AstraZeneca

Drug product:	NEXIUM®	**SYNOPSIS**	
Drug substance(s):	Esomeprazole magnesium		
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A Multicenter, Double-blind, Three-way Crossover Intraesophageal and Intragastric pH Study of Three Esomeprazole Treatment Regimens in Documented Barrett's Esophagus Patients

Study center(s)

This study was conducted at 5 centers in the US. Two additional sites were initiated, but did not enroll any patients.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	6 March 2002	Therapeutic exploratory (II)
Last patient completed	15 April 2003	

Objectives

The primary objective of this study was to compare the total percent of time during the 24-hour monitoring period that intragastric pH was above 4.0 at steady-state (Day 5) in patients with documented Barrett's esophagus when they were taking:

- esomeprazole 40 mg bid
- esomeprazole 40 mg tid
- esomeprazole 20 mg tid.

The secondary objectives were to compare the total percent time distal intraesophageal pH was above 4.0 at steady-state for each treatment period (ie, treatment regimen). Also, a comparison was to be made of the total percent time distal intraesophageal and intragastric pH were above *x* (where *x* = 3, 3.5, 4.5, 5, 5.5, and 6.0) at steady-state of each treatment period (ie, treatment regimen).

Study design

This Phase II, multicenter, randomized, multiple-dose, double-blind, 3-way crossover, pharmacodynamic study in patients with Barrett's esophagus was designed to compare the duration of intragastric and intraesophageal acid suppression at steady state among 3 different esomeprazole dosing regimens: esomeprazole 40 mg 3 times daily (E40 tid), esomeprazole 40 mg twice daily (E40 bid), and esomeprazole 20 mg 3 times daily (E20 tid).

Target patient population and sample size

A total of 30 adult, male or female, patients with previously documented Barrett's esophagus (columnar-lined epithelium ≥3 cm) and no evidence of adenocarcinoma or high-grade dysplasia within the previous 12 months were to complete the study. It was estimated that 30 completed patients would provide 89% power to detect a 9% difference between dosing regimens in percent of time that intragastric pH was >4.0, and that approximately 50 patients would need to be screened in order to meet this target.

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

Esomeprazole magnesium (NEXIUM®) 20 mg capsules (batch number H1189-04-01-06) and 40 mg capsules (batch number H1222-04-01-09), and matching placebo capsules (batch number H0459-06-03-09), for oral consumption. The dosing regimens were 40 mg tid, 40 mg bid, and 20 mg tid for 5 days each. Each patient was to complete all 3 dosing regimens in this 3-way crossover study. For the bid regimen, patients took a placebo capsule at bedtime.

GELUSIL® tablets were provided as a rescue medication for relief of acid reflux symptoms (batch number 069XOB).

Duration of treatment

There were three 5-day treatment periods, with a 10- to 14-day washout period between Periods 1 and 2, and between Periods 2 and 3.

Criteria for evaluation (main variables)

Pharmacodynamics

- Primary variable: Percent of time intragastric pH was above 4.0 at steady state (Day 5) during the 24-hour monitoring period for each dosing regimen.

- Secondary variables:

- percent of time distal intraesophageal pH was above 4.0 at steady state
- percent of time intraesophageal and intragastric pH were above *x* (where *x* = 3.0, 3.5, 4.5, 5.0, 5.5, and 6.0) at steady state.

Safety

Standard safety assessments included medical history, adverse event reports, clinical laboratory data (hematology, serum chemistry, and urinalysis), vital signs, and physical examination.

Statistical methods

The pH data were analyzed using the 'All Available' dataset, which included all data collected. The primary analysis dataset was the 'Evaluable' dataset, which was a subset of the All Available dataset, determined after examining each patient's compliance, concomitant medication, and pH versus time plots in a blinded fashion. Major protocol deviations or evidence of malfunctioning of the pH probe could result in non-evaluability of patient data.

