AstraZeneca

Clinical Study Report

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Date:	24 February 2006

A randomized double-blind placebo-controlled study to assess the prevention of low-dose acetylsalicylic acid (ASA) associated gastroduodenal lesions and upper gastrointestinal symptoms in patients taking esomeprazole 20 mg once daily (od) for 26 weeks

Study dates:	First patient randomized: 6 May 2004 Last patient completed: 26 September 2005
Phase of development:	IIIb

This study was performed in compliance with Good Clinical Practice.

Drug product:	Nexium	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
Document No.:			
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A randomized double-blind placebo-controlled study to assess the prevention of low-dose acetylsalicylic acid (ASA) associated gastroduodenal lesions and upper gastrointestinal symptoms in patients taking esomeprazole 20 mg once daily (od) for 26 weeks

This was a multicenter study with 78 centers in 10 countries.

Study center(s)

Australia	10 centers
Bulgaria	7 centers
Canada	14 centers
Germany	20 centers
Greece	5 centers
Hong Kong	1 center
Hungary	10 centers
Italy	6 centers
South Africa	4 centers
Spain	1 center

Publications

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

Study dates

First patient randomized 6 May 2004

Phase of development

Therapeutic confirmatory (III)

Last patient completed 26 September 2005

Objectives

Primary objective:

The primary objective was to evaluate the effect of esomeprazole 20 mg once daily (od) versus placebo for up to 26 weeks for the prevention of gastric and/or duodenal ulcers in patients taking low-dose acetylsalicylic acid (ASA).

Secondary objectives:

Secondary objectives of the study were to:

1. Over a 26-week period, evaluate the effect of esomeprazole 20 mg od versus placebo for the prevention of lesions in the esophagus by using the Los Angeles (LA) classification in patients taking low-dose ASA.

2. Measure investigator-assessed symptoms, defined as none or mild symptoms, from the upper GI tract for up to 26 weeks of treatment with esomeprazole 20 mg od versus placebo in patients taking low-dose ASA.

3. Over a 26-week period, assess safety and tolerability of treatment with esomeprazole 20 mg od in a population of low-dose ASA users.

Study design

This was a 26-week, randomized, double-blind, parallel-group, 2-armed, placebo-controlled trial studying the effect of esomeprazole 20 mg od for the prevention of gastroduodenal lesions, erosive esophagitis, and upper GI symptoms in patients taking low doses of ASA (75-325 mg daily) and expected to continue for the duration of the study (daily was defined as at least 5 days per week).

Target patient population and sample size

Male or female patients 60 years or older, with no active/current gastric and/or duodenal ulcer (GU and/or DU), who were *Helicobacter pylori* (*H. pylori*) negative and were at moderate to high risk of developing gastroduodenal ulcers while taking low-dose ASA.

A sample size of 960 patients (480 randomized patients per group) was needed to provide 90% power to detect a 6.5% difference in ulcer occurrence rates of 6.5% for the esomeprazole group and 13% for the placebo group at the significance level of 0.05 and with a drop-out rate of 15%.

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

Esomeprazole (NEXIUM™), 20 mg capsules orally once daily, batch numbers:
H 1189-04-01-09

Placebo, orally once daily, batch number: H 0459-06-03-11

Duration of treatment

The duration of treatment was 26 weeks.

Criteria for evaluation (main variables)

Efficacy

– **Primary outcome variable:**

- The primary variable was presence of gastric and/or duodenal ulcers at endoscopy over a 26-week period in patients taking low-dose ASA.

– **Secondary outcome variables:**

- LA classification for the esophagus at endoscopy.

- Upper GI symptoms assessed by the investigator at each study visit.

Safety

Safety assessments included adverse events (AEs), clinical laboratory tests including hematology, clinical chemistry, physical examination, vital signs including blood pressure, and pulse rate.

Statistical methods

The main approach in the analysis of primary and secondary efficacy variables was the intention-to-treat (ITT) population. For the primary efficacy variable the per-protocol (PP) population was also to be evaluated.

Kaplan-Meier life-table estimate was used for the primary efficacy variable time until occurrence of gastric and/or duodenal ulcer, throughout 26 weeks of treatment. The life-table approach was implemented by predefining windows corresponding to nominal 'months.' These months were used as the discrete time points in the life-table analysis. The log-rank test was used to assess differences between esomeprazole treatment group and the placebo group.

The proportions of patients with no symptoms at all and the proportion of patients with at most "mild" symptoms were analyzed by a Cochran-Mantel-Haenszel (CMH) chi-square test, stratified by the baseline rating of the symptom.

Wilcoxson rank sum test, stratified by the baseline rating of the LA classification, was used to assess the differences of the LA classification between esomeprazole treatment group and the placebo group.

