AstraZeneca

Clinical Study Report

Drug Substance	Esomeprazole
Edition Number	1
Study Code	D961DC00001
Date	31 March 2008

A randomized, double-blind, parallel-group, placebo controlled study of esomeprazole iv (bolus infusion of 80 mg followed by a continuous infusion of 8 mg per hour) administered for 72 hours to assess prevention of rebleeding in patients that have undergone successful primary endoscopic haemostasis of a bleeding peptic ulcer – the PUB study

Study dates: First patient enrolled: 30 October 2005
Last patient completed: 14 December 2007

Phase of development: III

This study was performed in compliance with Good Clinical Practice.

Drug Product	Nexium	**SYNOPSIS**	
Drug Substance(s)	Esomeprazole		
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Study centre(s)

This study was conducted in 16 countries and 91 centres randomized patients into the study: Austria (6 centres), Denmark (7 centres), Finland (1 centre), France (8 centres), Germany (7 centres), Greece (2 centres), Hong Kong (1 centre), Netherlands (7 centres), Norway (6 centres), Romania (5 centres), Russia (13 centres), South Africa (4 centres), Spain (5 centres), Sweden (12 centres), Turkey (4 centres), and UK (3 centres). An additional 3 centres enrolled but never randomized any patients (1 centre in Denmark and 2 centres in Germany).

Publications

Sung JJY, Mössner J, Barkun A, Kuipers EJ, Lau J, Jensen D, Stuart R, Junghard O, Olsson G. Intravenous esomeprazole for prevention of peptic ulcer re-bleeding: rationale/design of the Peptic Ulcer Bleed study. Aliment Pharmacol Ther 2008;27:666-677

Study dates		**Phase of development**
First patient enrolled	30 October 2005	Therapeutic confirmatory (III)
Last patient completed	14 December 2007	

Objectives

Primary objective

The primary objective was to compare, in patients with peptic ulcer bleeding (PUB) after successful endoscopic haemostasis, the efficacy of 72 hours continuous iv infusion of either esomeprazole or placebo by assessment of the rate of clinically significant rebleeding during the iv treatment period.

Secondary objectives

The secondary objectives were to compare, in patients with PUB after successful endoscopic haemostasis, 72 hours continuous iv infusion of either esomeprazole or placebo with regard to the following, where the time period begins at start of iv treatment:

1. The rate of clinically significant rebleeding within 7 days and 30 days

2. Proportion of mortalities within 72 hours and 30 days

3. Rate of "bleed-related" mortalities within 30 days, based on the assessments by the Endpoint Committee (EpC)

4. Proportion of patients who, within 72 hours and 30 days, had surgery (except endoscopic treatment) due to rebleeding

5. Proportion of patients who within 72 hours and 30 days, had endoscopic re-treatment due to rebleeding

6. Number of blood units transfused within 72 hours and 30 days

7. Number of days hospitalized due to rebleeding within 30 days

8. Safety and tolerability

In addition, the safety and tolerability of open oral treatment of esomeprazole 40 mg for 27 days were assessed.

Study design

This was an international, randomized, multicentre, prospective, double-blind, parallel-group, placebo controlled study comparing the efficacy and safety of esomeprazole iv and placebo iv given for 72 hours (a bolus infusion of 80 mg followed by a continuous infusion of 8 mg per hour). After the 72-hour iv treatment period, all patients received active treatment with 40 mg oral esomeprazole once daily (od) for 27 days.

Target patient population and sample size

The target population was male and female patients, 18 years or above who had undergone successful endoscopic haemostatic treatment of a bleeding gastric or duodenal ulcer.

A sample size of 760 randomized patients (380 randomized patients per treatment group) was needed to provide 90% power to detect a 8% difference in rebleeding rate within the first 72 hours assuming 7% rebleeding rate in the esomeprazole treatment group and 15% rebleeding rate in the placebo treatment group at the significance rate of 0.05 and 10% of the patients excluded from the per-protocol (PP) analysis. To reach 760 to 800 randomized patients in the study it was estimated that 2500 patients needed to be enrolled.

A majority of centres declared that the clinical protocol was identical to normal clinical practice, and obtained ethics committee approval to obtain informed consent from the patient after the initial endoscopic treatment was carried out. The expected number of enrolled patients was therefore reduced, and at the completion of the study 1313 patients had been enrolled and 767 of those were randomized into the study.

