AstraZeneca

Drug product:	Nexium	**SYNOPSIS**	
Drug substance(s):	esomeprazole		
Document No.:			
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Study code:	SH-NEN-0004/D9617C00004		
Date:	1 September 2003		

Efficacy of esomeprazole 40 mg once daily versus placebo or esomeprazole 20 mg once daily versus placebo in prevention of upper gastrointestinal symptoms associated with continuous use of NSAIDs including COX-2 selective NSAIDs

Study centre(s)

This was a multi-centre study with 80 centres participating in 11 countries.

- Australia: 4 centres
- Canada: 13 centres
- Czech Republic: 2 centres
- Italy: 5 centres
- Norway: 10 centres
- Poland: 4 centres
- Slovak Republic: 3 centres
- South Africa: 4 centres
- Sweden: 10 centres

- United Kingdom: 11 centres
- USA: 14 centres

Publications

No publications based on this report have been made prior to the date of the report.

Study dates		**Phase of development**
First patient enrolled	02 April 2001	Therapeutic Confirmatory (III)
Last patient completed	28 February 2003	

Objectives

Primary objective:

To assess the efficacy of esomeprazole 40 mg orally once daily (qd) versus placebo orally qd and esomeprazole 20 mg orally qd versus placebo orally qd through 6 months of treatment for the prevention of relapse of upper GI symptoms associated with nonsteroidal anti-inflammatory drug (NSAID) use in patients receiving daily NSAID therapy. The primary variable is the proportion of patients who have a relapse of their upper GI symptoms after 6 months of treatment. Relapse is defined as "Moderate or severe upper GI symptoms for 3 days or more in any period of 7 days rated by the patients on a 7-graded severity scale in daily diary cards".

Secondary objectives:

To assess the safety and tolerability of esomeprazole 40 mg orally qd versus placebo orally qd and esomeprazole 20 mg orally qd versus placebo orally qd when administered for 6 months to patients receiving daily NSAID therapy and to assess the impact of preventing upper GI symptoms on relevant aspects of Patient-Reported Outcomes (PRO).

Note: The term HRQL was used in the protocol instead of PRO. The current preferred term is PRO. In this document HRQL is used when referring to QOLRAD and SF-36 only. PRO is otherwise used throughout the document.

Additional objectives:

To monitor changes in HRQL the standard version of Short Form-36 (SF-36) was filled in at visit 7 (or at premature withdrawal). Any changes will be compared to the assessment at visit 2 in the study SH-NEN-0003.

Study design

This study was a multicentre, double-blind, randomised, placebo-controlled parallel group study consisting of 4 visits over a period of 6 months. The primary variable was to assess the

efficacy of esomeprazole 40 mg orally qd (E40) or esomeprazole 20 mg orally qd (E20) versus placebo orally qd after 6 months of treatment for the prevention of relapse of upper GI symptoms associated with NSAID use, including COX-2 selective NSAIDs, in patients receiving daily NSAID therapy.

Approximately 300 patients who had successfully completed a 4-week study (SH-NEN-0003) evaluating the efficacy and safety of esomeprazole in the treatment for relief of upper GI symptoms associated with continuous use of NSAIDs, including COX-2 selective NSAIDs were considered for randomisation in this study. Visit 4 corresponds to the last visit in SH-NEN-0003 and the first visit in the current study and is regarded as baseline, visit 5 equals the 1 month visit, visit 6 the 3 month visit and visit 7 the 6 month visit (visits 1-3 were made in the SH-NEN-0003 study). The patients were randomised into one of the treatment arms at visit 4.

Target patient population and sample size

Helicobacter pylori negative male and female patients, aged 18 years and above, with a chronic condition (eg, osteoarthritis or rheumatoid arthritis) requiring continuous treatment with NSAIDs (including COX-2 selective NSAIDs, multiple NSAIDs, and high-dose acetylsalicylic acid [>325 mg/day]) who completed the SH-NEN-0003 study with relief of upper GI symptoms were considered for enrolment and randomisation in this study.

A sample size of 300 patients (100 randomised patients per treatment group) was considered as needed to provide 90% power to detect a difference in the symptom relapse rates of 19% for the esomeprazole groups and 42% for the placebo group at the significance level of 0.025 for using Fischer's exact test. The log-rank test was used which, in cases with a small proportion of censored observations, is more sensitive. The expected symptom relapse rates are based on the ASTRONAUT (Yeomans et al 1998) and OMNIUM (Hawkey et al 1998) studies.

