AstraZeneca

Clinical Study Report

Drug Substance	Esomeprazole
Edition Number	1
Study Code	D961FC00003
Date	18 December 2008

A randomized, double-blind, parallel-group, multicentre, phase III study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA)

Study dates: First subject randomized: 22 February 2007
Last subject completed: 28 August 2008

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice.

Drug Product:	Nexium	**SYNOPSIS**	
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A randomized, double-blind, parallel-group, multicentre, phase III study to assess the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA)

This was a multicenter study with 204 centers in 20 countries.

Study center(s)

Country	**No of centers**	**Country**	**No of centers**
Argentina	9	Philippines	4
Australia	9	Poland	17
Bulgaria	11	Portugal	4
Canada	18	Romania	5
Czech Republic	11	Russia	13
Finland	5	Slovakia	10
Germany	14	South Africa	6
Indonesia	2	South Korea	6
Mexico	5	Thailand	2
Norway	10	USA	43

Publications

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

Study dates		**Phase of development**
First subject randomized	22 February 2007	Therapeutic confirmatory (III)
Last subject completed	28 August 2008	

Objectives

Primary objective:

The primary objective of the study was to compare the effect of esomeprazole 20 and 40 mg once daily (od) versus placebo on the occurrence of peptic ulcers during 26 weeks in subjects on continuous low-dose acetylsalicylic acid (ASA).

Secondary objectives:

Secondary objectives of the study were to:

1. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of gastric ulcers during 26 weeks in subjects on continuous low-dose ASA

2. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on the occurrence of duodenal ulcers during 26 weeks in subjects on continuous low-dose ASA

3. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported dyspeptic symptoms at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by Reflux Disease Questionnaire (RDQ) in subjects on continuous low-dose ASA

4. Compare the effect of esomeprazole 20 and 40 mg od versus placebo on subject-reported gastroesophageal reflux disease (GERD) symptoms (heartburn and regurgitation) at the 26-week visit or the last visit, unless the last visit is the baseline visit, assessed by RDQ in subjects on continuous low-dose ASA

5. Study the number of gastric and/or duodenal erosions during 26 weeks in subjects on continuous low-dose ASA, by treatment

6. Assess safety and tolerability of treatment with esomeprazole 20 and 40 mg od during 26 weeks in subjects on continuous low-dose ASA

Study design

This was a 26-week, randomized, double-blind, parallel-group, placebo-controlled study to investigate the effect of esomeprazole 20 and 40 mg od on the occurrence of peptic ulcers, in subjects on continuous low-dose ASA (75 to 325 mg daily; daily was defined as ≥5 days/week) treatment during the course of the study.

Target subject population and sample size

Male and female subjects requiring low-dose ASA (75 to 325 mg daily) who were *Helicobacter pylori (H. pylori)* negative and who were at increased risk of developing peptic ulcers.

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

Esomeprazole, 20 mg capsules orally od, batch numbers: H 1189-04-01-11

Esomeprazole, 40 mg capsules orally od, batch numbers: H 1222-04-01-16, H 1222-04-01-17

Placebo, orally od, batch number: H 0459-06-03-14, H 0459-06-03-15

Duration of treatment

The duration of treatment was 26 weeks

Criteria for evaluation (main variables)

Efficacy

- Primary outcome variable:

  The primary variable was time to occurrence of peptic ulcer(s).

- The secondary outcome variables were:

  – Time to occurrence of gastric ulcer

  – Time to occurrence of duodenal ulcer

  – Dichotomized RDQ score (0 versus >0) for the dyspepsia dimension during the week prior to the 26-week visit or the week prior to the last visit, as reported by the subject

  – Dichotomized RDQ score (0 versus >0) for the GERD dimension (heartburn and regurgitation) during the week prior to the 26-week visit or the week prior to the last visit, as reported by the subject

  – Number of gastric and/or duodenal erosions

Subject-reported outcomes (PROs)

The RDQ, as a self-administered questionnaire, that includes 12 items answered using a modified 6-point Likert scale (see secondary efficacy outcome variables).

Safety

Adverse events, clinical laboratory tests and vital signs

Statistical methods

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

The primary objective, efficacy for peptic ulcers, and the 2 secondary objectives concerning efficacy for gastric and duodenal ulcers were tested in a hierarchical closed test procedure. The closed test procedure was done in parallel for the 2 different doses of esomeprazole and in each step adjustment for multiplicity was done according to the Hochberg procedure.

To assess differences between the esomeprazole groups and the placebo group the log rank test was used. Low-dose ASA dose group (75 to 100 mg and 101 to 325 mg) was included as strata in the log rank analysis.

