Drug Substance(s)	Esomeprazole	**SYNOPSIS**	(For national authority use only)
Study Code	D9612C00026		
Date	1 December 2006		

An Open, Single-Centre, Randomized, 6-way Crossover, Dose-Response Comparative Study of Esomeprazole 20, 40 and 80 mg and Pantoprazole 20, 40 and 80 mg regarding 24-hour Intragastric pH following 5 Days Repeated Oral Dose Administration in Patients with Symptoms of Gastroesophageal Reflux Disease

Study centre(s)

This was a single-centre study

Study dates		**Phase of development**
First patient enrolled	15 February 2006	Clinical pharmacology (I)
Last patient completed	19 July 2006	

Objectives

The primary objective of this study was to investigate the dose-response relationship of esomeprazole and pantoprazole following repeated once daily (od) administration of 20, 40 and 80 mg esomeprazole and 20, 40 and 80 mg pantoprazole in patients with symptoms of Gastroesophageal Reflux Disease (GERD), by assessment of the percentage of time with intragastric pH>4 over the 24-hour period on study day 5.

The secondary objectives were:

1. To compare 20, 40 and 80 mg esomeprazole versus 20, 40 and 80 mg pantoprazole following repeated od administration in patients with symptoms of GERD, by assessment of the percentage of time with intragastric pH>4 over the 24-hour period, the 24-hour median pH and the area under the H^+ versus time curve on study day 5.

2. To investigate the dose-response relationship of esomeprazole and pantoprazole following repeated od administration of 20, 40 and 80 mg esomeprazole and 20, 40 and 80 mg pantoprazole in patients with symptoms of GERD, by assessment of the 24-hour median pH and the area under the H^+ versus time curve on study day 5.

3. To evaluate safety and tolerability of esomeprazole 20, 40 and 80 mg.

Study design

The study was conducted as a single-centre, open, randomized, 6-way crossover study in which patients with symptoms of GERD received 20, 40 or 80 mg esomeprazole or 20, 40 or 80 mg pantoprazole od for 5 days.

Target patient population and sample size

Thirty-nine (39) male and female patients with symptoms of GERD, with a minimum of 30% of either gender, were included in the study in order for at least 30 patients to complete the study.

With 30 evaluable patients, a two-sided 95% confidence interval (CI) for the difference in percentage of time with pH>4 between two doses, was to extend no more than 6.5% points from the observed mean difference, with 80% probability, assuming that the true standard deviation for the difference was 15.6% points. This assumption was based on data from previous studies.

Investigational products: dosage, mode of administration and batch numbers

Esomeprazole 20 mg capsules (batch number: H1189-04-01-09) and 40 mg capsules (batch number: H1222-04-01-15) given orally od for 5 days.

Esomeprazole 80 mg, given as two 40 mg capsules (batch number: H1222-04-01-15) orally od for 5 days.

Pantoprazole 20 mg tablets (batch number: H1560-01-02-01) and 40 mg tablets (batch number: H1131-04-02-01) given orally od for 5 days.

Pantoprazole 80 mg, given as two 40 mg tablets (batch number: H1131-04-02-01) orally od for 5 days.

Duration of treatment

Six (6) treatment periods of 5 days each. Each treatment period was separated by a wash-out period of at least 13 days.

Variables

- **Pharmacodynamic**

  The percentage of time with intragastric pH>4 during the 24-hour period (primary variable), the 24-hour median intragastric pH and the area under the H^+ versus time curve.

- **Safety**

  Adverse events, laboratory variables, blood pressure (BP), pulse and electrocardiogram (ECG).

Statistical methods

Consecutive doses of esomeprazole and pantoprazole respectively were compared regarding the percentage of time with intragastric pH>4, the 24-hour median pH and the area under the H^+ versus time curve during the 24-hour period following drug administration on day 5. A mixed model ANOVA (Analysis of variance) with fixed effects for period, sequence and treatment and a random effect for patient within sequence was used. The mean for each treatment and the mean difference between treatments (esomeprazole 40 mg vs. esomeprazole 20 mg, esomeprazole 80 mg vs. esomeprazole 40 mg, pantoprazole 40 mg vs. pantoprazole 20 mg and pantoprazole 80 mg vs. pantoprazole 40 mg) were estimated and stated with symmetric 95% CIs and p-values.

The same ANOVA model as above was used to compare esomeprazole vs. pantoprazole regarding the percentage of time with intragastric pH>4, the 24-hour median pH and the area under the H^+ versus time curve during the 24-hour period following drug administration on day 5. The mean for each treatment and the mean difference between treatments (esomeprazole 20 mg vs. pantoprazole 20 mg, esomeprazole 20 mg vs. pantoprazole 40 mg, esomeprazole 40 mg vs. pantoprazole 40 mg, esomeprazole 40 mg vs. pantoprazole 80 mg and esomeprazole 80 mg vs. pantoprazole 80 mg) were estimated and stated with symmetric 95% CIs. The p-value for each treatment comparison was calculated.

Adverse events (AEs), laboratory variables, BP, pulse and ECG are presented descriptively.

A Per Protocol approach was used for the statistical analysis.

Analysis and evaluation of safety variables were done in the safety population, defined as all patients who received at least one dose of randomized treatment with the investigational product and for whom post-dose data are available.