For both analysis datasets, the percent time with pH (both intragastric and intraesophageal) above a threshold x (where x = 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, and 6.0) during the 24-hour monitoring period (excluding meal times) was calculated and summarized for Baseline and for Day 5 of each treatment regimen. Analysis of 24-hour pH studies was done at each individual study site as instructed in the protocol. Patients recorded meal times on their pH monitoring equipment and these times were excluded from analysis. These variables were also analyzed using an Analysis of Variance model (ANOVA) with terms for sequence, patient, period and dosing regimen.

All patients who took at least 1 dose of esomeprazole were included in the descriptive summary of safety results. No formal treatment comparisons were made.

Patient population

In total, 50 patients were screened, 34 were randomized to a study treatment sequence, and 34 completed the study.

As shown in Table S1, the patients were predominantly male (94%) and Caucasian (97%), with a mean age of 63 years.

Table S1 Patient disposition, demographics, and baseline characteristics

		All patients
Disposition:		
N screened		50
N randomized (N planned)		34 (30)
N (%) of patients who:	Completed	34 (100%)
	Discontinued	0
N with pH data (All Available dataset)		34
N with evaluable pH data for all 3 regimens (Evaluable dataset)		31
N analyzed for safety[a]		34
Demographics:		
Gender, n (%):	Male	32 (94%)
	Female	2 (6%)
Age (years):	Mean (SD)	62.9 (10.1)
	Range	45 - 87
Race, n (%):	Caucasian	33 (97%)
	Hispanic[b]	1 (3%)
Weight (lbs)	Mean (SD)	198.7 (34.9)
	Range	144 - 282
Baseline characteristics:		
Mean (SD) % of time intragastric pH >4		18.0% (18.7)
Mean (SD) % of time distal intraesophageal pH >4.0		77.5% (22.4)

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.
[b] Although it is an ethnic group designation, rather than a race, 'Hispanic' was entered as race for 1 patient.

Pharmacodynamic results

Mean intragastric pH was >4.0 for 88.8% of the 24-hour monitoring period (ie, 21.3 hours) following treatment with E40 tid for the Evaluable dataset. Following treatment with E40 bid and E20 tid, mean intragastric pH was >4.0 for 81.4% and 80.0% of the 24-hour monitoring period, respectively (ie, 19.5 hours and 19.2 hours, respectively). In comparison to the post-treatment values, the mean Baseline value in these patients was 16.8% (4.0 hours) for intragastric pH.

Following treatment with E40 tid, E40 bid, and E20 tid, mean intraesophageal pH was >4.0 for 97.0%, 96.0%, and 96.5% of the 24-hour monitoring period, respectively (ie, 23.3 hours,

23.0 hours, and 23.2 hours, respectively). As compared to the post-treatment values, the mean Baseline value in these patients was 77.0% (18.5 hours) for intraesophageal pH.

The mean percent time pH was >4.0 for the Evaluable dataset for intragastric and intraesophageal pH is presented in Table S2.

Table S2 Mean percent time intragastric and intraesophageal pH>4.0 (Evaluable data)

Treatment	N	Mean	STD	Range
Intragastric pH				
Baseline	31	16.8	18.1	2.2 - 90.7
E40 tid	31	88.8	10.9	56.5 - 100
E40 bid	31	81.4	14.1	49.0 - 99.6
E20 tid	31	80.0	13.3	53.5 - 100
Intraesophageal pH				
Baseline	31	77.0	23.1	9.3 - 99.9
E40 tid	31	97.0	4.3	82.1 - 100
E40 bid	31	96.0	6.4	73.3 - 100
E20 tid	31	96.5	5.9	73.6 - 100

E40 tid=esomeprazole 40 mg tid; E40 bid=esomeprazole 40 mg bid; E20 tid=esomeprazole 20 mg tid

As shown in Table S3, for the Evaluable dataset, the mean percent of time intragastric pH was above 4.0 was significantly greater for the E40 tid regimen than for either of the other regimens. The values for E40 bid and E20 tid were not significantly different from each other.

All 3 of the dose regimens provided adequate intraesophageal pH control for the majority of the patients; however 5 of 31 E40 tid patients, 7 of 31 E40 bid patients, and 6 of 31 E20 tid patients had intraesophageal pH >4 less than 95% of the time.

