up (2 patients), and other (missed visit due to weather; 1 patient). These 13 patients were excluded from the PP analysis population due to lack of valid pH data for 1 or more of the 3 treatment periods.

Table S1 Patient population

		N (%) or mean (SD)
Disposition		
N randomized		90 (100)
N (%) of patients who	Completed	77 (85.6%)
	Discontinued	13 (14.4%)
N (%) analyzed for safety[a]		90 (100.0%)
N (%) analyzed for efficacy (ITT)		84 (93.3%)
N (%) analyzed for efficacy (MITT/PP)		77 (85.6%)
Demographic characteristics (PP population)		

		N (%) or mean (SD)
Sex, n (%)	Male	25 (32.5)
	Female	52 (67.5)
Age (years)	Mean (SD)	44.8 (13.8)
	Range	18 to 70
Race, n (%)	Caucasian	62 (80.5%)
	Black	13 (16.9%)
	Oriental	2 (2.6%)
Baseline characteristics (PP population)		
NSAID type, n (%)	Nonselective	39 (50.6%)
	COX-2 & ASA[b]	6 (7.8%)
	COX-2 only	38 (49.4%)
History of reflux, n (%)	Yes	43 (55.8%)
	Mean (SD) years	6 (7.9)
	No	34 (44.2%)

[a] Number of patients who took at least 1 dose of study treatment.
[b] A subgroup of the nonselective NSAID group.
N=Number; SD = standard deviation; ASA = aspirin; ITT=Intention-to-treat; MITT = Modified Intention-to-treat; PP=Per-protocol.

Pharmacodynamic results

As shown in Table S2, E40 provided a significantly longer time with intragastric pH >4.0 over the 24-hour monitoring period.

Table S2 Analysis of percent time (of 24 hours) intragastric pH was above 4.0 and comparisons between treatments (PP population, n=77)

	% time pH >4.0		LS mean (SEM) difference:	
PPI	Mean (SEM)	LS Mean (SEM)	E40 minus other PPI	p-value
E40	74.29 (2.02)	74.22 (2.38)	NA	NA
L30	66.44 (2.53)	66.45 (2.38)	7.77 (2.09)	0.0003
P40	60.73 (2.55)	60.78 (2.38)	13.44 (2.09)	<0.0001

PP = Per-protocol; SEM = standard error of the mean; PPI = proton pump inhibitor; E40 = esomeprazole 40 mg qd; NA=not applicable; L30 = lansoprazole 30 mg qd; P40 = pantoprazole 40 mg qd.

The mean percent time with intragastric pH above 4.0 was 7.8 percentage points higher with E40 than with L30, or 1.9 more hours over a 24-hour period. The difference versus P40 was greater: 13.6 percentage points or 3.3 hours. Similar results were obtained for both the subgroup of patients taking COX-2 selective NSAIDs and the subgroup of patients taking nonselective NSAIDs.

The results for percent time with pH above the other pH thresholds were consistent with the results of the primary variable.

E40 provided significantly lower IGA than P40 from 1130 hours on Day 5 through 0430 hours on Day 6 (ie, for 18/24 hours), and significantly lower IGA than L30 from 2330 hours on Day 5 through 0030 hours on Day 6 (ie, for 2/24 hours). There were no other significant treatment differences.

During the nocturnal period, the percent time with intragastric pH above 4.0 was consistently numerically higher for E40 than for both L30 and P40 at each pH threshold; however, none of the treatment differences was statistically significant.

Safety results

All 3 PPIs were well tolerated over the 5 days of treatment. There were no deaths, serious adverse events, or discontinuations due to adverse events. Adverse events are summarized by category in Table S3, and the incidences of the more common events are shown in Table S4.

Table S3 Summary of adverse events (safety population)

Category of adverse event (AE)	E40 (n=83)	L30 (n=85)	P40 (n=82)
	n (%) of patients who had an AE in each category[a]		
Any AE	8 (9.6%)	10 (11.8%)	12 (14.6%)
Treatment-related AE	1 (1.2%)	2 (2.4%)	1 (1.2%)
	Total number of AE		
AEs	11	13	13
Treatment-related AEs	1	2	2

[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.

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[a] post-treatment adverse events (safety population)

Adverse event (preferred term)	Number (%) of patients who had an adverse event			
	E40 (n=83)	L30 (n=85)	P40 (n=82)	Total (n=90)
Nausea	2 (2.4%)	2 (2.4%)	1 (1.2%)	4 (4.4%)
Abdominal pain	0	3 (3.5%)	0	3 (3.3%)
Dyspepsia	0	2 (2.4%)	1 (1.2%)	3 (3.3%)
Diarrhea	0	1 (1.2%)	1 (1.2%)	2 (2.2%)

[a] Events with a total frequency of ≥2% (ie, 2 patients) across all treatments are included in this table.

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

Date of the report

4 April 2005