Study drug and comparator(s): dosage, mode of administration and batch numbers

Esomeprazole 40 mg, orally once daily, batch numbers: H 1222-04-01-09, H 1222-04-01-10

Esomeprazole 20 mg, orally once daily, batch numbers: H 1189-04-01-06, H 1189-04-01-07

Placebo, orally once daily, batch number: H 0459-06-03-09

Rescue medication, antacids, tablets with acid binding capacity <16 mmol HCL. Purchased and delivered locally by each marketing company.

Duration of treatment

6 months

Criteria for evaluation (main variables)

Efficacy

- Primary variable: The proportion of patients who have a relapse of their upper GI symptoms (pain, discomfort or burning in the upper abdomen) after 6 months of treatment.
  Relapse was defined as "Moderate or severe upper GI symptoms for 3 days or more in any period of 7 days recorded by the patients on a 7-graded severity scale in diary cards." The definition of relapse corresponds to one of the main entry criteria for the study SH-NEN-0003 from which the patients were recruited.

- Secondary variables:
  - Mean change in the upper GI symptom score from baseline to the 1, 3 and 6 months visits.
  - The proportion of days with an upper GI symptom score of None at 1, 3 and 6 months of treatment.
  - Mean upper GI symptom score by week over the duration of the study.
  - Mean number of days during a week with nocturnal episodes of pain, discomfort or burning in the upper abdomen by week over the duration or the study
  - Mean number of tablets per day of rescue medication intake over the duration of the study
  - The proportion of patients with resolution of investigator-recorded symptoms of heartburn, acid regurgitation, nausea and upper abdominal bloating at the 1-, 3- and 6 month visits. Resolution was defined as a symptom rating of None on the 4-point scale.
  - The proportion of patients with relief of investigator-recorded symptoms of heartburn, acid regurgitation, nausea and upper abdominal bloating at the 1-, 3- and 6 month visits. Relief was defined as a symptom rating of None or Mild on the 4-point scale.
  - Endoscopic findings at visit 7 (month 6) or premature withdrawal
  - The mean change in the three dimensions Reflux, Abdominal pain and Indigestion of the Gastrointestinal Symptom Rating Scale (GSRS) from baseline to last visit.
  - The mean change in the three dimensions Emotional distress, Sleep disturbance and Food/Drink problems of the Quality of Life in Reflux and Dyspepsia (QOLRAD) instrument from baseline to last visit.
  - Patient's global evaluation of relief of upper GI symptom (Overall Treatment Evaluation, OTE) at last visit.

Safety

Safety assessments included adverse events (AEs), clinical laboratory data (haematology and clinical chemistry), vital signs and physical examination.

Statistical methods

The primary efficacy variable (the proportion of patients who have a relapse of their upper GI symptom after 6 months of treatment) was estimated using Kaplan-Meier method. The log-

rank test was used to assess differences between each esomeprazole treatment group and the placebo group. Hochberg's method was applied in this primary analysis as the multiple-testing adjustment for the comparisons of interest, E40 vs. placebo and E20 vs. placebo, in order to protect the experiment-wise alpha error rate at 0.05.

For the proportion of patients with resolution or relief of investigator-recorded symptoms, the Cochran-Mantel-Haenszel chi-square test was used, stratified by the baseline rating of the symptom.

The secondary variables based on mean change in symptom score, mean change in PRO dimensions or proportion of days without upper GI symptom, were analysed using an analysis of covariance (ANCOVA) model, with treatment as the main effect and the corresponding baseline value as a covariate.

Patient population

The demographic characteristics of the study population are given in Table S1.