Peptic ulcer occurrence rates at the different low-dose ASA ranges of 75 to 100 mg and 101 to 325 mg were presented descriptively, by treatment. Absolute and relative risk reduction of peptic ulcers was presented for each of the esomeprazole groups as compared to placebo. Corresponding descriptive statistics were presented for gastric and duodenal ulcers.

The Mantel-Haenszel chi-square test was used for the proportion of subjects without any dyspeptic symptoms at the 26-week visit or the last visit, unless the last visit is the baseline visit, defined as subjects with RDQ score equal to 0 for the dyspepsia dimension. The test was stratified for baseline severity. The GERD symptoms were analyzed accordingly.

The number of gastric and duodenal erosions are presented by treatment group as descriptive statistics in terms of frequency tables.

Baseline and demographic data are presented descriptively.

Investigator-reported symptoms are presented by using descriptive statistics for the ITT cohort.

Upper gastrointestinal (GI) complications are presented by using descriptive statistics for the ITT cohort.

Adverse events, clinical laboratory tests and vital signs are presented using descriptive statistics for the safety population.

Subject population

The target population was male and female subjects requiring low-dose ASA (75 to 325 mg daily) who were at risk of developing peptic ulcers. The disposition and demographic characteristics of the randomized population are shown in Table S1.

Table S1 Subject population and disposition

		E40	E20	Placebo	Total
Disposition					
N randomized		817	804	805	2426
N (%) of subjects who:	Completed	711(87.0%)	686(85.3%)	637(79.1%)	2034(83.8%)
	Discontinued	106(13.0%)	118(14.7%)	168(20.9%)	392(16.2%)
N (%) analyzed for safety[a]		814(99.6%)	799(99.4%)	801(99.5%)	2414(99.5%)
N (%) analyzed for efficacy (ITT)		817(100.0%)	804(100.0%)	805(100.0%)	2426(100.0%)
N (%) analyzed for efficacy (PP)		525(64.3%)	526(65.4%)	483(60.0%)	1534(63.2%)
Demographic characteristics (ITT)					
Gender (n and % of subjects)	Male	437(53.5%)	429(53.4%)	403(50.1%)	1269(52.3%)
	Female	380(46.5%)	375(46.6%)	402(49.9%)	1157(47.7%)
Age (years)	Mean (SD)	67.7(8.2)	67.7(8.1)	67.4(8.0)	67.6(8.1)
	Range	21 to 87	24 to 89	24 to 94	21 to 94
Race (n and % of subjects)	White	669(81.9%)	651(81.0%)	661(82.1%)	1981(81.7%)
	Black/African American	30(3.7%)	31(3.9%)	23(2.9%)	84(3.5%)
	Asian	76(9.3%)	77(9.6%)	82(10.2%)	235(9.7%)
	Native Hawaiian/ Pacific Islander	0(0.0%)	1(0.1%)	0(0.0%)	1(0.0%)
	American Indian/Alaska Native	0(0.0%)	0(0.0%)	1(0.1%)	1(0.0%)
	Other	42(5.1%)	44(5.5%)	38(4.7%)	124(5.1%)
Baseline characteristics, n(%)					
LA classification					
None		693(84.8%)	704(87.6%)	697(86.6%)	2094(86.3%)
Grade A		86(10.5%)	73(9.1%)	77(9.6%)	236(9.7%)
Grade B		38(4.7%)	27(3.4%)	30(3.7%)	95(3.9%)
Grade C		0(0.0%)	0(0.0%)	1(0.1%)	1(0.0%)
Hiatal hernia		218(26.7%)	208(25.9%)	182(22.6%)	608(25.1%)
Esophagus, abnormal finding(s)		68(8.3%)	69(8.6%)	77(9.6%)	214(8.9%)
Stomach erosion(s)		353(43.2%)	361(44.9%)	342(42.5%)	1056(43.5%)
Stomach, abnormal finding(s)		317(38.8%)	300(37.3%)	332(41.2%)	949(39.1%)