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

- Esomeprazole powder for solution for infusion 40 mg, batch numbers H 1516-03-02-01 and H 1516-03-02-02, was used for the iv administration according to the following specifications:
  - 80 mg esomeprazole iv was given as a bolus infusion during 30 minutes
  - 8 mg esomeprazole iv per hour was given during 71.5 hours
- Placebo for esomeprazole powder for solution for infusion, batch numbers H 1530-01-02-01 and H 1530-01-02-02, was used as comparator and administered according to the following specifications:
  - Placebo iv given as bolus infusion during 30 minutes
  - Placebo iv per hour during 71.5 hours
- Esomeprazole capsules 40 mg, batch numbers H 1222-04-01-12 and H 1222-04-01-15, were used for the oral treatment period. All patients received oral 40 mg esomeprazole capsules od during 27 days after the initial iv treatment.

Duration of treatment

The iv treatment period was 72 hours and it was followed by 27 days of oral treatment.

Criteria for evaluation (main variables)

Efficacy

- Primary outcome variable:
  - Clinically significant rebleeding within 72 hours of continuous infusion of esomeprazole or placebo
- Secondary outcome variables:
  - Clinically significant rebleeding within 7 days and 30 days
  - Death within 72 hours and 30 days

- Death related to rebleeding within 30 days as judged by the EpC
- Requirement for surgery within 72 hours and 30 days
- Requirement for endoscopic re-treatment within 72 hours and 30 days
- Number of blood units transfused within 72 hours and 30 days
- Number of days hospitalized due to rebleeding during the 30-day treatment period

Safety

Adverse events (AEs), clinical laboratory findings, physical examination, vital signs including blood pressure (BP) and pulse rate

Statistical methods

The primary variable, rebleeding within 72 hours, was analyzed with a Mantel-Haenszel test, stratified for type of endoscopic treatment at baseline. Standard statistical methods, Mantel-Haenszel test or log-rank test for dichotomous variables and Wilcoxon two-sample test for continuous variables, were used in the analysis of secondary variables, with adjustment for type of endoscopic treatment at baseline. Fisher's exact test was used in the analysis of mortality. Safety variables are presented using descriptive statistics.

Patient population

Male and female patients, 18 years or above whom had undergone successful endoscopic haemostatic treatment of a bleeding gastric or duodenal ulcer (Table S1).

Table S1 Patient population and disposition at baseline

Characteristic	Eso[a] (n=375)	Placebo[b] (n=389)
Gender, n(%)		
Male	254(67.7%)	268(68.9%)
Female	121(32.3%)	121(31.1%)
Race, n(%)		
Caucasian	325(86.7%)	342(87.9%)
Black	4(1.1%)	5(1.3%)
Oriental	27(7.2%)	27(6.9%)
Other[c]	19(5.1%)	15(3.9%)
Below and above 65 years of age, n(%)		
<65	182(48.5%)	210(54.0%)
>=65	193(51.5%)	179(46.0%)
Age, years		
Mean(SD)	62.1(17.1)	60.2(17.6)

Characteristic	Eso[a] (n=375)	Placebo[b] (n=389)
Min-Max	18-95	18-98
ASA class, n(%)		
1	139(37.1%)	161(41.4%)
2	188(50.1%)	178(45.8%)
3	48(12.8%)	50(12.9%)
Shock, n(%)[d]		
No	356(94.9%)	370(95.1%)
Yes	19(5.1%)	19(4.9%)
H. pylori status, n(%)[e]		
Negative	92(24.5%)	119(30.6%)
Positive	246(65.6%)	226(58.1%)
Trace	18(4.8%)	26(6.7%)
Missing	19(5.1%)	18(4.6%)
Forrest class, n(%)		
Ia	28(7.5%)	40(10.3%)
Ib	166(44.3%)	163(41.9%)
IIa	136(36.3%)	151(38.8%)
IIb	42(11.2%)	34(8.7%)
Missing	3(0.8%)	1(0.3%)
Ulcer location, n(%)		
Stomach	157(41.9%)	155(39.8%)
Duodenum	216(57.6%)	233(59.9%)
Missing	2(0.5%)	1(0.3%)
Endoscopic treatment, n(%)		
Single	175(46.7%)	180(46.3%)
Combination	192(51.2%)	200(51.4%)
Prohibition	4(1.1%)	4(1.0%)
Missing	4(1.1%)	5(1.3%)
Haemoglobin, g/L		
N	373	382
Mean(SD)	97.7(24.9)	97.4(25.9)
Min-Max	29-158	36-178
Hospitalized at time of upper GI bleeding prior to enrollment, n(%)		
Not hospitalized	338(90.1%)	354(91.0%)
Hospitalized	37(9.9%)	35(9.0%)
History of gastric or duodenal ulcer, n(%)		
No	263(70.1%)	268(68.9%)
Yes	112(29.9%)	118(30.3%)
Missing	0(0.0%)	3(0.8%)
Previous complications related to gastric or duodenal ulcer, n(%)		

