AstraZeneca

Drug product:	Esomeprazole	**SYNOPSIS**	
Drug substance(s):	Esomeprazole		
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A randomised, comparative, double-blind, parallel group, multi-centre Phase IIIa study to eradicate Helicobacter Pylori, heal gastric ulcer and prevent relapse in gastric ulcer subjects with esomeprazole in combination with amoxicillin and clarithromycin

Study centres

This study was conducted in 73 active centres in 9 countries: Bulgaria (10 centres), Czech Republic (10 centres), Germany (6 centres), Hong Kong (3 centres), Hungary (9 centres), Philippines (3 centres), Poland (17 centres), Romania (7 centres) and Slovakia (8 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	16 October 2001	Therapeutic confirmatory (IIIa)
Last subject completed	23 February 2004	

Objectives

Primary:

- To compare gastric ulcer recurrence during the 12-month period after treatment. The treatment groups receiving esomeprazole triple therapy were compared with the group receiving esomeprazole alone.
- To estimate eradication rates of *H. pylori* in gastric ulcer subjects in the different treatment groups.

Secondary:

- To compare gastric ulcer recurrence during the 6-month period after treatment. The treatment groups receiving esomeprazole triple therapy were compared with the group receiving esomeprazole alone.
- To document gastric ulcer healing rates in the different treatment groups after 4 weeks' treatment.
- To evaluate the frequency and severity of gastrointestinal (GI) symptoms in the different treatment groups.
- To estimate the type and degree of inflammation in biopsies from the antrum and corpus in the different treatment groups.
- To assess the primary antimicrobial susceptibility of *H. pylori* to amoxicillin and clarithromycin.
- To assess antimicrobial susceptibility of *H. pylori* to amoxicillin and clarithromycin in subjects who were not cured by the eradication treatment.
- To evaluate the tolerability of esomeprazole in combination with amoxicillin and clarithromycin.

Study design

This was a randomised, double-blind, international multi-centre study with three parallel treatment groups:

1. a seven-day regimen with esomeprazole in combination with amoxicillin and clarithromycin without additional esomeprazole, (EAC+placebo),
2. a seven-day regimen with esomeprazole in combination with amoxicillin and clarithromycin followed by esomeprazole monotherapy for an additional three weeks, (EAC+E20),
3. a seven day regimen consisting of esomeprazole plus placebo antimicrobials, followed by esomeprazole monotherapy for an additional three weeks (E + E20).

The study was aimed to determine efficacy of one week's triple therapy consisting of esomeprazole in combination with amoxicillin and clarithromycin, for eradication of *H. pylori* and prevention of relapse of gastric ulcer (GU) after successful GU healing.

Target subject population and sample size

Subjects with not more than two gastric ulcers with a maximum of 2 cm in diameter and at least one ulcer with at least 5 mm in diameter verified by endoscopy and a *H. pylori*-positive dagnosis at entry by a rapid *Helicobacter* urease test (HUT test®).

450 subjects (150 per group), were required to achieve an approximately 95% power for a two-sided log rank test at 5% significance level of equality of survival curves between the eradication therapy groups combined versus the group without eradication therapy. 88% were expected to be in remission after 6 months with eradication therapy, and 73% without eradication therapy. In total 480 subjects were randomised.

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

Investigational product or other treatment	Dosage form and strength	Batch number
esomeprazole	capsules 20 mg	H 1189-04-01-06, H 1189-04-01-07
esomeprazole PLACEBO	capsules 20 mg	H 0459-06-03-09
amoxicillin	tablets 500 mg	H 1034-02-01-05, H 1034-02-01-06
amoxicillin PLACEBO	tablets 500 mg	H 1081-02-01-03
clarithromycin	tablets 250 mg	H 1031-04-01-08, H 1031-04-01-09
clarithromycin PLACEBO	film-coated tablets 250 mg	H 1147-03-01-01

Duration of treatment

The duration of the treatment was 4 to 8 weeks. The eradication therapy or placebo was taken during the first week that was followed with the three-week esomeprazole or placebo treatment and with an additional four-week period with esomeprazole for subjects with unhealed ulcers after the 4 weeks of treatment. The subjects with healed ulcers subsequently entered a 12-month follow-up period with no further study drugs.

The subjects were in the study for a maximum of 15 months and visited the clinic on seven scheduled occasions at most.