Patient population

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

Table S1 Patient population and disposition

		E20	Placebo	Total
Disposition				
N randomized		494	498	992
N (%) of patients who	Completed	425(86.0)	390(78.3)	815(82.2)
	Discontinued	69(14.0)	108(21.7)	177(17.8)
N (%) analyzed for safety[a]		487(98.6)	494(99.2)	981(98.9)
N (%) analyzed for efficacy (ITT)		493(99.8)	498(100.0)	991(99.9)
N (%) analyzed for efficacy (PP)		304(61.5)	308(61.8)	612(61.7)
Demographic characteristics (ITT)				
Gender (n and % of patients)	Male	280(56.8)	286(57.4)	566(57.1)
	Female	213(43.2)	212(42.6)	425(42.9)
Age (years)	Mean (SD)	69.5(6.6)	69.1(6.5)	69.3(6.5)
	Range	60 to 90	57 to 91	57 to 91
Race (n and % of patients)	Caucasian	437(88.6)	443(89.0)	880(88.8)
	Black	15(3.0)	11(2.2)	26(2.6)
	Oriental	25(5.1)	28(5.6)	53(5.3)
	Other	16(3.2)	16(3.2)	32(3.2)
Baseline characteristics, n(%)				
LA grade				
None		444(90.1)	442(88.8)	886(89.4)
Grade A		48(9.7)	56(11.2)	104(10.5)
Grade B		1(0.2)		1(0.1)
Endoscopic Barrett's esophagus		2(0.4)	1(0.2)	3(0.3)
Hiatal hernia		86(17.4)	88(17.7)	174(17.6)
Esophagus, abnormal finding(s)		33(6.7)	46(9.2)	79(8.0)
Stomach erosion(s)		152(30.8)	138(27.7)	290(29.3)
Stomach, abnormal finding(s)		198(40.2)	196(39.4)	394(39.8)
Deformation of duodenal bulb		6(1.2)	11(2.2)	17(1.7)
Duodenum erosion(s)		40(8.1)	29(5.8)	69(7.0)
Duodenum, abnormal findings		56(11.4)	43(8.6)	99(10.0)

	E20	Placebo	Total
H. pylori. status			
Negative	360(73.0)	368(73.9)	728(73.5)
Positive	112(22.7)	112(22.5)	224(22.6)
Missing	21(4.3)	18(3.6)	39(3.9)
Duration of low-dose ASA intake			
<1 week	31(6.3)	38(7.6)	69(7.0)
1-4 weeks	21(4.3)	19(3.8)	40(4.0)
>4 weeks	441(89.5)	441(88.6)	882(89.0)
Reason for low-dose ASA treatment			
Cardiovascular and/or cerebrovascular protection	483(98.0)	489(98.2)	972(98.1)
Other	10(2.0)	9(1.8)	19(1.9)

[a] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing.
E20 esomeprazole 20 mg od; ITT intention-to-treat; N number; PP Per-protocol

More patients in the esomeprazole group than in the placebo group completed the study (86.0% versus 78.3%, respectively). The greatest difference in reasons for discontinuation observed between the groups was the lack of therapeutic response (5.2% for the placebo group, 0.4% for the esomeprazole group). The treatment groups were well balanced with regard to demographics and baseline characteristics.

Efficacy results

In this study of patients taking low-dose ASA, the estimated cumulative proportion of patients with gastric and/or duodenal ulcer at Month 6 was significantly lower for patients in the E20 group (1.8%) than for patients in the placebo group (6.2%). This result was observed for both the ITT and PP populations.

In patients taking low-dose ASA, esomeprazole 20 mg od was significantly more effective than placebo at reducing the risk of lesions in the esophagus as determined by using the LA classification. Among the patients with symptoms at baseline, more patients in the E20 group than in the placebo group experienced absence of their symptoms by Month 2, Month 4, and Month 6. The differences in absence of symptoms (defined as “none”) at Month 2 between the E20 group and the placebo group were significant for epigastric pain, epigastric burning, heartburn, and acid regurgitation. The differences in symptoms assessed by the investigator as at most “mild” at Month 2 between the E20 group and the placebo group were significant for epigastric pain and epigastric discomfort in favour for the E20 group.

The results for the primary efficacy objective are summarized in Table S2.

Table S2 Summary of efficacy results

	ITT population		PP population	
	E20 (n=493)	**Placebo (n=498)**	**E20 (n=304)**	**Placebo (n=308)**
Cumulative proportions of patients without GU and/or DU by Month 6				
Statistic				
Observed response rate	485/493(98.4%)	471/498(94.6%)	299/304(98.4%)	291/308(94.5%)
95% confidence intervals	96.8%-99.3%	92.2%-96.4%	96.2%-99.5%	91.3%-96.8%
Life table estimate	98.2%	93.8%	98.3%	93.9%
95% confidence intervals	96.9%-99.4%	91.5%-96.1%	96.8%-99.8%	91.1%-96.7%
Log rank p-value (vs placebo)	0.0007		0.0067	
Cumulative observed proportion of patients without GU and/or DU by Month 6				
Ulcer status				
Maintained ulcer free	413/493(83.8%)	368/498(73.9%)	279/304(91.8%)	243/308(78.9%)
Ulcer occurred	8/493(1.6%)	27/498(5.4%)	5/304(1.6%)	17/308(5.5%)
Discontinued, ulcer free	67/493(13.6%)	94/498(18.9%)	17/304(5.6%)	42/308(13.6%)
No endoscopy performed in the time period, ulcer free	5/493(1.0%)	9/498(1.8%)	3/304(1.0%)	6/308(1.9%)