Characteristic	Eso[a] (n=375)	Placebo[b] (n=389)
No	331(88.3%)	347(89.2%)
Yes	44(11.7%)	41(10.5%)
Missing	0(0.0%)	1(0.3%)
Medication prior to enrollment[f], n(%)		
NSAID[g]	151(40.3%)	157(40.4%)
- COX-2 selective	3(0.8%)	1(0.3%)
- Non-selective NSAID	63(16.8%)	73(18.8%)
- Acetyl salicylic acid	103(27.5%)	103(26.5%)
Clopidogrel	12(3.2%)	11(2.8%)
Warfarin	9(2.4%)	13(3.3%)
SSRI[h]	9(2.4%)	14(3.6%)
Disposition		
n randomized	376	391
n(%) of patients who completed[i]	337(89.6%)	349(89.3%)
n(%) of patients who discontinued	39(10.4%)	42(10.7%)
n(%) analyzed for safety[j]	375(99.7%)	389(99.5%)
n(%) analyzed for efficacy (ITT[k])	375(99.7%)	389(99.5%)
n(%) analyzed for efficacy (PP[l])	292(77.9%)	316(81.2%)

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[c] Other refers to 31 mixed races, 1 Maghreb, 1 Arubaan and 1 Cape coulored
[d] Shock defined as a systolic bloodpressure ≤90 mm Hg or a peripheral pulse ≥110 beats/min
[e] The following cut-off values were applied for *H. pylori* IgG antibodies in serum:
positive: ≥1.1 U/mL
trace: ≥0.9 U/ml and <1.1 U/mL
negative: <0.9 U/mL
[f] Any dose given within 2 weeks prior to enrollment
[g] Non-steroidal anti-inflammatory drugs
[h] Serotonin selective reuptake inhibitor
[i] For 5 patients in the eso group and 2 in the placebo treatment group information on termination was not completed via the WBDC-system and therefore the information is not availible in the database, however, the information has been collected via paper CRFs
[j] Number of patients who took at least 1 dose of study treatment and had at least 1 data point after dosing
[k] ITT=Intention-to-treat
[l] PP=Per-protocol

Efficacy results

A summary of the efficacy results obtained in the study are shown in Table S2. The primary objective was to compare, in patients with PUB after successful endoscopic haemostasis, the efficacy of 72 hours continuous iv infusion of either esomeprazole or placebo by assessment of the rate of clinically significant rebleeding during the iv treatment period. The obtained study results demonstrate that the number of clinically significant rebleedings within 72 h with continuious iv infusion was statistically significantly fewer in patients treated with esomeprazole compared with placebo. This result was observed for both the ITT (p=0.026) and the PP populations (p=0.0093).

Furthermore, esomeprazole iv also reduces the number of clinically significant rebleedings within 7 days and 30 days. Placebo treated patients needed more blood transfusions and about twice as many of the placebo treated patients needed surgery and endoscopic re-treatment due to rebleeding compared with patients treated with esomeprazole iv both within 72 hours and 30 days. Esomeprazole iv also reduced the number of days hospitalized due to rebleeding within 30 days after start of treatment. One single death was reported during the iv treatment period, ie, within 72 hours, and it was in the esomeprazole treatment group. Within 30 days there were 3 deaths reported in the esomeprazole treatment group and 8 in the placebo treatment group. The corresponding bleed related mortalities within 30 days after start of treatment was 2 in the esomeprazole treatment group and 3 in the placebo arm.

