AstraZeneca

Drug product:	NEXIUM® 20 mg capsules	**SYNOPSIS**	
Drug substance:	Esomeprazole		
Edition No.:			
Study code:	D9619C00001 (318)		
Date:	3 November 2004		

A Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Efficacy Study Comparing 4 Weeks of Treatment with Esomeprazole 20 mg qd to Placebo qd for the Resolution of Upper Abdominal Pain in Patients with Symptomatic Gastroesophageal Reflux Disease (sGERD)

Study centers

This study was initiated at 67 centers in the United States; 47 of these centers randomized at least 1 patient.

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	31 March 2003	Therapeutic confirmatory (III)
Last patient completed	16 February 2004	

Objectives

Primary Objective:
To demonstrate a difference in the resolution of upper abdominal pain between esomeprazole 20 mg qd (E20) and placebo qd (placebo) after 4 weeks of treatment in patients with sGERD.

Secondary Objectives:
1. To demonstrate a difference in the resolution and relief of upper abdominal pain after 1, 2, and 4 weeks of treatment between E20 and placebo in patients with sGERD.

2. To demonstrate a difference in the percentage of days with, days to resolution of, and severity of upper abdominal pain through 4 weeks of treatment between E20 and placebo in patients with sGERD.

3. To assess the safety and tolerability of E20 through 4 weeks of treatment.

Study design

This multicenter, double-blind, randomized, placebo-controlled, parallel-group study assessed the efficacy and safety of esomeprazole 20 mg (E20) given once daily (qd) for 4 weeks compared with placebo in patients with upper abdominal pain (UAP). It comprised a screening visit and a run-in period, followed by randomization for a 4-week treatment period.

Target patient population and sample size

This study was conducted in male and female patients, between 18 and 75 years of age, with symptomatic gastroesophageal reflux disease (sGERD). At study entry, patients were required to have the following: (1) a history of heartburn (defined as a burning feeling rising from the stomach or lower part of the chest towards the neck); (2) heartburn on at least 2 of the last 7 days before screening; (3) an abnormal intraesophageal pH test result (defined as pH <4 for 4% or more of the 24-hour period); and (4) a normal endoscopy result (simple erythema in the esophagus was allowed). In addition, patients were required to have had episodes of UAP (defined as a feeling of pain, burning, or discomfort located in the area of the central upper abdomen or stomach region) for 6 months or longer, and moderate to severe UAP on at least 3 of any 7 consecutive days of the run-in period.

It was estimated that a total of 250 patients per treatment arm were required for 90% power to detect a 15% difference in resolution rates, assuming a 70% resolution rate for the E20 treatment group and 55% for the placebo treatment group.

When this study encountered recruitment difficulties, so that the planned sample size could not be achieved in any reasonable timeframe, it was decided to revisit the initial assumptions to determine if there was a level of recruitment that was obtainable that would still provide an acceptable level of power. Part of this reassessment involved a blinded evaluation of overall resolution rates in the ongoing study, which indicated that a higher-than-assumed resolution rate difference (>15%) from placebo was unlikely and that the study would be underpowered, regardless of any incremental enrollment that could be attained. The study team believed that it would be unethical to continue, and patient enrollment ended.

Investigational product and comparators: dosage, mode of administration, and batch numbers

Esomeprazole 20 mg (qd), oral administration, batch numbers H1189-04-01-06 and H1189-04-01-08.

Matching placebo (qd), oral administration, batch numbers H0459-06-03-09 and H0459-06-03-10.

GELUSIL® tablets were provided as rescue medication for relief of GERD symptoms.

Duration of treatment

Four weeks of once-daily (morning) dosing.

