AstraZeneca

Drug product	NEXIUM	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
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An Open, Randomized, Two-Way Crossover Study Comparing the Effect of 40 mg Esomeprazole Administered Orally and Intravenously as a 3-minute Injection on Basal and Pentagastrin-Stimulated Acid Output in Patients with Symptoms of Gastroesophageal Reflux Disease (GERD)

Study center(s): The study was conducted at 2 study sites in the US.

Publications: None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	21 September 2002	Therapeutic confirmatory (III)
Last patient completed	22 November 2002	

Objectives: Primary objective: To compare the maximal acid output (MAO) during pentagastrin stimulation after 10 days of oral dosing with esomeprazole to the MAO after 10 days of intravenous dosing with esomeprazole as a 3-minute injection. Both time points represent pharmacodynamic steady state.

Secondary objectives:

- To compare the basal acid output (BAO) at steady state and when switching (after Day 2 in the second treatment period versus after Day 10 in the first treatment period) from oral to intravenous dosing and from intravenous to oral dosing.
- To compare MAO when switching (after Day 2 in the second treatment period versus after Day 10 in the first treatment period) from oral to intravenous dosing and from intravenous to oral dosing.
- To evaluate the safety of intravenous esomeprazole in patients with symptoms of gastroesophageal reflux disease (GERD).

Study design: This was an open-label, randomized, multicenter, two-way crossover study. During each treatment period, patients with symptoms of GERD were administered a once-daily dose of esomeprazole 40 mg by study personnel either orally or intravenously as a 3-minute injection for 10 days (Days 1 to 10 and Days 11 to 20). There was no washout period between treatment periods. BAO and pentagastrin-stimulated MAO were measured on Days 11 and 13, prior to administration of study drug, and on Day 21.

Target patient population and sample size: Male and female patients aged 18 (or the legal age of consent) to 75 years who had heartburn on at least 2 of the 7 days prior to screening, with or without a history of erosive esophagitis (EE), or who had a documented diagnosis of GERD within 6 months prior to screening, with or without a history of EE were eligible. If the patient had a history of EE, it was to be documented by a previous endoscopy (either an endoscopy at any time in the past or the screening endoscopy). However, patients with Los Angeles Classification Grade (LA Grade) C or D esophageal erosions (ie, moderate to severe EE) confirmed on endoscopy during screening were not eligible for enrollment.

Up to a total of 60 patients were to be enrolled to ensure at least 40 patients were evaluable. A sample size of 38 patients would provide 90% power to reject the null hypothesis that the intravenous formulation was inferior to the oral formulation.

To ensure adequate representation of patients with and without a history of EE, the following targets were set: at least 25% of the randomized patients were to have active EE (LA Grades A or B) or a history of EE; and at least 25% were to have no history of EE and no active EE. Additionally, the randomized population was to be at least 25% male and at least 25% female.

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

-Esomeprazole powder for solution for injection, 40 mg, dissolved in sodium chloride solution (9 mg/mL) administered intravenously as a 3-minute injection, once daily. Batch number H 1516-03-01-02.
-Esomeprazole 40 mg delayed-release capsules administered orally, once daily. Batch number H 1222-04-01-09.
-Pentagastrin solution for injection, 0.025% w/v, administered subcutaneously on Days 11, 13, and 21 at a dose of 6 μg/kg. Batch number H 1580-01-01-03 (Manufacturer's lot number 1KK).

Additionally, the investigator supplied GELUSIL® tablets from commercial supplies at the site as rescue medication.

Duration of treatment: Each patient was administered 20 days of once-daily treatment by study personnel in this two-way crossover study; 10 days of esomeprazole 40 mg orally and 10 days of esomeprazole 40 mg intravenously as a 3-minute injection. There was no washout period between treatment periods.

Criteria for evaluation (main variables)

Pharmacodynamics: Primary variable: The MAO during pentagastrin stimulation 23-24 hours after 10 days of administration of 40 mg esomeprazole for both treatment periods.