Table S1 Patient population and disposition

		E40	E20	Placebo
Disposition				
N randomised		90	92	94
N (%) of patients who	completed[a]	65 (72.2)	65 (70.7)	64 (68.1)
	discontinued	25 (27.8)	27 (29.3)	30 (31.9)
N analysed for safety[b]		90	92	94
N analysed for efficacy (ITT)		90	92	94
N analysed for efficacy (PP)		65	64	73
Demographic characteristics (ITT)				
Sex, n (%) of patients	Male	24 (26.7)	18 (19.6)	19 (20.2)
	Female	66 (73.3)	74 (80.4)	75 (79.8)
Age (years)	Mean (SD)	54 (13.3)	53 (11.8)	56 (11.9)
	Range	19 – 78	21 – 80	21 – 81
Race, n (%) of patients	Caucasian	86 (95.6)	85 (92.4)	88 (93.6)
	Black	0 (0.0)	0 (0.0)	0 (0.0)
	Oriental	0 (0.0)	1 (1.1)	1 (1.1)
	Other	4 (4.4)	6 (6.5)	5 (5.3)
Baseline characteristics, n (%)				
Type of chronic condition				
Rheumatoid arthritis		24 (26.7)	15 (16.3)	29 (30.9)

	E40	E20	Placebo
Osteoarthritis	32 (35.6)	43 (46.7)	39 (41.5)
Other chronic condition	34 (37.8)	34 (37.0)	26 (27.7)
H. pylori status (histology)			
Negative	86 (95.6)	85 (92.4)	91 (96.8)
Positive	4 (4.4)	6 (6.5)	2 (2.1)
Unknown	0 (0.0)	1 (1.1)	1 (1.1)
NSAID type			
COX-2 selective NSAID	36 (40.0)	33 (35.9)	40 (42.6)
Non-selective NSAID	54 (60.0)	59 (64.1)	54 (57.4)

[a] Completed 6 months of treatment
[b] Number of patients who had taken at least one dose of study drug and had any available post-dose information
ITT Intention to treat; N Number; PP Per-protocol

The demographic characteristics and type of condition requiring NSAID treatment and type of NSAID used were similar in the three groups.

The main reasons for discontinuation of study treatment were lack of therapeutic response and adverse events.

Efficacy results

This efficacy evaluation failed to demonstrate that treatment with E40 and E20 was superior to placebo in preventing upper GI symptoms relapse during continued NSAID use in the ITT population. In the PP population, however, a significantly lower proportion of symptom relapses was noted in the E40 and E20 groups than in the placebo group. Furthermore, the mean upper GI score was lower, there were more days without and symptoms, and there were fewer nocturnal episodes in the E40 and E20 groups than in the placebo group. Moreover, the investigator assess symptom score, the average symptoms score assessed with GSRS, the HRQL assessment (QOLRAD and SF-36), and the OTE were in favour of E40 and E20 over placebo.

Table S2 Summary of efficacy results

Variable	E40	p-value vs placebo	E20	p-value vs placebo	Placebo
Primary variable					
Cumulative proportion of patients with relapse of upper GI symptoms (estimated rate, %)					
ITT population					
Month 1	13.9	-	12.8	-	31.3
95% CI	6.6, 21.2	-	5.7, 19.8	-	21.9, 40.8
Month 3	21.4	-	19.6	-	34.8

Variable	E40	p-value vs placebo	E20	p-value vs placebo	Placebo
Primary variable					
95% CI	12.6, 30.2	-	10.9, 28.3	-	25.0, 44.6
Month 6	28.4	NS [a]	30.7	NS [a]	39.8
95% CI	18.5, 38.3	-	20.0, 41.4	-	29.7, 50.0
PP population					
Month 1	11.0	-	9.9	-	34.9
95% CI	3.3, 18.7	-	2.4, 17.4	-	23.9, 46.0
Month 3	19.2	-	17.0	-	38.0
95% CI	9.4, 29.1	-	7.4, 26.7	-	26.7, 49.3
Month 6	26.7	0.0192 [a]	27.5	0.0226 [a]	42.9
95% CI	15.4, 38.0	-	15.5, 39.6	-	31.2, 54.6
Secondary variables, ITT population					
Mean change of upper GI symptom score from baseline					
Month 1	-0.08	0.003	-0.08	0.0012	0.28
Month 3	-0.08	NS	-0.2	NS	-0.03
Month 6	-0.014	NS	-0.27	NS	-0.08
Proportion of days (%) with an upper GI symptom score of None					
Month 1	56.3	0.0112	59.3	0.0016	41.7
Month 3	59	0.0182	63.4	0.0011	45.5
Month 6	60.2	0.0167	65.2	0.0007	46.5

NS: No significant difference.
[a] logrank test of time until relapse during 6 months.