Table S3 Treatment comparisons of percent time pH>4.0 during the 24-hour monitoring period (Evaluable data)

Treatment comparison	LS mean difference[a]	SEM	95% confidence interval		p-value
			Lower limit	Upper limit	
Intragastric pH					
E40 tid – E40 bid	7.0	2.4	2.3	11.7	0.0043
E40 tid – E20 tid	8.0	2.9	2.2	13.9	0.0078
E40 bid – E20 tid	1.0	2.4	-3.8	5.9	0.6761
Distal intraesophageal pH					
E40 tid – E40 bid	0.4	1.0	-1.6	2.3	0.7008
E40 tid – E20 tid	-1.0	1.2	-3.4	1.4	0.4106
E40 bid – E20 tid	-1.4	1.0	-3.4	0.6	0.1738

[a] LS mean differences values are derived from the analyses described in Section 7.2.1 (Table 13) and Section 7.2.2.1 (Table 15).

E40 tid=esomeprazole 40 mg tid; E40 bid=esomeprazole 40 mg bid; E20 tid=esomeprazole 20 mg tid

When intragastric pH thresholds of 3.0, 3.5, 4.5, 5.0, 5.5, and 6.0 were used for comparison, the treatment differences between E40 tid and E40 bid and between E40 tid and E20 tid for pH 3.0 - 5.0 were consistent with those seen for the threshold of pH 4.0, and were statistically significant. No consistent trends for intraesophageal pH were observed.

Safety results

Overall, all 3 esomeprazole dosing regimens were well tolerated, and had a similar incidence of treatment-related adverse events (AEs). There were no dose-related trends in the type or severity of AEs reported. No patient was discontinued due to AEs. Two patients experienced serious AEs (SAEs), neither of which was attributed by the Investigator to study treatment (1 occurred prior to study drug intake).

Table S4 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (safety population)

Category of adverse event (AE)	Baseline (N=34)	E40 tid (N=34)	E40 bid (N=34)	E20 tid (N=34)
	Number (%) of patients who had an adverse event in each category[a]			
Any AE	4 (11.8%)	6 (17.6%)	10 (29.4%)	7 (20.6%)
Serious AE (SAE)	0	1 (2.9%)	0	0
Discontinuations of study treatment due to AEs	0	0	0	0
Treatment-related AEs	1 (2.9%)	2 (5.9%)	3 (8.8%)	4 (11.8%)
	Total number of adverse events			
Any AE[b]	8	14	16	9
SAE[b]	0	1	0	0
Treatment-related AE[b]	3	3	6	4

[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.

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

E40 tid=esomeprazole 40 mg tid; E40 bid=esomeprazole 40 mg bid; E20 tid=esomeprazole 20 mg tid

Table S5 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarized over all treatment regimens (safety population)

Adverse event (preferred term)	Number (%) of patients who had a post-treatment adverse event			
	E40 tid (N=34)	E40 bid (N=34)	E20 tid (N=34)	Total (N=34)
Diarrhea NOS	1 (2.9%)	2 (5.9%)	2 (5.9%)	4 (11.8%)
Headache	1 (2.9%)	3 (8.8%)	1 (2.9%)	4 (11.8%)
Dyspepsia	0	1 (2.9%)	0	3 (8.8%)
Vomiting NOS	1 (2.9%)	2 (5.9%)	0	3 (8.8%)
Nausea	1 (2.9%)	1 (2.9%)	0	2 (5.9%)
Upper respiratory tract infection NOS	0	2 (5.9%)	0	2 (5.9%)
Bronchitis	0	2 (5.9%)	0	2 (5.9%)

[a] Events that occurred post-Baseline in at least 2 patients are included in this table.

E40 tid=esomeprazole 40 mg tid; E40 bid=esomeprazole 40 mg bid; E20 tid=esomeprazole 20 mg tid

Regarding the other safety parameters, review of the clinical laboratory, physical examination, and vital sign data did not reveal any trends or other issues of concern with any of the 3 treatment regimens. The safety data for this study were consistent with the known safety profile of esomeprazole.

Date of the report

10 August 2004