Secondary variables: BAO 22-23 hours after 10 days of administration of 40 mg esomeprazole for both treatment periods. BAO and MAO 22-24 hours after 2 days of administration of 40 mg esomeprazole in the second treatment period. This gave information on any initial changes in BAO and MAO when switching from oral to intravenous (iv) esomeprazole and vice versa.

Safety: Safety endpoints included adverse event (AE) reports, clinical laboratory assessments (ie, chemistry, hematology, urinalysis), clinical assessments (ie, physical examination, vital signs), and 12-lead electrocardiogram assessments (ECG).

Statistical methods: All analyses of MAO and BAO were performed on the per-protocol (PP) population. The PP population included all patients who completed both treatment periods and who had MAO available for both treatment periods, with no major protocol violation. The intent-to-treat (ITT) population included all patients who were administered at least 1 dose of study medication, and had MAO available for at least 1 treatment period.

For the primary comparison (MAO after the last intravenous dose versus MAO after the last oral dose), log-transformed MAO was analyzed using mixed model analyses of variance with effects for sequence, patient (sequence), period, and formulation. First, the means and their 95% confidence intervals (CIs) for each formulation and the mean differences between formulations and their 1-sided upper limit of 95% confidence were estimated. These estimates were then anti–log-transformed to obtain the least squares (LS) geometric means of MAO for each formulation and their 95% CIs as well as the LS geometric mean ratios of MAO (intravenous versus oral) and their 1-sided upper limit of 95% confidence.

For the remaining comparisons of MAO (ie, when switching between iv and oral esomeprazole treatment), paired t-statistics for the log-transformed MAO were used to estimate mean differences between Period 1 and Period 2 and their 95% CIs. These estimates were then anti–log-transformed to obtain the LS geometric mean ratios and their 95% CIs.

BAO was analyzed using the Hodges-Lehmann method. For comparison of BAO after the last iv dose versus BAO after the last oral dose, the difference in BAO between Period 1 and Period 2 (Period 2 minus Period 1) was calculated. The two-sample Hodges-Lehmann method was then applied to the differences to estimate the median difference between treatment sequence (oral/iv minus iv/oral) and its 1-sided 95% upper confidence limit. For the remaining comparisons of BAO (ie, when switching between iv and oral esomeprazole

treatment), the paired Hodges-Lehmann method was used to estimate median differences between Period 1 and Period 2 and their 95% CIs.

Safety analyses included patients who were administered at least 1 dose of study medication. AEs, clinical laboratory tests, vital signs, and ECG results were summarized using descriptive statistics.

Patient population: Of the 53 patients randomized to treatment, 52 patients completed the study. The 1 patient (in the oral/iv sequence) who did not complete the study, discontinued because informed consent was withdrawn. The number of patients in the PP population was 50. Of the patients who completed the study but were not included in the PP analysis (1 from the iv/oral sequence and 1 from the oral/iv sequence), 1 was excluded because the Period 1 MAO value was missing and the other because the patient used a prohibited concomitant medication (a PPI) within 14 days of the screening endoscopy. The number of patients in the ITT population was 52 (26 in each treatment sequence). There were 53 patients in the safety population.

Table S1 Patient disposition

	E40 oral		E40 IV inj		Total	
Disposition	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Randomized	53	(100.0)	53	(100.0)	53	(100.0)
Completed study	52	(98.1)	52	(98.1)	52	(98.1)
Discontinued study	1	(1.9)	0	(0)	1	(1.9)
Analyzed for pharmacodynamics (ITT) [a]	52	(98.1)	52	(98.1)	52	(98.1)
Analyzed for pharmacodynamics (PP) [b]	50	(94.3)	50	(94.3)	50	(94.3)
Analyzed for safety [c]	53	(100.0)	52	(98.1)	53	(100.0)

[a] Intention-to-treat population: Patients who were administered at least 1 dose of the study medication and had MAO available for at least 1 treatment period.
[b] Per-protocol population (primary analysis population): Patients who completed both treatment periods and had MAO available for both treatment periods, with no major protocol violation.
[c] Safety population: Patients who took at least 1 dose of the study medication.
E40 oral Esomeprazole 40 mg once daily oral capsule.
E40 IV inj Esomeprazole 40 mg once daily 3-minute injection.