Table S2 Summary of efficacy results; ITT population

Variable	Treatment period	Status / Statistics	Eso[a] (n=375)	Placebo[b] (n=389)	p-value
Rebleeding	72 hours	No rebleed	353(94.1%)	349(89.7%)	
		Rebleed	22(5.9%)	40(10.3%)	0.0256[d]
	7 days	No rebleed	348(92.8%)	339(87.1%)	
		Rebleed	27(7.2%)	50(12.9%)	0.0096[d]
	30 days	No rebleed	346(92.3%)	336(86.4%)	
		Rebleed	29(7.7%)	53(13.6%)	0.0092[c]
Death	72 hours	No death	374(99.7%)	389(100%)	
		Death	1(0.3%)	0(0.0%)	0.4908[e]
	30 days	No death	372(99.2%)	381(97.9%)	
		Death	3(0.8%)	8(2.1%)	0.2240[e]
Death related to rebleeding	30 days	No rebleed related death	373(99.5%)	386(99.2%)	
		Rebleed related death	2(0.5%)	3(0.8%)	1.0000[e]
Surgery due to rebleeding	72 hours	No surgery	370(98.7%)	380(97.7%)	
		Surgery	5(1.3%)	9(2.3%)	0.3124[d]
	30 days	No surgery	365(97.3%)	368(94.6%)	
		Surgery	10(2.7%)	21(5.4%)	0.0587[c]
Endoscopic re-treatment due to rebleeding	72 hours	No endoscopic re-treatment	359(95.7%)	357(91.8%)	
		Endoscopic re-treatment	16(4.3%)	32(8.2%)	0.0244[d]
	30 days	No endoscopic re-treatment	351(93.6%)	344(88.4%)	
		Endoscopic re-treatment	24(6.4%)	45(11.6%)	0.0121[c]
Number of blood units transfused	72 hours	Total number of blood units	492	738	0.0472[f]
	30 days	Total number of blood units	589	935	0.0339[f]

Variable	Treatment period	Status / Statistics	Eso[a] (n=375)	Placebo[b] (n=389)	p-value
Days hospitalized due to rebleeding	30 days	Total number of days hospitalized due to rebleeding	284	500	0.0080[f]

a Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
b Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
c log-rank test stratified by endoscopic treatment at baseline
d Cochran-Maentel-Haenzel test stratified by endoscopic treatment at baseline
e Fisher's exact test
f Wilcoxon-two-sample test stratified by endoscopic treatment at baseline

Safety results

The safety profile of esomeprazole iv was similar to placebo iv, and no safety concerns were raised concerning the esomeprazole oral treatment period. The number of deaths was numerically fewer in the esomeprazole treatment group compared with the placebo treatment group. The frequency of patients reporting AEs and SAEs was similar for the 2 treatment groups. AEs related to infusion site reactions were reported in a higher frequency for patients treated with esomeprazole compared to placebo. However, the events were all of mild intensity and did not lead to study drug termination. The reactions appeared to be of minor clinical importance. ALP values increased within the reference range in both treatment groups, to a slightly higher degree in the esomeprazole treatment group. The increase in ALP was not associated with increases in other liver function tests, ie, ALAT, ASAT or bilirubin. Moreover, there were only single occurrences of AEs from the SOC "Hepatobiliary disorders". The mechanism behind the ALP increase is not clear, however, the overall data do not indicate any safety concern. There were no clinically relevant trends in either treatment group with regard to other laboratory variables, physical examinations, or vital signs.

Adverse events are summarized in Table S3 and Table S4 and the most commonly reported AEs are presented in Table S5 and Table S6.

The frequencies of AEs in the different categories were similar in both treatment groups within 72 hours (Table S3).

Table S3 Number (%) of patients who had at least 1 AE in any category, and total numbers of AE (safety analysis set) within 72 hours after start of treatment

Category of AE	n(%) of patients who had an AE in each category[a]			
	Eso[b] (375)		Placebo[c] (389)	
Any AEs	147	(39.2%)	163	(41.9%)
SAEs	35	(9.3%)	44	(11.3%)
SAEs leading to death[d]	2	(0.5%)	3	(0.8%)

Category of AE	n(%) of patients who had an AE in each category[a]			
	Eso[b] (375)		Placebo[c] (389)	
SAEs not leading to death	33	(8.8%)	41	(10.5%)
Discontinuations of study treatment due to AEs	31	(8.3%)	39	(10.0%)
Other significant AEs	0	(0.0%)	0	(0.0%)
	Total number of AEs			
AEs	224		264	
SAEs	44		47	

[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] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[c] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[d] The AE started within 72 h, but death occurred after 72 hours for 4 patients

The frequencies of AEs in the different categories were similar in both treatment groups wihin days 4 to 30 (Table S4).