Criteria for evaluation (main variables)

Efficacy

The following efficacy endpoints were based on the patients' daily diary responses [None (no UAP), Mild, Moderate, or Severe] to the question: "Over the last 24 hours (yesterday and last night), what was the severity of your most intense episode of UAP?":

- Primary endpoint: Complete resolution of UAP on the patient's last 7 days in the study, defined as a daily diary response of "None" on 7 consecutive days
- Secondary endpoints:
  - Complete resolution of UAP after 1, 2, and 4 weeks of treatment
  - Relief of UAP after 1, 2, and 4 weeks of treatment, and on the patient's last 7 days in the study. Relief of UAP was defined as a daily diary response of "None" on 7 consecutive days, but allowing a response of "Mild" on up to 2 of those 7 days
  - Mean severity of UAP after 1, 2, and 4 weeks, and on the patient's last 7 days in the study.
  - Mean percentage of days without UAP over the 4-week treatment period.
  - Days to first resolution of UAP (first day with a diary response of "None.")
  - Days to first **complete** resolution of UAP (first day of the first 7 consecutive days with a diary response of "None.").

Safety

Standard safety assessments included physical examinations, vital sign measurements, clinical laboratory evaluations, and review of adverse events.

Statistical methods

The primary efficacy analysis was performed on the intention-to-treat (ITT) population; ie, all randomized patients who had at least 1 efficacy measurement while on treatment. The per-protocol population included all ITT patients who were deemed, under blinded conditions, to be evaluable, based on a prospectively defined set of evaluability guidelines. The safety population included all patients who took at least 1 dose of study drug and for whom post-randomization data exist.

The primary endpoint (complete resolution of UAP, as recorded in the daily diary on the patient's last 7 days in the study) was analyzed using a chi-square test to assess the difference in the resolution rates between E20 and placebo.

The secondary endpoints of complete resolution of UAP at 2 and 4 weeks of treatment and relief of UAP at 1, 2, and 4 weeks of treatment and in the last 7 days of the study were also analyzed using chi-square tests. Because of data sparseness, complete resolution at Week 1 was analyzed using a Fisher's Exact Test. Days without UAP and mean severity of UAP at 1, 2, and 4 weeks of treatment and in the last 7 days of the study were analyzed using a 1-way analysis of variance (ANOVA). Kaplan-Meier estimates were obtained for the survival distribution of days to first resolution and days to first complete resolution. Log-rank tests were used to test for differences in the distributions for E20 and placebo.

All safety variables were summarized descriptively. No formal comparisons were made.

Patient population

While a total of 500 patients (250 per treatment arm) were planned for this study, recruiting that number of patients became difficult, and enrollment was stopped after 208 patients had been enrolled.

As shown in Table S1, the 2 treatment groups were balanced with respect to demographic and baseline characteristics. In each group, there were approximately twice as many women as men. Two thirds of the patients were white. Mean age was in the mid-40s. The majority of patients had a body mass index (BMI) higher than 30.

To be eligible for the study, patients were required to have an abnormal intraesophageal pH at screening, defined as a pH measurement of less than 4 for at least 4% of the 24-hour monitoring period. As shown in Table S1, the mean percentage of time that esophageal pH was less than 4 during a 24-hour monitoring period was 12%. Note that the range indicates that some patients were randomized to the study even though they did not meet this criterion (n=8).