Patient population

In total, 53 patients from a single centre were enrolled into the study, of whom 39 were randomized (22 males and 17 females). Thirty-six (36) patients, 21 males and 15 females, completed the study. Forty (40) patients were planned to be included in the study in order to have 30 evaluable patients completing the study. However, 42 patients came for the baseline testing, of whom 3 dropped out on the baseline day. Therefore, a total of 39 patients were randomized into the study. Enough patients completed the study to fulfill the aim of 30 patients completing the study, as defined in the Clinical Study Protocol (CSP).

One (1) patient discontinued participation in the study due to AE (urticaria) in the wash-out period after treatment period 2. Two (2) patients discontinued the study after treatment periods 1 and 4, respectively, with the reason “not willing to continue”. These patients are included in the statistical analysis where data from two comparing study periods are available.

Thirty-nine (39) patients are included in the safety analysis.

Table S 1 gives descriptive statistics of the demographic data for the patients included in the safety population. All randomized patients were Caucasians.

Table S 1 Summary of baseline characteristics for all patients included in the safety population (n=39)

Statistic	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m²)
Mean	30.4	70.9	175.8	22.9
SD	8.0	9.5	8.7	2.0
Min	20.0	51.0	158.0	19.6
Median	28.0	72.0	174.0	22.5
Max	54.0	90.0	197.0	28.4

Summary of pharmacodynamic results

Increasing doses from 20 mg to 40 mg and from 40 mg to 80 mg of both esomeprazole and pantoprazole provided significantly increased acid control in terms of percentage of time with intragastric pH>4 over the 24-hour period (Table S 2 and Table S 3).

Esomeprazole 20 mg was shown to provide significantly greater acid control than both pantoprazole 20 mg and 40 mg, and esomeprazole 40 mg provided significantly greater acid control than both pantoprazole 40 mg and 80 mg. Also, esomeprazole 80 mg provided a significantly longer time with intragastric pH>4 than pantoprazole 80 mg (Table S 4).

The 24-hour median pH and the area under the H^+ versus time curve showed a similar pattern of effect to that for the percentage of time with intragastric pH>4, regarding the comparisons both within each drug and between the drugs.

Table S 2 Means and mean difference in percentage of time with intragastric pH>4 on Day 5 following repeated od administration of esomeprazole 20, 40 and 80 mg in patients with symptoms of GERD. Estimates, 95% CIs and p-values are presented

	n	Estimate	95% confidence interval		p-value
			Lower	Upper	
Esomeprazole 20 mg	36	47.66	42.00	53.33	.
Esomeprazole 40 mg	36	58.54	52.88	64.20	.
Esomeprazole 40 mg - esomeprazole 20 mg		10.88	5.35	16.40	0.0004
Esomeprazole 40 mg	35	58.60	53.99	63.22	.
Esomeprazole 80 mg	35	65.46	60.85	70.07	.
Esomeprazole 80 mg - esomeprazole 40 mg		6.85	2.16	11.54	0.0057

Table S 3 Means and mean difference in percentage of time with intragastric pH>4 on Day 5 following repeated od administration of pantoprazole 20, 40 and 80 mg in patients with symptoms of GERD. Estimates, 95% CIs and p-values are presented

	n	Estimate	95% confidence interval		p-value
			Lower	Upper	
Pantoprazole 20 mg	35	28.36	22.78	33.93	.
Pantoprazole 40 mg	35	36.87	31.30	42.44	.
Pantoprazole 40 mg - pantoprazole 20 mg		8.51	2.96	14.06	0.0039
Pantoprazole 40 mg	36	37.65	33.26	42.03	.
Pantoprazole 80 mg	36	44.72	40.34	49.11	.
Pantoprazole 80 mg - pantoprazole 40 mg		7.08	2.71	11.44	0.0024

Table S 4 Means and mean difference in percentage of time with intragastric pH>4 on Day 5 following repeated od administration of 20, 40 and 80 mg esomeprazole and pantoprazole in patients with symptoms of GERD. Estimates, 95% CIs and p-values are presented

	n	Estimate	95% confidence interval		p-value
			Lower	Upper	
Esomeprazole 20 mg	35	46.97	40.79	53.15	
Pantoprazole 20 mg	35	28.75	22.57	34.93	
Esomeprazole 20 mg - pantoprazole 20 mg		18.23	13.79	22.66	<0.0001
Esomeprazole 20 mg	35	47.41	41.69	53.14	
Pantoprazole 40 mg	35	37.59	31.86	43.31	
Esomeprazole 20 mg - pantoprazole 40 mg		9.83	4.97	14.69	0.0003
Esomeprazole 40 mg	35	59.01	54.02	63.99	
Pantoprazole 40 mg	35	37.73	32.75	42.72	
Esomeprazole 40 mg - pantoprazole 40 mg		21.27	16.46	26.08	<0.0001
Esomeprazole 40 mg	36	58.35	53.81	62.89	
Pantoprazole 80 mg	36	44.22	39.67	48.76	
Esomeprazole 40 mg - pantoprazole 80 mg		14.13	9.73	18.54	<0.0001
Esomeprazole 80 mg	36	65.69	61.75	69.64	
Pantoprazole 80 mg	36	43.58	39.63	47.52	
Esomeprazole 80 mg - pantoprazole 80 mg		22.12	17.87	26.36	<0.0001

Summary of safety results

The occurrence of AEs was similar in the different treatment groups. There were no serious adverse events (SAEs) and all pregnancy tests were negative. There was no discontinuation of investigational product due to AE but one patient discontinued participation in the study due to an AE (urticaria) in a wash-out period. No patients had any clinically significant laboratory

abnormalities and there were no clinically significant changes in laboratory values or vital signs.

No safety concerns were raised in the study.