Safety results

The frequency of AEs was higher in the E40 and E20 groups compared to the placebo group, 62% in the E40 and E20 groups and 49% in the placebo group.

The most commonly reported AEs in the esomeprazole groups were abdominal pain, gastroenteritis, headache, diarrhoea and nausea/nausea (aggravated).

Two deaths were reported in the study. One patient in the E40 group experienced metastatic primitive endocrine pancreas carcinoma during study drug treatment and died 1.5 months after last dose of study drug. One patient in the placebo group experienced metastatic pancreatic carcinoma during study drug treatment and died 3 weeks after last dose of study drug. None of these events were assessed as related to study drug by the investigator.

There were 13 non-fatal SAEs reported for 11 patients, 5 patients in the E40 group, 2 patients in the E20 group and 4 patients in the placebo group. The non-fatal SAEs reported were from several different system organ classes. None of the SAEs were assessed as related to study drug by investigator.

The number of patients who discontinued study drug due to an AE was higher in the E20 group (13%) compared to the E40 group (9%) and the placebo group (6%). Discontinuations due to GI symptoms were more common in the E20 and placebo groups.

There were no clinically significant trends found in any of the treatment groups regarding laboratory values, physical examination and vital signs.

Table S3 Number (%) of patients who experienced an adverse event in any category, safety population

Category of adverse events	N (%) of patients who had an adverse event in each category[a]					
	E40 (n=90)		E20 (n=92)		Placebo (n=94)	
Any adverse events	56	(62.2)	57	(62.0)	46	(48.9)
Serious adverse events	6	(6.7)	2	(2.2)	5	(5.3)
Serious adverse events leading to death	1	(1.1)	0		1	(1.1)
Serious adverse events not leading to death	5	(5.6)	2	(2.2)	4	(4.3)
Discontinuations of study treatment due to adverse events[d]	8	(8.9)	12	(13.0)	6	(6.4)
Other significant adverse event	0		0		0	
Attributable adverse events[c]	9	(10.0)	3	(3.3)	1	(1.1)
	Total number of adverse events					
Any adverse events[b]	162		123		113	
Serious adverse events[b]	7		2		6	
Discontinuations adverse events[b]	11		19		10	
Other significant adverse event[b]	0		0		0	
Attributable adverse events	13		6		1	

[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.

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

[d] Data derived from appendix 12.2.7.1. Number of patients may differ from section 6 as only study drug treatment discontinued due to an AE is listed in this table.

Table S4 Number (%) of patients with the most commonly reported adverse events, sorted by the total for both esomeprazole groups combined, safety population

Preferred term	E40 (n=90)		E20 (n=92)		Placebo (n=94)	
	n	(%)	n	(%)	n	(%)
Abdominal pain	9	(10.0)	5	(5.4)	3	(3.2)
Gastroenteritis	7	(7.8)	6	(6.5)	0	
Headache	9	(10.0)	3	(3.3)	3	(3.2)
Diarrhoea	7	(7.8)	3	(3.3)	3	(3.2)

Preferred term	**E40 (n=90)**		**E20 (n=92)**		**Placebo (n=94)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Nausea/nausea (aggravated)	8	(8.9)	2	(2.2)	2	(2.1)
Bronchitis	7	(7.8)	2	(2.2)	1	(1.1)
Hypertension/hypertension aggravated	6	(6.7)	3	(3.3)	1	(1.1)
Sinusitis	5	(5.6)	4	(4.3)	6	(6.4)
Arthralgia	3	(3.3)	5	(5.4)	1	(1.1)
Back pain	5	(5.6)	3	(3.3)	4	(4.3)
Dizziness/vertigo	6	(6.7)	2	(2.2)	0	
Constipation/constipation aggravated	4	(4.4)	3	(3.3)	2	(2.1)
Flatulence	4	(4.4)	3	(3.3)	3	(3.2)
Gastroesophageal reflux	1	(1.1)	4	(4.3)	5	(5.3)
Accident and/or injury	0		4	(4.3)	1	(1.1)
Dyspepsia	1	(1.1)	2	(2.2)	9	(9.6)
Respiratory infection	3	(3.3)	0		7	(7.4)

AE experienced by at least 4% and 4 patients in any treatment group are included in the table.