Table S1 Patient disposition, demographics, and baseline characteristics

		E20	Placebo	Total
Patient disposition				
N planned		250	250	500
N randomized		104 (100%)	104 (100%)	208 (100%)
N (%) completed study		99 (95.2%)	92 (88.5%)	191 (91.8%)
N (%) discontinued from study		5 (4.8%)	12 (11.5%)	17 (8.2%)
N (%) analyzed for safety[a]		104 (100%)	104 (100%)	208 (100%)
N (%) analyzed for efficacy (ITT)[a]		104 (100%)	104 (100%)	208 (100%)
N (%) analyzed for efficacy (PP)[b]		85 (81.7%)	84 (80.8%)	169 (81.3%)
Demographic and baseline characteristics (ITT population)				
Sex (n, %)	Male	33 (31.7%)	37 (35.6%)	70 (33.7%)
	Female	71 (68.3%)	67 (64.4%)	138 (66.3%)
Age (years)	Mean (SD)	47.2 (12.3)	45.7 (12.7)	46.5 (12.5)
	Range	19.0-75.0	23.0-73.0	19.0-75.0
Race (n, %)	White	80 (76.9%)	75 (72.1%)	155 (74.5%)
	Black	13 (12.5%)	21 (20.2%)	34 (16.3%)
	Asian	1 (1.0%)	1 (1.0%)	2 (1.0%)
	Other	10 (9.6%)	7 (6.7%)	17 (8.2%)
Body mass index (kg/mm)	Mean (SD)	32.3[c] (8.9)	31.0 (6.8)	31.6 (7.9)
	Range	18.3-61.3	20.0-58.3	18.3-61.3
% time with esophageal pH <4 during a 24-hour monitoring period	Mean (SD)	11.7 (13.5)	12.2 (12.5)	12.0 (13.0)
	Range	1.7-77.6	1.0-71.1	1.0-77.6

[a] Number of randomized patients who took at least 1 dose of study treatment and had at least 1 post-baseline safety/efficacy assessment.

[b] Number of ITT patients who were considered to have adequately met certain pre-specified criteria for protocol compliance.

[c] One patient in the E20 group did not have this calculation performed.

E20 = esomeprazole 20 mg qd; N = number; ITT = intention to treat; PP = per protocol

Efficacy results

The efficacy results are presented in Table S2. The E20 patients had a significantly higher rate of complete resolution of UAP associated with sGERD during their last 7 days in the study than the placebo patients. For this primary outcome variable, the rates were 17.3% for the E20 group and 5.8% for the placebo group.

The data for the secondary outcome measures provide further evidence of the advantages of E20 over placebo in treating UAP associated with sGERD. For all but 1 measure (complete resolution of UAP at Week 1), the differences in efficacy between E20 and placebo were statistically significant.

Table S2 Summary of efficacy results (ITT population)

Outcome variable	E20 (n=104)	Placebo (n=104)	p-value
n (%) patients with complete resolution of UAP during their last 7 days in the study (primary endpoint)	18 (17.3%)	6 (5.8%)	0.0092
n (%) patients with complete resolution of UAP at Week 1[a]	3 (2.9%)	0 (0%)	0.2464
n (%) patients with complete resolution of UAP at Week 2[b]	13 (12.5%)	2 (1.9%)	0.0032
n (%) patients with complete resolution of UAP at Week 4[b]	19 (18.3%)	6 (5.8%)	0.0056
n (%) patients with relief of UAP at Week 1[c]	14 (13.5%)	3 (2.9%)	0.0054
n (%) patients with relief of UAP at Week 2[c]	22 (21.2%)	9 (8.7%)	0.0114
n (%) patients with relief of UAP at Week 4[c]	33 (31.7%)	11 (10.6%)	0.0002
n (%) patients with relief of UAP during last 7 days in the study[d]	32 (30.8%)	12 (11.5%)	0.0007
Mean (SD) severity of UAP during Week 1[e]	1.27 (0.75)	1.49 (0.56)	0.0162
Mean (SD) severity of UAP during Week 2[e]	1.06 (0.81)	1.30 (0.66)	0.0174
Mean (SD) severity of UAP during Week 4[e]	0.88 (0.78)	1.23 (0.70)	0.0010
Mean (SD) severity of UAP during last 7 days in the study[e]	0.90 (0.79)	1.24 (0.69)	0.0010
Mean (SD) percentage of days without UAP during the study[f]	35.4% (34.6)	17.8% (24.4)	<0.0001
Kaplan-Meier estimate of UAP resolution rate (95% CI)[g]	70.5% (61.6%-79.4%)	58.3% (48.1%-68.5%)	0.0160
Kaplan-Meier estimate of rate of complete UAP resolution (95% CI)[h]	34.2% (25.0%-43.4%)	14.3% (7.3%-21.3%)	0.0005

