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Clinical Study Report

Drug substance:	Esomeprazole sodium
Edition No.:	FINAL
Study code:	D9612L00080
Date:	7 July 2006

A Randomized, Open-Label, Comparative, Two-Treatment, Crossover Study of the 24-hour Intragastric pH Profiles of Esomeprazole 40 mg and Lansoprazole 30 mg in Healthy Volunteer Subjects on Days 1 and 5 of Intravenous Treatment

Study dates: First subject enrolled: 1 September 2005
Last subject enrolled: 10 January 2006

Phase of development: Therapeutic use (IV)

This study was performed in compliance with Good Clinical Practice.

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Drug product:	NEXIUM® I.V.	**SYNOPSIS**	
Drug substance(s):	Esomeprazole sodium		
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A Randomized, Open-Label, Comparative, Two-Treatment, Crossover Study of the 24-hour Intragastric pH Profiles of Esomeprazole 40 mg and Lansoprazole 30 mg in Healthy Volunteer Subjects on Days 1 and 5 of Intravenous Treatment

Coordinating investigator (Not applicable)

Study center(s)

This study was conducted at 2 centers in the United States.

Publications

None at the time of writing this report.

Study dates

First subject enrolled: 1 September 2005
Last subject completed: 14 February 2006

Phase of development

Therapeutic use (IV)

Objectives

- *Primary:* To compare the pharmacodynamic efficacy in controlling intragastric pH (percent time pH >4.0) of esomeprazole 40 mg (E40) and lansoprazole 30 mg (L30) on Day 5 of once daily (qd) intravenous (iv) administration to healthy volunteers.
- *Secondary:* To compare the pharmacodynamic efficacy in controlling intragastric pH (percent time pH >2.5, 6.0) of E40 iv and L30 iv on Day 5 of qd administration to healthy volunteers
- *Secondary:* To compare the pharmacodynamic efficacy in controlling intragastric pH (percent time pH >2.5, 4.0, 6.0) of E40 iv and L30 iv on Day 1 of qd administration to healthy volunteers
- *Secondary:* To assess the short-term safety and tolerability of E40 iv qd and L30 iv qd in healthy volunteers

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Study design

Randomized, open-label, comparative, 2-treatment, crossover study of the 24-hour intragastric pH profiles of E40 iv qd and L30 iv qd on Days 1 and 5 in healthy volunteers. Subjects were randomized into 1 of 2 dosing sequences (A, B or B, A) where each letter represents 1 of the 2 treatment regimens (A = E40 iv qd and B = L30 iv qd).

Target subject population and sample size

Approximately 100 male and female healthy volunteer subjects, ages 18 to 70 years inclusive, were to be enrolled to obtain 78 completed subjects. (In fact, 101 subjects were enrolled and 97 completed the study.)

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

- E40 iv qd, administered approximately 4 hours prior to breakfast on Days 1 and 5 (pH study days) and approximately 30 minutes prior to breakfast on Days 2-4 (NDC # 0186-6040-01, lot # 408068)

- L30 iv qd, administered approximately 4 hours prior to breakfast on Days 1 and 5 (pH study days) and approximately 30 minutes prior to breakfast on Days 2-4 (NDC # 0300-3954-25, lot # 29003RX)

Duration of treatment

Two 5-day dosing periods, separated by a 10-17 day washout period

Criteria for evaluation (main variables)

- ***Primary:*** Day 5 percent time intragastric pH >4.0 over 24 hours

- ***Secondary:*** Day 5 percent time intragastric pH >2.5, 6.0 over 24 hours

- ***Secondary:*** Day 1 percent time intragastric pH >2.5, 4.0, 6.0 over 24 hours

- ***Secondary:*** Standard safety assessments, including adverse events (AEs), clinical laboratory tests, vital signs, and physical examinations

Statistical methods

Intent-to-treat (ITT) and evaluable, or per-protocol (PP), populations were created and utilized for all analyses and efficacy data summaries. The PP population was considered primary. The pharmacodynamic efficacy variables were summarized by treatment and analyzed using a mixed model with fixed effects for treatment period and treatment. Subjects were treated as random effects. The PP models also included treatment sequence as a fixed effect. The ITT models did not include treatment sequence as an effect, because of a subject (not included in the PP population) who received a unique treatment sequence due to a dosing error. The least

squares mean and 95% confidence interval were calculated for each treatment and for the difference between treatments.