Table S4 Number (%) of patients who had at least 1 AE in any category, and total numbers of AE (safety analysis set), day 4 to 30

Category of AE	n(%) of patients who had an AE in each category[a]			
	Eso[b] (347)		Placebo[c] (352)	
Any AEs	116	(33.4%)	131	(37.2%)
SAEs				
SAEs leading to death	1	(0.3%)	3	(0.9%)
SAEs not leading to death	29	(8.4%)	28	(8.0%)
Discontinuations of study treatment due to AEs	15	(4.3%)	17	(4.8%)
Other significant AEs	0	(0.0%)	0	(0.0%)
	Total number of AEs			
AEs	202		217	
SAEs	31		35	

[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] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[c] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days

The most commonly reported AEs during the iv treatment phase occured in the SOC "Gastrointestinal disorders" (Table S5) with more events occurring in the placebo treatment group than in the esomeprazole treatment group (19.8% and 12.3%, respectively).

Table S5 Number (%) of patients who had at least 1 AE by preferred term, presented by decreasing order of Eso frequency within 72 hours after start of treatment, safety population

System organ class/Preferred term	Number(%) of patients[c] Eso[a] (n=375)	Placebo[b] (n=389)
Patients with any AE	147(39.2%)	163(41.9%)
Gastrointestinal disorders	46(12.3%)	77(19.8%)
Duodenal ulcer haemorrhage	16(4.3%)	16(4.1%)
Nausea	8(2.1%)	8(2.1%)
Constipation	6(1.6%)	9(2.3%)
Abdominal pain upper	5(1.3%)	9(2.3%)
Gastric ulcer haemorrhage	4(1.1%)	13(3.3%)
Abdominal pain	1(0.3%)	11(2.8%)
General disorders and administration site conditions	27(7.2%)	20(5.1%)
Pyrexia	13(3.5%)	11(2.8%)
Vascular disorders	24(6.4%)	16(4.1%)
Phlebitis	9(2.4%)	2(0.5%)
Cardiac disorders	13(3.5%)	14(3.6%)
Infections and infestations	13(3.5%)	16(4.1%)
Respiratory, thoracic and mediastinal disorders	12(3.2%)	13(3.3%)
Nervous system disorders	11(2.9%)	11(2.8%)
Metabolism and nutrition disorders	10(2.7%)	6(1.5%)
Musculoskeletal and connective tissue disorders	10(2.7%)	9(2.3%)
Psychiatric disorders	10(2.7%)	20(5.1%)
Skin and subcutaneous tissue disorders	9(2.4%)	6(1.5%)
Investigations	4(1.1%)	11(2.8%)

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[c] Number of patients who reported at least 1 AE for a preffered term
A cut off at 2% in either treatment group has been set for both the SOC and PT level

For the oral treatment period, day 4 to 30, the most commonly reported AEs were in the SOC "Gastrointestinal disorders" (Table S6).

Table S6 Number (%) of patients who had at least 1 AE by preferred term, presented by decreasing order of Eso frequency during day 4 to 30 after start of treatment; safety population

System organ class/Preferred term	Number(%) of patients[c]	
	Eso[a] (n=347)	Placebo[b] (n=352)
Patients with any AE	116(33.4%)	131(37.2%)
Gastrointestinal disorders	33(9.5%)	46(13.1%)
Constipation	7(2.0%)	12(3.4%)
Duodenal ulcer haemorrhage	4(1.2%)	9(2.6%)
Abdominal pain	1(0.3%)	7(2.0%)
General disorders and administration site conditions	24(6.9%)	18(5.1%)
Pyrexia	9(2.6%)	9(2.6%)
Infections and infestations	18(5.2%)	26(7.4%)
Urinary tract infection	4(1.2%)	9(2.6%)
Vascular disorders	15(4.3%)	9(2.6%)
Respiratory, thoracic and mediastinal disorders	14(4.0%)	8(2.3%)
Musculoskeletal and connective tissue disorders	9(2.6%)	10(2.8%)
Nervous system disorders	9(2.6%)	10(2.8%)
Cardiac disorders	8(2.3%)	8(2.3%)
Metabolism and nutrition disorders	7(2.0%)	10(2.8%)
Skin and subcutaneous tissue disorders	7(2.0%)	9(2.6%)
Psychiatric disorders	6(1.7%)	8(2.3%)
Blood and lymphatic system disorders	5(1.4%)	8(2.3%)
Renal and urinary disorders	4(1.2%)	8(2.3%)

[a] Eso: esomeprazole iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[b] Placebo: placebo iv for 72 h followed by esomeprazole oral 40 mg od for 27 days
[c] Number of patients who reported at least 1 AE for a preffered term
A cut off at 2% in either treatment group has been set for both the SOC and PT level

Date of the report

31 March 2008