Cumulative occurrence of GU and/or DU by Month 6 (ITT population)		
Ulcer occurrence	**E20 (n=493)**	**Placebo (n=498)**
Gastric	6/493(1.2%)	19/498(3.8%)
Duodenum	2/493(0.4%)	8/498(1.6%)
Gastric and duodenum	0/493(0.0%)	0/498(0.0%)

ITT intention-to treat; PP per protocol; GU gastric ulcer; DU duodenal ulcer; E20 esomeprazole 20 mg od

Safety results

In this population of low-dose ASA users, esomeprazole 20 mg od was well tolerated and no safety concerns were raised. The number of patients reporting AEs and serious AEs (SAEs) was similar for both treatment groups. The most frequently reported AEs were in the infections and infestations organ class and the GI disorders organ class. These AEs were reported with similar frequencies in both treatment groups. The frequency of causally-related AEs was similar in the 2 treatment groups. The most commonly reported causally-related AEs were from the GI disorders organ class.

Two patients died during the study; both patients were from the placebo group. One patient with a history of cerebrovascular ischemic disease and ischemic heart disease died due to ischemic stroke. The other patient died due to urine bladder cancer. The deaths were considered by the investigator not causally related to study medication.

The most commonly reported SAEs were from the cardiac disorders organ class. Overall, a higher number of adverse events leading to discontinuation (DAEs) occurred in the placebo group than in the E20 group. The most commonly reported DAEs occurred in the GI disorders organ class; these DAEs were reported more frequently by patients in the placebo group than by patients in the E20 group. DAEs were reported in similar numbers by the patients in both treatment groups for the other organ classes.

No event was classified as other significant adverse event (OAE).

There were no clinically relevant trends in either treatment group with regard to laboratory variables, physical examinations, or vital signs. Isolated changes both within and outside the laboratory reference ranges were observed for most of the laboratory variables. These findings did not raise any safety concerns.

Adverse events are summarized in Table S3 and the most commonly reported adverse events are presented in Table S4.

Table S3 Number (%) of patients who had at least 1 adverse event in any category, and total numbers of adverse events (Safety population)

	N(%) of patients who had an adverse event in each category[a]					
Category of adverse event	**E20 n=487**		**Placebo n=494**		**All n=981**	
Any adverse events	204	(42)	211	(43)	415	(42)
Serious adverse events	32	(7)	37	(7)	69	(7)
Serious adverse events leading to death	0	(0)	2	(0.4)	2	(0.2)
Discontinuations[b] of study treatment due to adverse events	18	(4)	36	(7)	54	(6)
Other significant adverse events	0	(0)	0	(0)	0	(0)
	Total number of adverse events					
Adverse events	395		421		816	
Deaths	0		2		2	
Serious adverse events	35		51		86	
Other significant adverse events	0		0		0	

[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] Investigational product permanently stopped due to adverse event.

E20 esomeprazole 20 mg od

Table S4 Number of patients with the most commonly reported[a] adverse events in decreasing order of frequency[b] (Safety population)

Preferred term	E20 n=487 N(%)	Placebo n=494 N(%)	All n=981 N(%)
Upper respiratory tract infection	17 (3.5)	13 (2.6)	30 (3.1)
Constipation	10 (2.1)	16 (3.2)	26 (2.7)
Nasopharyngitis	14 (2.9)	8 (1.6)	22 (2.2)
Nausea	10 (2.1)	11 (2.2)	21 (2.1)
Dizziness	8 (1.6)	9 (1.8)	17 (1.7)
Headache	5 (1.0)	11 (2.2)	16 (1.6)
Diarrhea	10 (2.1)	6 (1.2)	16 (1.6)
Bronchitis	7 (1.4)	9 (1.8)	16 (1.6)
Urinary tract infection	8 (1.6)	7 (1.4)	15 (1.5)
Back pain	9 (1.8)	5 (1.0)	14 (1.4)
Influenza	7 (1.4)	5 (1.0)	12 (1.2)
Dyspepsia	3 (0.6)	9 (1.8)	12 (1.2)
Abdominal pain upper	2 (0.4)	8 (1.6)	10 (1.0)

[a] AEs reported by at least 1% of patients.
[b] AEs were sorted by the number of events for the total safety population (All column)
E20 esomeprazole 20 mg od

Date of the report

24 February 2006