Criteria for evaluation (main variables)

Efficacy

- Primary variables:

  Time to endoscopic relapse of GU during 12 months (Proportion of subjects in remission by number of days) after treatment cessation

  Presence of *H. pylori* (yes/no) (Proportion of subjects being *H. pylori* negative) at first visit of the follow-up part (Visit 5)

- Secondary variables:

  Time to endoscopic relapse of GU during 6 month (Proportion of subjects in remission by number of days) after treatment cessation

  Proportion of subjects with healed ulcer after 4 weeks of treatment

  Proportion of subjects with upper GI symptoms graded according to severity and frequency at each study visits

  Proportion of subjects with inflammation in the biopsies from the antrum and corpus

  Proportion of subjects with *H. pylori* infection susceptible to amoxicillin and clarithromycin at baseline and 6 months after treatment cessation

Safety

Standard assessments included adverse event (AE) reports and clinical laboratory (haematology and clinical chemistry). Measurements of vital signs and physical examination were done at baseline. AEs were recorded during the treatment period and serious adverse events (SAEs) were reported during the whole study.

Statistical methods

A comprehensive Statistical Analysis Plan (SAP) was prepared before unbinding the data.

The primary endpoints were analysed both for an intention to treat (ITT) population and for a per protocol (PP) population for the eradication phase and the follow-up phase, respectively. Analyses of efficacy variables other than eradication and relapse of GU were done according to the ITT approach. The safety population was used for evaluating the safety variables.

The primary endpoint, relapse of gastric ulcer during the 12-month period after the healing of the ulcer, was evaluated using a two-sided log rank test at a 5% significance level of equality of survival curves between the eradication therapy groups combined versus the group without eradication therapy. A 95% confidence interval (CI) for the difference between treatments in the proportion of subjects still in remission after 12 months (Life Table estimates) was calculated as well as separate CI's for the treatments.

To estimate eradication rates of *H. pylori* the proportion of subjects who were *H. pylori* negative after treatment was calculated for the different treatment groups together with 95% CI.

The gastric ulcer recurrence during the 6-month period after treatment was evaluated in the same way as gastric ulcer relapse during the 12-month period.

Gastric healing rates after 4 weeks' treatment in the different treatment groups were evaluated by calculation of 95% CI for the different treatment groups respectively. Eight weeks healing rates are also presented, calculated with 95% CIs.

The presence and severity of GI symptoms (heartburn, epigastric pain and acid regurgitation) are shown in tables as the frequency (number of days/week) of epigastric pain and heartburn.

The antimicrobial susceptibility of *H. pylori* to amoxicillin and clarithromycin, and type and degree of inflammation in biopsies from the antrum and corpus are presented in tables (and descriptively where appropriate) by treatment group.

Analysis of safety variables

Adverse event data are presented descriptively.

The laboratory data for randomised subjects are presented in terms of median, mean and standard deviation for the baseline values, the Visit 2 and 3/4 value and the change from baseline to Visit 2 and 3/4. A cross-table showing the number of subjects with the values below, within or above the normal range at baseline versus the same classification at the last visit is provided for each laboratory variable. Graphs showing Visit 2 and 3/4 values versus the baseline values are presented for each treatment group and each laboratory variable.

Subject population

Table S1 Subject population and disposition

		EAC+plac.	EAC+E20	E+E20	Total
Population					
N randomised (N planned)		152(150)	164(150)	164(150)	480(450)
Disposition					
N (%) of subjects who	Completed	112(73.7%)	123(75.0%)	105(64.0%)	340(70.8%)
	Discontinued	40(26.3%)	41(25.0%)	59(36.0%)	140(29.2%)
N analysed for safety[a]		151	164	164	479
N analysed for efficacy (ITT)		133	131	137	401
N analysed for efficacy (PP)					
PP (eradication)		111	110	124	345
PP (follow-up)		107	102	116	325
Demographic characteristics (ITT)					
Sex (n and % of subjects)	Male	76(57.1%)	76(58.0%)	78(56.9%)	230(57.4%)
	Female	57(42.9%)	55(42.0%)	59(43.1%)	171(42.6%)
Age (years)	Mean (SD)	54.9(12.1)	53.9(13.7)	55.2(12.7)	54.7(121.8)

