

Drug product:	NEXIUM [®]	SYNOPSIS	
Drug substance(s):	Esomeprazole		
Edition No.:			
Study code:	D9612L00066		
Date:	21 April 2005		

A Randomized, Open-Label, Comparative, Two-Treatment, Crossover Study of the 24-Hour Intra-gastric pH Profile After 5 Days of Once Daily Oral Administration of Either Esomeprazole 40 mg or Pantoprazole 40 mg Following Once Daily Infusion of Intravenous Pantoprazole 40 mg for 5 Days in Healthy Volunteer Subjects

Study center(s)

This study was conducted at a single center in the United States.

Publications

None at the time of writing this report.

Study dates

First subject enrolled: 4 October 2004
 Last subject completed: 9 December 2004

Phase of development

Therapeutic use (IV)

Objectives

- **Primāry:** To compare intra-gastric acid control (the percent time intra-gastric pH>4.0 during the 24-hour intra-gastric pH monitoring period), on oral dosing Day 5, in subjects taking oral esomeprazole (NEXIUM[®] Delayed-Release Capsules¹) 40 mg once daily (qd) or oral pantoprazole (PROTONIX[®] Delayed-Release Tablets²,

¹ NEXIUM[®] is a trademark of the AstraZeneca group of companies.

² PROTONIX[®] Delayed-Release Tablets is a trademark, the property of Wyeth Laboratories, USA.

Wyeth) 40 mg qd for 5 days, following 5 days of intravenous (iv) pantoprazole (PROTONIX[®] I.V. for Injection³, Wyeth) 40 mg qd

- **Secondary:** To compare intragastric acid control, on oral dosing Day 1, in subjects taking oral esomeprazole 40 mg qd versus oral pantoprazole 40 mg qd for 5 days, following 5 days of iv pantoprazole 40 mg qd
- **Secondary:** To compare integrated gastric acidity (IGA), on oral dosing Days 1 and 5, in subjects taking esomeprazole, 40 mg qd, versus pantoprazole, 40 mg qd for 5 days, following 5 days of iv pantoprazole 40 mg qd
- **Secondary:** To assess the safety and tolerability of oral esomeprazole 40 mg qd and oral pantoprazole 40 mg qd following administration of iv pantoprazole

Study design

This was a randomized, open-label, comparative 2-way crossover study of the steady-state 24-hour intragastric pH profile of oral (po) administration of esomeprazole 40 mg qd (E40) and pantoprazole 40 mg qd (P40) following iv administration of pantoprazole 40 mg qd (P40 IV) for 5 days in healthy volunteer subjects. There were two 10-day treatment periods, with 10-21 days of washout between the 2 periods. The pH studies were done on oral dosing (po) Days 1 and 5 of each period.

Approximately 40 eligible subjects were to be randomized to receive 1 of 2 dosing sequences (IV:A, IV:B or IV:B, IV:A), where IV represents 5 days of P40 IV; and A and B represent the 5-day po treatment regimens, E40 and P40, respectively.

Target subject population and sample size

Healthy male and female subjects aged 18-70 years, inclusive, were eligible to participate in this study. Enrollment was to continue until 32 subjects had completed the study with evaluable pH data from po Day 5 of both treatment periods and no apparent major protocol deviations or violations that might affect gastric pH. It was anticipated that at least 28 of these 32 completed subjects would be deemed eligible for inclusion in the evaluable (per-protocol) population during the poststudy, blinded review of all available data, which would provide 95% power to detect a difference of 2.4 hours between the treatment groups with pH >4.0.

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

- Esomeprazole delayed-release capsules, 40 mg, taken orally approximately 30 minutes prior to breakfast (batch number H1222-04-01-11)

³ PROTONIX[®] I.V. for Injection is a trademark of Wyeth Pharmaceuticals, Inc., USA.

- Pantoprazole delayed-release tablets, 40 mg, taken orally approximately 30 minutes prior to breakfast (batch number A78098)
- Pantoprazole I.V. for Injection, 40 mg, administered as an injection over 2 minutes, given approximately 30 minutes prior to breakfast (batch numbers 14020A, 24058A, 24061A, 34085A, 34088A)

Duration of treatment

The total duration of treatment was 20 days, with a 10-21 day washout period between the two 10-day dosing periods. Each 10-day dosing period included 5 days of P40 IV, followed by 5 days of E40 or P40.

Criteria for evaluation (main variables)

- **Primary:** The percent of time with intragastric pH >4.0 during the 24-hour monitoring period on po Day 5
- **Secondary:** The percent of time with intragastric pH >4.0 during the 24-hour monitoring period on po Day 1
- **Secondary:** The hourly IGA during the 24-hour intragastric pH monitoring period on po Days 1 and 5
- **Secondary:** Standard safety assessments, including adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations

Statistical methods

All pharmacodynamic efficacy variables were summarized by treatment and analyzed using a mixed model with fixed effects for treatment sequence, treatment period, and treatment. Subjects 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 P40 were calculated.