[a] Defined as a diary response of "None" on each of the 7 previous days; p-value is from a Fischer's exact test.
[b] Defined as a diary response of "None" on each of the 7 previous days; p-value is from a chi-square test.
[c] Relief was defined as a diary response of "None" on ≥5 of the 7 previous days, with a response of "Mild" on ≤2 of the remaining days; p-value is from a chi-square test.
[d] Relief was defined as a diary response of "None" on ≥5 of these 7 days, with a response of "Mild" on ≤2 of the remaining days; p-value is from a chi-square test.
[e] Severity was scored as follows: 0 = None; 1 = Mild; 2 = Moderate; 3 = Severe. This is the mean of the within-patient means. P-value is from 1-way analysis of variance.
[f] P value is from 1-way analysis of variance.
[g] From the time-to-event curve for first day with a diary response of "None." P-value is from a log-rank test.
[h] From the time-to-event curve for first day of the first 7 consecutive days with a diary response of "None." P-value is from a log-rank test.

E20 = esomeprazole 20 mg qd; ITT = intent to treat; UAP = upper abdominal pain; CI = confidence interval; SD = standard deviation.

Safety results

Overall, E20 was safe and well-tolerated throughout 4 weeks of treatment. The most common gastrointestinal effects were diarrhea and nausea (3.8% incidence for both treatments combined). Some patients experienced discomfort from the endoscopy. Serious adverse events were reported for 2 E20 patients; both experienced chest pain that required hospitalization; however, both events were of mild intensity and were not related to study drug, in the opinion of the investigator. Neither led to discontinuation from the study.

Three patients (2 in the E20 group and 1 in the placebo group) were discontinued from the study due to adverse events. All events were considered nonserious and moderate in intensity. One patient in the E20 group had a total of 5 events, 3 of which (diarrhea, abdominal distension, and headache) were considered by the investigator to be related to study drug. These 3 events are consistent with the known safety profile of esomeprazole. All other events in these patients were considered unrelated to study drug.

No patients died during the study.

Table S3 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	E20 (n=104)	Placebo (n=104)	Total (N=208)
	Number (%) of patients who had an adverse event in each category[a]		
All adverse events	30 (28.8%)	31 (29.8%)	61 (29.3%)
Serious adverse events leading to death	0 (0%)	0 (0%)	0 (0%)
Serious adverse events not leading to death	2 (1.9%)	0 (0%)	2 (1.0%)
Discontinuations of study drug due to adverse events	2 (1.9%)	1 (1.0%)	3 (1.4%)
Treatment-related adverse events	4 (3.8%)	5 (4.8%)	9 (4.3%)
	Total numbers of adverse events		
All adverse events[b]	70	55	125
Serious adverse events leading to death	0	0	0
Serious adverse events not leading to death	2	0	2
Discontinuations of study drug due to adverse events	6	1	7
Treatment-related adverse events	6	9	15

[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.

E20 = esomeprazole 20 mg qd

Table S4 **Number (%) of patients with the most commonly reported adverse events, reported at a frequency of >2% in either treatment group, summarized by preferred term (safety population)**

	Number (%) of patients who had an adverse event		
Adverse event by preferred term[a]	**E20 (n=104)**	**Placebo (n=104)**	**Total (N=208)**
Diarrhea	4 (3.8%)	4 (3.8%)	8 (3.8%)
Nausea	6 (5.8%)	2 (1.9%)	8 (3.8%)
Postprocedural discomfort	4 (3.8%)	2 (1.9%)	6 (2.9%)
Nasopharyngitis	1 (1.0%)	4 (3.8%)	5 (2.4%)

[a] Medical Dictionary for Regulatory Activities (MedDRA) term.
E20 = esomeprazole 20 mg qd