		EAC+plac.	EAC+E20	E+E20	Total
	Range	23 to 79	23 to 89	23 to 86	23 to 89
	< 60 years	86(64.7%)	87(66.4%)	92(67.2%)	265(66.1%)
	≥ 60 years	47(35.3%)	44(33.6%)	45(32.8%)	136(33.9%)
Race (n and % of subjects)	Caucasian	131(98.5%)	127(96.9%)	133(97.1%)	391(97.5%)
	Oriental	2(1.5%)	4(3.1%)	4(2.9%)	10(2.5%)
Baseline characteristics (ITT)					
BMI (kg/m^2)	Mean	25.2	25.2	25.3	25.3
	SD	4.2	4.7	4.2	4.4
	Min/Max	17/37	16/40	16/41	16/41
Stomach abnormal findings	No	84(63.2%)	83(63.4%)	87(63.5%)	254(63.3%)
	Yes	49(36.8%)	48(36.6%)	50(36.5%)	147(36.7%)
History of GI disease	< 1 year	82(61.7%)	88(67.2%)	97(70.8%)	267(66.6%)
	1-5 years	23(17.3%)	19(14.5%)	18(13.1%)	60(15.0%)
	>5 years	28(21.1%)	24(18.3%)	22(16.1%)	74(18.5%)
One previous attempt of HP eradication	No	126(94.7%)	126(96.2%)	133(97.1%)	385(96.0%)
	Yes	7(5.3%)	5(3.8%)	4(2.9%)	16(4.0%)
Days with heartburn	None	82(61.7%)	67(51.1%)	86(62.8%)	235(58.6%)
	1 day	1(0.8%)	6(4.6%)	3(2.2%)	10(2.5%)
	2 days	3(2.3%)	7(5.3%)	3(2.2%)	13(3.2%)
	3 days	7(5.3%)	13(9.9%)	10(7.3%)	30(7.5%)
	4 days	8(6.0%)	9(6.9%)	7(5.1%)	24(6.0%)
	5 days	6(4.5%)	3(2.3%)	8(5.8%)	17(4.2%)
	6 days	2(1.5%)	0(0.0%)	4(2.9%)	6(1.5%)
	7 days	24(18.0%)	26(19.8%)	16(11.7%)	66(16.5%)
Days with epigastric pain	None	14(10.5%)	22(16.8%)	14(10.2%)	50(12.5%)
	1 day	3(2.3%)	0(0.0%)	1(0.7%)	4(1.0%)
	2 days	5(3.8%)	6(4.6%)	8(5.8%)	19(4.7%)
	3 days	17(12.8%)	9(6.9%)	13(9.5%)	39(9.7%)
	4 days	14(10.5%)	9(6.9%)	15(10.9%)	38(9.5%)
	5 days	12(9.0%)	10(7.6%)	11(8.0%)	33(8.2%)

		EAC+plac.	EAC+E20	E+E20	Total
	6 days	4(3.0%)	5(3.8%)	8(5.8%)	17(4.2%)
	7 days	64(48.1%)	70(53.4%)	67(48.9%)	201(50.1%)
Smoking status	Non smoker	56(42.1%)	55(42.0%)	58(42.3%)	169(42.1%)
	Ex smoker	15(11.3%)	13(9.9%)	20(14.6%)	48(12.0%)
	Occasional	14(10.5%)	10(7.6%)	13(9.5%)	37(9.2%)
	Habitual	43(38.7%)	45(40.9%)	45(36.3%)	133(38.6%)
	Missing	0(0.0%)	1(0.9%)	0(0.0%)	1(0.3%)
NSAID usage at baseline	No	133(100.0%)	131(100.0%)	136(99.3%)	400(99.8%)
	Yes	0(0.0)%)	0(0.0%)	1(0.7%)	1(0.2%)

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number; PP=Per-protocol

The treatment groups were generally well balanced in demographic and baseline characteristics. The most common reason for discontinuation in all treatment groups was the development of study specific exclusion criteria.

Efficacy results

- There were statistically significant differences (p=0.0005 and p< 0.0001) regarding ulcer relapse rates between the combined EAC groups (EAC+placebo and EAC+E20) and the group without antibiotics treatment (E+E20) during the 12-month therapy in the ITT and PP population respectively.