An evaluable population of 38 patients was necessary to give 90% power to reject the null hypothesis that the iv formulation was inferior to the oral formulation. The 50 evaluable patients in this study met this goal.

The PP population was 38% male and 62% female. More than 35% of these patients had a history of GERD of more than 5 years; and nearly all (94%) had a history of GERD of more than 1 year. Fifty-six percent of the PP population was positive for EE. Thus, the study population met the targets established in the Clinical Study Protocol that the enrolled

population should include at least: 25% males; 25% females; 25% with active EE (LA Grades A or B) or a history of EE; and 25% with no history of EE and no active EE.

Table S2 Patient demographics and baseline characteristics

Demographic or baseline characteristic		All randomized (n=53)		Per-protocol (n=50)	
Demographic characteristics					
Gender, n (%)	Male	20	(37.7)	19	(38.0)
	Female	33	(62.3)	31	(62.0)
Age (years)	Mean (SD)	41.7	(11.9)	41.9	(11.8)
	Range	20 to 64		20 to 64	
Race, n (%)	Caucasian	28	(52.8)	26	(52.0)
	Black	25	(47.2)	24	(48.0)
	Oriental	0	(0.0)	0	(0.0)
BMI (kg/m^2)	Mean (SD)	29.4	(4.6)	29.3	(4.5)
	Range	19.2 to 35.1		19.2 to 35.1	
Baseline characteristics					
Erosive esophagitis status, n (%)	Positive	30	(56.6)	28	(56.0)
	Negative	23	(43.4)	22	(44.0)
GERD history, n (%)	<1 year	3	(5.7)	3	(6.0)
	1-5 years	30	(56.6)	28	(56.0)
	>5 years	20	(37.7)	19	(38.0)
Heartburn ≥2 days, n (%) [a]	Yes	53	(100.0)	50	(100.0)
H. pylori status, n (%) [b]	Positive	0	(0.0)	0	(0.0)
	Negative	53	(100.0)	50	(100.0)

[a] Patient reported heartburn symptoms on at least 2 days of the last 7 days prior to screening.
[b] The test for *H. pylori* status was performed for consistency with the methodology of prior studies.
SD=Standard deviation. BMI=Body mass index. GERD=Gastroesophageal reflux disease.

Pharmacodynamic results: Both oral and iv (3-minute injection) treatment with esomeprazole for 10 days resulted in mean BAO values of <0.4 mmol/h (0.31 mmol/h and 0.36 mmol/h for oral and iv treatment, respectively) and mean MAO values of <5.1 mmol/h. Following treatment with iv esomeprazole, mean MAO and BAO values were numerically higher than after oral esomeprazole treatment. Although the observed differences between the arithmetic or LS geometric means of the MAO values for the 2 esomeprazole formulations were small, the LS geometric mean ratio of MAO results (iv/oral) did not meet the statistical criterion for pharmacodynamic non-inferiority of the intravenous formulation (a value of <1.25 for the 1-sided 95% upper confidence limit of the LS geometric mean ratio). There was no indication of a major change in pharmacodynamic efficacy when switching between oral and iv esomeprazole. After both oral and iv treatment, the observed mean MAO values were

lower in female compared to male patients; BAO values for both formulations were very low and only minor differences were observed between the subgroups.

Table S3 MAO after 10 days of esomeprazole administration (PP)

	E40 oral (n=50)		E40 IV inj (n=50)		Ratio (IV/Oral)	
Acid output	**LS geometric mean (95% CI)**	**Arith. Mean (SD)**	**LS geometric mean (95% CI)**	**Arith. Mean (SD)**	**LS geometric mean**	**1-Sided 95% upper confidence limit [a]**
MAO (mmol/h)	2.75 (1.97 to 3.85)	4.41 (3.11)	3.88 (2.76 to 5.47)	5.06 (3.90)	1.41	1.82

[a] A value <1.25 would have met the statistical criterion for pharmacodynamic non-inferiority of the IV formulation to the oral formulation.