Subject 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 29 years. All were *Helicobacter pylori*-negative. Four subjects were discontinued from the study: 3 for lack of valid Period 1 pH data, 1 for study drug administration errors. The remaining 97 subjects completed the study and 96 of these subjects were included in the PP population.

Table S1 Subject population and disposition

Disposition			
N (%) randomized		101	(100.0%)
N (%) of subjects who:	Completed	97	(96.0%)
	Discontinued	4	(4.0%)
N (%) analyzed for safety[a]		101	(100.0%)
N (%) analyzed for efficacy (ITT)[b]		98	(97.0%)
N (%) analyzed for efficacy (PP)[c]		96	(95.0%)
Demographic characteristics (PP population)			
Gender, n (%):	Male	62	(64.6%)
	Female	34	(35.4%)
Age (years):	Mean (SD)	28.8	(11.1)
	Range	18	to 65
Race, n (%):	Caucasian[d]	90	(93.8%)
	Black	2	(2.1%)
	Other[d]	4	(4.2%)
BMI (kg/m^2)	Mean (SD)	25.5	(4.9)
	Range	16.3	to 42.0

[a] Number of subjects who took at least 1 dose of study treatment.
[b] Number of subjects who received drug and had evaluable pH data on Day 5 of ≥1 treatment period.
[c] Number of ITT subjects who met predefined guidelines for evaluability.
[d] Of the 4 subjects who identified themselves as Hispanic, 2 are in the Caucasian group, and 2 are in the Other group.
N=Number; SD = standard deviation; ITT=Intention to treat; PP=Per-protocol.

Pharmacodynamic results

As shown in Table S2, on both Day 1 and Day 5, E40 iv provided a significantly greater percentage of the 24-hour monitoring period with intragastric pH >4.0 than L30 iv. The 16.5 percentage point difference between the treatment means for the primary variable (Day 5) is equivalent to 4.0 more hours in a 24-hour period with pH >4.0.

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

PPI	n	LS Mean (SEM) % time pH >4.0	LS mean (SEM) difference: E40 iv minus L30 iv	p-value
Dosing Day 1				
E40 iv	96	39.98 (1.85)	6.42 (1.35)	<0.0001
L30 iv	96	33.56 (1.85)		
Dosing Day 5				
E40 iv	96	61.94 (1.44)	16.54 (1.22)	<0.0001
L30 iv	96	45.41 (1.44)		

PP = Per-protocol; PPI = proton pump inhibitor; SEM = standard error of the mean; E40 iv = iv esomeprazole 40 mg qd; L30 iv = iv lansoprazole 30 mg qd.

The results for the secondary pH thresholds were similar, and the ITT results were consistent with the PP results.

Safety results

As shown in Table S3 and Table S4, both treatments were well tolerated. There were no serious AEs or AEs leading to discontinuation. The AEs that were attributed to study treatment by the investigators were a moderate headache [began on Day 1, Period 1 (E40 iv) and lasted for 6 days] and mild chest discomfort [began on Day 2, Period 1 (L30 iv) and continued for 17 days, until Day 4, Period 2 (E40 iv)].

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

Category	E40 iv (n=98)	L30 iv (n=100)
Any AE	24 (24.5%)	22 (22.0%)
Serious AE (SAE)	0	0
AEs leading to discontinuation	0	0
Treatment-related AE	2 (2.0%)	1 (1.0%)

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. An event that began prior to Period 2 and continued after the first dose in Period 2 is counted under both treatments.

E40 iv = iv esomeprazole 40 mg qd; L30 iv = iv lansoprazole 30 mg qd.

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

AE (preferred term)	E40 iv (n=98)	L30 iv (n=100)
Infusion site reaction	11 (11.2%)	8 (8.0%)
Gastroenteritis viral	0	3 (3.0%)
Nausea	1 (1.0%)	2 (2.0%)
Upper respiratory tract infection	1 (1.0%)	3 (3.0%)
Headache	2 (2.0%)	0
Sinus congestion	2 (2.0%)	0

[a] Events that occurred in at least 2 subjects on a given treatment are included in this table.

Note: Subjects with multiple episodes of an AE are counted only once for that AE. An event that began prior to Period 2 and continued after the first dose in Period 2 is counted under both treatments.

E40 iv = iv esomeprazole 40 mg qd; L30 iv = iv lansoprazole 30 mg qd.

Isolated changes were observed in clinical laboratory test values, physical examinations, and vital signs, but there were no clinically important trends within or between treatments. The findings did not raise any safety concerns.

Date of the report

7 July 2006