Table S2 Test of EAC treatment (the two EAC groups) vs no eradication treatment (the group with no eradication treatment) during 6 and 12 months' follow-up (n=401), ITT

Log-Rank test	Length of follow-up	df	Chi^2	P-value
EAC vs Esomeprazole	12 Months	1	12.20	0.0005
	6 Months	1	6.73	0.0095

- The esomeprazole-based eradication therapy (EAC) reduces the relapse rate of the *H. pylori* positive gastric ulcers compared to the esomeprazole treatment alone during the 12-month period after treatment both in the ITT and PP populations.
- The eradication rates are given in Tables S3 and S4

Table S3 *H. pylori* eradication rates (%) with 95% CI (exact), ITT

			95 % CI	
Treatment	**N**	**Hp neg.(%)**	**Lower**	**Upper**
EAC + plac.	133	76.7	68.6	83.6
EAC + E20	131	82.4	74.8	88.5
E + E20	137	9.5	5.1	15.7

Table S4 *H. pylori* eradication rates (%) with 95% CI (exact), PP (eradication)

			95 % CI	
Treatment	**N**	**Hp neg.(%)**	**Lower**	**Upper**
EAC + plac.	111	82.0	73.6	88.6
EAC + E20	110	86.4	78.5	92.2
E + E20	124	10.5	5.7	17.3

- There were statistically significant differences (p=0.0095 and p=0.0001) regarding ulcer relapse rates between the combined EAC groups (EAC+placebo, EAC+E20) and the group without antibiotics treatment (E+E20) at 6 month after the end of therapy in the ITT and in the PP population respectively.

- The esomeprazole-based eradication therapy (EAC) reduced the relapse rate of the *H. pylori* positive gastric ulcers compared to the esomeprazole treatment alone during the 6-month period after treatment both in the ITT and PP populations.

- The 4-week healing rate was 63.9% in the EAC+placebo treatment group while it was 81.7 % and 84.7% in the EAC+E20 and E+E20 treatment groups where esomeprazole had been given after the first week. The 8-week healing rates were 89.9%, 96.2 and 92.7% in the EAC+placebo, EAC+E20 and E+E20 treatment groups respectively.

- Esomeprazole reduced the severity and frequency of upper GI symptoms (epigastric pain, heartburn and acid regurgitation).
  There were no marked differences in the frequency or severity of the gastrointestinal symptoms after the therapy with the three treatment groups during the follow up.
  Heartburn or acid regurgitation (typical GERD symptoms) did not increase after *H. pylori* eradication even after 12-month follow-up.

- Both EAC treatments (EAC+placebo, EAC+E20) reduced the activity and the grade of inflammation of gastric mucosa already at 1 month and the findings were

persistent up to 12 month after therapy. E+E20 treatment resulted only a temporary improvement in the activity and grade of inflammation during and shortly after the therapy. Neither therapy had a significant effect on atrophy and metaplasia during the 12-month period after therapy.

- The pre-treatment and post treatment antibiotic resistance was low.

Safety results

Non-serious AEs were collected from first dose until healing treatment week 8. SAEs were collected during the entire study.

Eradication treatment week 1

During the eradication week 26% and 23.8% of subjects receiving EAC reported an AE compared with 7.9% of those subjects given Esomeprazole. No AE were considered as severe. One SAE was reported during this period. Four subjects were discontinued due to an AE. Taste perversion, diarrhoea, headache, dry mouth, constipation, abdominal pain, nausea and vomiting were most commonly reported. Apart from headache which evenly dispersed between treatment groups. EAC treatment was afflicted with the majority of collected events.

Ulcer healing treatment week 2-4

The frequency of subjects reporting an AE was between 15.4 % and 11.2% in the different treatment groups. Four AE were reported as severe. Eight SAEs were reported. Two subjects discontinued due to an AE. The most commonly reported events were, diarrhoea, vomiting, abdominal pain and headache without any obvious difference between treatment groups.

Ulcer healing period week 5-8

About 10% of all subjects reported an AE irrespective of what treatment group. Six SAEs were reported and 4 subjects discontinued due to an AE. There were between 42 and 30 subjects in each treatment group during this period. Three gastric carcinoma and 2 malignant lymphoma were reported. Other occurring AEs were single reports on accident, bronchitis, cholecystits, atrial fibrillation, flatulence, hypertension and urinary tract infection.

No-drug follow-up period

During the 1-year no-drug follow-up period only SAEs were collected. One death occurred in each randomisation group. The frequency of subjects with SAEs was similar in all randomisation groups (5.3% - 6.3%). No SAE was considered to be causally related to study treatment/procedures.

Conclusions

- The esomeprazole-based eradication therapy (EAC) reduces the relapse rate of the *H. pylori* positive gastric ulcers compared to the esomeprazole treatment alone during a 6- and 12-month period after treatment cessation.

Date of the report

7 October 2004