An evaluable, or per-protocol (PP), dataset was created and utilized for all analyses and efficacy data summaries. The primary efficacy variable was also analyzed using an Intent-to-treat (ITT) population.

Subject population

Disposition and demographic data of the study population are shown in Table S1. These healthy volunteers were all *Helicobacter pylori*-negative Caucasians, predominantly male, with a mean age of 25 years. Four subjects were discontinued from the study due to problems with the pH probe. The remaining 38 subjects completed the study and were included in the PP population.

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Table S1 Subject disposition and demographics

		N (%) or mean (SD)
Disposition		
N randomized		42 (100.0%)
N (%) of subjects who:	Completed	38 (90.5%)
	Discontinued	4 (9.5%)
N (%) analyzed for safety ^a		42 (100.0%)
N (%) analyzed for efficacy (ITT) ^b		39 (92.9%)
N (%) analyzed for efficacy (PP) ^c		38 (90.5%)
Demographic characteristics (PP population)		
Sex, n (%):	Male	24 (63.2%)
	Female	14 (36.8%)
Age (years):	Mean (SD)	25 (8.1)
	Range	19 to 57
Race, n (%):	Caucasian	38 (100.0%)

^a Number of subjects who took at least 1 dose of study treatment.

^b Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing.

^c Number of ITT subjects who met predefined guidelines for evaluability.

N=Number; SD = standard deviation; ITT=Intention to treat; PP=Per-protocol.

Pharmacodynamic results

As shown in Table S2, on both po Day 1 and po Day 5, E40 provided a significantly greater percentage of the 24-hour monitoring period with intragastric pH >4.0. The 16.1 percentage point difference between the treatment means for the primary variable (po Day 5) is equivalent to 3.9 more hours in a 24-hour period with pH >4.0.

Table S2 Percent time (of 24 hours) with intragastric pH > 4.0 (PP population)

PPI	n	% time pH >4.0		LS mean (SEM) difference: E40 minus P40	p-value
		Mean (SEM)	LS Mean (SEM)		
Oral dosing Day 1					
E40	36	56.9% (2.3)	56.3% (2.6)	11.7 (2.1)	<0.0001
P40	38	44.6% (3.0)	44.6% (2.6)		
Oral dosing Day 5					
E40	38	62.6% (1.7)	62.6% (2.3)	16.1 (2.1)	<0.0001
P40	38	46.5% (2.7)	46.5% (2.3)		

PP = Per-protocol; PPI = proton pump inhibitor; SEM = standard error of the mean; E40 = po esomeprazole 40 mg qd; P40 = po pantoprazole 40 mg qd.

There were also significant treatment differences for IGA on both Day 1 and Day 5 of oral dosing, with E40 providing significantly lower 24-hour IGA than P40 at both timepoints.

Safety results

As shown in Table S3 and Table S4, all 3 treatments (E40, P40, and P40 IV) were well tolerated. The 1 SAE (exertional rhabdomyolysis) was considered unrelated to study treatment (this SAE was based on final visit laboratory tests, following treatment with P40).

Table S3 Number (%) of subjects who had an adverse event in each category (safety population)

Category of adverse event (AE)	P40 IV (n=42)	E40 (n=41)	P40 (n=40)
Any AE	7 (16.7%)	8 (19.5%)	9 (22.5%)
Serious AE (SAE)	0	0	1 (2.5%)
AEs leading to discontinuation	0	0	0
Treatment-related AE	1 (2.4%)	1 (2.4%)	1 (2.5%)

Note: Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

P40 IV = iv pantoprazole 40 mg qd; E40 = po esomeprazole 40 mg qd; P40 = po pantoprazole 40 mg qd.

Table S4 Number (%) of subjects with the most commonly reported^a adverse events (safety population)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event of each type			
	P40 IV (n=42)	E40 (n=41)	P40 (n=40)	Total (n=42)
Rhinitis	2 (4.8%)	1 (2.4%)	2 (5.0%)	5 (11.9%)
Headache	1 (2.4%)	2 (4.9%)	0	3 (7.1%)
Diarrhea	0	1 (2.4%)	1 (2.5%)	2 (4.8%)
Pharyngolaryngeal pain	1 (2.4%)	1 (2.4%)	0	2 (4.8%)

^a Events that occurred in at least 2 subjects are included in this table.

P40 IV = iv pantoprazole 40 mg qd; E40 = po esomeprazole 40 mg qd; P40 = po pantoprazole 40 mg qd.

There were no notable trends for any laboratory parameter or vital sign. No individual subject had a clinically significantly abnormal laboratory (other than the SAE), vital signs, or physical examination result.

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