	E40	E20	Placebo	Total
Duodenum erosion(s)	101(12.4%)	92(11.4%)	80(9.9%)	273(11.3%)
Duodenum, abnormal findings	120(14.7%)	127(15.8%)	150(18.6%)	397(16.4%)
H. pylori. status				
Negative	606(74.2%)	605(75.2%)	574(71.3%)	1785(73.6%)
Positive	159(19.5%)	149(18.5%)	171(21.2%)	479(19.7%)
Indetermin	41(5.0%)	41(5.1%)	42(5.2%)	124(5.1%)
Missing	11(1.3%)	9(1.1%)	18(2.2%)	38(1.6%)
Duration of low-dose ASA intake				
Missing	0(0.0%)	1(0.1%)	0(0.0%)	1(0.0%)
<2 week	73(8.9%)	82(10.2%)	71(8.8%)	226(9.3%)
2-4 weeks	31(3.8%)	37(4.6%)	34(4.2%)	102(4.2%)
>4 weeks	713(87.3%)	684(85.1%)	700(87.0%)	2097(86.4%)
Reason for low-dose ASA treatment				
• Primary prevention of cardiovascular and cerebrovascular disease	363(44.4%)	368(45.8%)	386(48.0%)	1117(46.0%)
• Secondary prevention of cardiovascular and cerebrovascular disease	435(53.2%)	421(52.4%)	401(49.8%)	1257(51.8%)
• Other	19(2.3%)	14(1.7%)	18(2.2%)	51(2.1%)
• Missing	0(0.0%)	1(0.1%)	0(0.0%)	1(0.0%)

E20 and E40 esomeprazole 20 mg od and esomeprazole 40 mg od; ITT intention-to-treat; N number; ASA acetylsalicylic acid; PP per-protocol; SD standard deviation; LA grade Los Angeles classification
[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing.

Efficacy results

The estimated cumulative proportion of subjects with peptic ulcers was statistically significantly lower in subjects treated with esomeprazole at doses of both 20 mg od and 40 mg od compared with placebo. This result was observed for both the ITT ($p<0.0001$) and the PP populations ($p<0.0001$).

When looking at gastric and duodenal ulcers separately the estimated cumulative proportion of subjects with gastric ulcers was statistically significantly lower in subjects treated with esomeprazole 20 and 40 mg compared with placebo ($p<0.0001$), as was the estimated cumulative proportion of subjects with duodenal ulcers ($p<0.0001$). The cumulative proportions of subjects with peptic (primary objective), gastric and duodenal ulcers are summarized in Table S2.

Furthermore, the proportion of subjects by week 26 with dyspeptic symptoms and GERD symptoms assessed by RDQ was lower ($p<0.0001$ and $p<0.0001$, respectively) in the subject group treated with esomeprazole at doses of both 20 mg od and 40 mg od compared with placebo.

The results also show that the observed number of gastric and duodenal erosions by week 26 was lower in subjects on low-dose ASA treated with esomeprazole doses of both 20 mg od and 40 mg od compared with placebo.

Table S2 Cumulative proportions of subjects with peptic, gastric and duodenal ulcers, ITT population

	Statistic	E40 n=817	E20 n=804	Placebo n=805
Primary variable: Peptic ulcers	Life table estimate	1.5%	1.1%	7.4%
	95% confidence intervals	0.6%-2.4%	0.3%-1.9%	5.5%-9.3%
	Observed response rate	11/817(1.3%)	8/804(1.0%)	53/805(6.6%)
	95% confidence intervals	0.7%-2.4%	0.4%-2.0%	5.0%-8.5%
	ARR (95% CI)	5.2%(3.4%-7.1%)	5.6%(3.7%-7.4%)	
	RRR	79.6	84.9	
	Log rank p-value (vs Placebo)	<0.0001	<0.0001	
	Statistical significance[a]	yes	yes	
Secondary variable: Gastric ulcers	Life table estimate	1.2%	0.8%	4.7%
	95% confidence intervals	0.4%-2.0%	0.2%-1.5%	3.1%-6.2%
	Observed response rate	9/817(1.1%)	6/804(0.7%)	33/805(4.1%)
	95% confidence intervals	0.5%-2.1%	0.3%-1.6%	2.8%-5.7%
	ARR (95% CI)	3.0%(1.5%-4.5%)	3.4%(1.9%-4.8%)	
	RRR	73.1	81.8	
	Log rank p-value (vs Placebo)	<0.0001	<0.0001	
	Statistical significance[a]	yes	yes	
Secondary variable: Duodenal ulcers	Life table estimate	0.3%	0.3%	3.1%
	95% confidence intervals	-0.1%-0.7%	-0.1%-0.6%	1.8%-4.4%
	Observed response rate	2/817(0.2%)	2/804(0.2%)	22/805(2.7%)
	95% confidence intervals	0.0%-0.9%	0.0%-0.9%	1.7%-4.1%
	ARR (95% CI)	2.5%(1.3%-3.7%)	2.5%(1.3%-3.7%)	
	RRR	91.0	90.9	
	Log rank p-value (vs Placebo)	<0.0001	<0.0001	
	Statistical significance[a]	yes	yes	

ITT=Intention To Treat; GU=Gastric Ulcer; DU=Duodenal ulcer; E40=esomeprazole 40 mg; E20=esomeprazole 20 mg; ARR=Absolute relative risk reduction; RRR=Relative risk reduction; CI=Confidence intervals

Two subjects in the placebo group had both gastric and duodenal ulcers and they are presented in the table for both variables.