MAO Maximal acid output (pentagastrin-stimulated) 23-24 hours after 10 days of esomeprazole 40 mg.
PP Per-protocol population.
E40 oral Esomeprazole 40 mg once daily oral capsule.
E40 IV inj Esomeprazole 40 mg once daily 3-minute injection.
LS Least squares. CI Confidence interval. Arith. Arithmetic.

Safety results: In this study, 53 patients were exposed to at least 1 dose of esomeprazole. Esomeprazole was safe and well tolerated, and the safety profiles of the 2 formulations were similar.

There were no serious adverse events (SAEs), other significant adverse events (OAEs), or discontinuations due to an AE. The AEs in the safety population, including the treatment-related ("attributable") events, were mostly gastrointestinal in nature; such AEs were not unexpected with this class of drug in the patient population under study. The most commonly reported AEs were those that the investigators considered to be related to the acid output procedure; the majority of these AEs were considered by the investigators to be pentagastrin-related, with the remainder being related to placement of the nasogastric tube. The pentagastrin-related AEs are not a safety issue because this agent is used as part of research investigations and patients would not be administered pentagastrin as part of any accepted treatment intervention for GERD.

For most laboratory variables, isolated changes both within and outside the reference range occurred during the study. There were no clear upward or downward trends for any of the variables. There were no hematology, clinical chemistry, urinalysis, vital sign, ECG, or physical finding abnormalities reported as AEs by the investigators.

Table S4 Number (%) of patients who had an adverse event and total number of adverse events in any category (safety population)

Category of adverse events	E40 oral (N=53)		E40 IV inj (N=52)		E40 total[a] (N=53)	
	n (%) of patients who had an AE in each category [b]					
Any adverse events	13	(24.5)	19	(36.5)	24	(45.3)
Serious adverse events	0		0		0	
Discontinuations due to adverse events	0		0		0	
Other significant adverse event	0		0		0	
Attributable adverse events [c]	1	(1.9)	3	(5.8)	3	(5.7)
Severe adverse events	1	(1.9)	0		1	(1.9)
	Total number of adverse events [d]					
Any adverse events	15		24		31	
Attributable adverse events [c]	1		4		4	
Severe adverse events	1		0		1	

[a] Patients having the same AE for both treatments (oral and IV) were counted once in each treatment period for the specific AE and only once in the Total column.

[b] For each treatment group, 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.

[c] Attributable AEs are those for which there was a relationship to study treatment as judged by the investigator.

[d] Events are counted by preferred term, ie, for patients with multiple events included under the same preferred term, only 1 occurrence of the event is counted.

N Total number of patients in each group.

E40 oral Esomeprazole 40 mg once daily oral capsule.

E40 IV inj Esomeprazole 40 mg once daily 3-minute injection.

Table S5 **Number (%) of patients with the most commonly reported adverse events, sorted by decreasing order of frequency as summarized across both treatments (safety population)**

	E40 oral (N=53)		E40 IV inj (N=52)		E40 total [b] (N=53)	
Preferred term [a]	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
AE associated with test procedure	9	(17.0)	11	(21.2)	15	(28.3)
Nausea	1	(1.9)	2	(3.8)	3	(5.7)
Flatulence	0		2	(3.8)	2	(3.8)
Paresthesia	0		2	(3.8)	2	(3.8)

[a] This table uses a cut-off of at least 2 patients in any treatment group.

[b] Patients having an AE for both treatments (oral and IV) were counted once in each treatment period for the specific AE and only once in the Total column.

E40 oral Esomeprazole 40 mg once daily oral capsule.

E40 IV inj Esomeprazole 40 mg once daily 3-minute injection.

N Total number of patients in each group.

n Number of patients with a specific AE.

Date of the report 14 July 2003