[a] A hierarchical closed test procedure, done in parallel for the 2 different doses, with adjustment according to the Hochbergs procedure

Due to the normal approximation used in the calculations of the CI, the lower CIs for E40 and E20 for duodenal ulcers become negative

Safety results

Adverse events (AEs) are summarized in Table S3, and the most commonly reported AEs are presented in Table S4.

In general, the difference in reporting frequency between the 3 treatment groups were minor and not assessed as clinically relevant. The most commonly reported AEs were diarrhoea and bronchitis. Adverse events were reported with similar frequencies in the 3 treatment groups.

Nine (9) subjects died during the study (4 on esomeprazole 40 mg od, 4 on esomeprazole 20 mg od and 1 on placebo). Four (4) of these subjects died suddenly without any confirmed preceeding diagnosis. The reported events in those 4 subjects were myocardial infarction (esomeprazole 40 mg od), sudden death (esomeprazole 40 mg od), death (esomeprazole 20 mg od) and cardiac arrest (esomeprazole 20 mg). The information in these reports was limited and no autopsy was performed in any of the subjects. The total number of fatal events was considered to be low. All reported deaths were judged by the investigators as not causally related to the investigational product.

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

Category of adverse events	Number(%) subjects who had an AE in each category[a] E40 n=814	E20 n=799	Placebo n=801
Any adverse events	295(36.2%)	297(37.2%)	298(37.2%)
Serious adverse events leading to death	4(0.5%)	4(0.5%)	1(0.1%)
Non-fatal serious adverse events	43(5.3%)	39(4.9%)	35(4.4%)
Adverse event leading to discontinuation of treatment[b]	30(3.7%)	37(4.6%)	42(5.2%)
Related adverse events[c]	34(4.2%)	39(4.9%)	31(3.9%)
	Total number of adverse events[d]		
Any adverse eventAE	548	551	538
Serious adverse events leading to death	4	5	1
Non-fatal serious advers events	50	47	37
Adverse event leading to discontinuation of treatment	46	56	61
Related adverse events	67	58	41

E40=esomeprazole 40 mg; E20=esomeprazole 20 mg; AE adverse event

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Investigational product permanently stopped due to AE.

[c] Related AEs are those for which there was a possible relationship to investigational product as judged by the investigator.

[d] Multiple occurences of AEs on a particular preferred term level in the same subject are counted as 1 occurrence.

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Table S4 Number of subjects with the most commonly reported adverse events in decreasing order of frequency (safety population)

Preferred term	E40 n=814	E20 n=799	Placebo n=801
Diarrhoea	21(2.6%)	27(3.4%)	18(2.2%)
Bronchitis	11(1.4%)	17(2.1%)	14(1.7%)
Abdominal pain upper	13(1.6%)	7(0.9%)	15(1.9%)
Headache	15(1.8%)	15(1.9%)	15(1.9%)
Upper respiratory tract infection	7(0.9%)	8(1.0%)	15(1.9%)
Nausea	15(1.8%)	6(0.8%)	6(0.7%)
Back pain	8(1.0%)	9(1.1%)	14(1.7%)
Influenza	11(1.4%)	9(1.1%)	13(1.6%)
Nasopharyngitis	7(0.9%)	13(1.6%)	10(1.2%)
Dizziness	7(0.9%)	9(1.1%)	12(1.5%)
Dyspepsia	7(0.9%)	3(0.4%)	12(1.5%)
Pain in extremity	3(0.4%)	2(0.3%)	11(1.4%)
Abdominal pain	5(0.6%)	10(1.3%)	6(0.7%)
Constipation	9(1.1%)	10(1.3%)	6(0.7%)
Urinary tract infection	6(0.7%)	10(1.3%)	8(1.0%)
Hypertension	10(1.2%)	8(1.0%)	7(0.9%)
Viral infection	0(0%)	3(0.4%)	10(1.2%)
Oedema peripheral	9(1.1%)	4(0.5%)	6(0.7%)
Vertigo	2(0.2%)	9(1.1%)	1(0.1%)
Arthralgia	5(0.6%)	5(0.6%)	8(1.0%)
Flatulence	6(0.7%)	6(0.8%)	8(1.0%)
Gastroenteritis	7(0.9%)	8(1.0%)	5(0.6%)

E40=Esomeprazole 40 mg od; E20=Esomeprazole 20 mg od
A cut off of 1% have been used.

D961C00001_C0017

Date of the report

18 December 2008