AstraZeneca

Drug product	Esomeprazole	**SYNOPSIS**	
Drug substance(s)	Esomeprazole		
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A randomised, double-blind, multicentre Phase III study to evaluate safety of esomeprazole 40 mg given intravenously or orally od for 1 week to subjects with erosive reflux oesophagitis, followed by 3 weeks' open oral treatment with esomeprazole 40 mg od.

Study centre(s)

This study was conducted in South Africa (10 centres).

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First subject enrolled	28 February 2002	Therapeutic confirmatory (III)
Last subject completed	28 June 2002	

Objectives

The primary objective of the study was:

- To evaluate safety after 1 week's treatment with intravenous (iv) injection, iv infusion and oral esomeprazole administration, respectively.

The evaluation was done by assessment of adverse events (AEs), physical examination,

laboratory measurements, blood pressure (BP), pulse, electrocardiogram (ECG) and ophthalmic examination (visual acuity test and visual field).

The secondary objectives of the study were:

- To evaluate safety after 4 weeks' treatment with esomeprazole:
  - 1 week's iv injection followed by 3 weeks' oral administration of esomeprazole
  - 1 week's iv infusion followed by 3 weeks' oral administration of esomeprazole
  - 4 weeks' oral esomeprazole intake

The evaluation was done by assessment of AEs, physical examination, laboratory measurements, BP, pulse and ophthalmic examination (visual acuity test and visual field).

- To evaluate efficacy by assessment of healing rates after 4 weeks' treatment of erosive reflux esophagitis according to Los Angeles (LA) classification (A-D or not present).

Study design

The study was a double-blind, randomised, multicentre study to evaluate the safety of esomeprazole 40 mg given intravenously or orally once daily (od) for 1 week, followed by 3 weeks of open oral treatment with esomeprazole 40 mg od.

Target subject population and sample size

Male and female subjects, aged 18 years or older, with erosive reflux esophagitis confirmed by endoscopy using the LA classification (A-D).

A sample size of 225 completed subjects (75 randomised subjects per group) was considered relevant to further document the safety of the intravenous formulation. To allow for a dropout rate of approximately 10% during the study, it was planned to randomise 250 subjects.

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

Investigational product

<u>Double-blind treatment period:</u>

Esomeprazole powder for solution for injection, 40 mg/placebo, dissolved in 5.2 ml of sodium chloride solution (9 mg/mL), was given od as a 3-minute injection for 1 week.
or
Esomeprazole powder for solution for infusion, 40 mg/placebo, dissolved in 5.2 ml of sodium chloride solution (9 mg/mL) and diluted to a final volume of 100 mL, which was administered intravenously over 30 (±10) minutes od for 1 week.

Batch numbers were:

Esomeprazole powder for solution for injection or infusion, 40 mg: H 1516-03-01-02

Esomeprazole powder for solution for injection or infusion, placebo: H 1530-01-01-02

Comparator

Esomeprazole 40 mg/placebo capsule was given orally od for 1 week.

Batch numbers were:

Esomeprazole 40 mg capsule: H 1222-04-01-10

Esomeprazole Placebo capsule: H 0459-06-03-09

Open treatment period:

Esomeprazole capsule 40 mg oral administration od for 3 weeks.

The batch number was:

Esomeprazole 40 mg capsule: H 1222-04-01-10

Duration of treatment

During the double-blind period, esomeprazole 40 mg was given od for 1 week either as iv injection (3 minutes), iv infusion over 30 (±10) minutes or orally.

In the open treatment period, esomeprazole 40 mg capsule was given orally od for 3 weeks.

Criteria for evaluation (main variables)

Safety

- Primary variables: Frequency and nature of AEs, physical examination, laboratory measurements, BP and pulse, ECG and ophthalmic examination (visual acuity and visual field) after 1 week's treatment.

- Secondary variables: Frequency and nature of AEs, physical examination, laboratory measurements, BP, pulse and ophthalmic examination (visual acuity and visual field) after 4 weeks' treatment.

Efficacy

- Secondary variable: Proportion of subjects with erosive reflux esophagitis healed after 4 weeks' treatment.

Statistical methods

All safety variables are presented descriptively.

The Intention To Treat (ITT) and the Per Protocol (PP) populations were used in the statistical analysis of efficacy, ie, healing rates after 4 weeks' treatment.

The healing rates in each treatment group and the difference in healing rates between iv administration and oral administration were evaluated with two-sided 95% confidence intervals (CI).

Subject population

A total of 246 subjects were randomised. All 246 were included in the ITT/Safety population and 224 were included in the PP population.

The subject population and disposition are given in Table S1.

Table S1 Subject population and disposition

		Esomeprazole 40 mg once daily[a]			
		3-min injection	30-min infusion	oral	Total
Population					
N randomised		79	81	86	246
Demographic characteristics					
Gender (n and % of subjects)	Male	35 (44.3%)	34 (42.0%)	47 (54.7%)	116 (47.2%)
	Female	44 (55.7%)	47 (58.0%)	39 (45.3%)	130 (52.8%)
Age (years)	Mean (SD)	47.7 (12.1)	43.8 (12.2)	45.7 (12.9)	45.7 (12.4)
	Range	22 to 70	18 to 71	19 to 79	18 to 79
Race (n and % of subjects)	Caucasian	41 (51.9%)	38 (46.9%)	47 (54.7%)	126 (51.2%)
	Black	7 (8.9%)	7 (8.6%)	9 (10.5%)	23 (9.3%)
	Oriental	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
	Other	30 (38.0%)	36 (44.4%)	30 (34.9%)	96 (39.0%)[b]
Baseline characteristics					
LA grade (n and % of subjects)	Grade A	26 (32.9%)	32 (39.5%)	27 (31.4%)	85 (34.6%)
	Grade B	36 (45.6%)	31 (38.3%)	37 (43.0%)	104 (42.3%)
	Grade C	16 (20.3%)	16 (19.8%)	19 (22.1%)	51 (20.7%)
	Grade D	1 (1.3%)	2 (2.5%)	3 (3.5%)	6 (2.4%)
Disposition					
N (%) of subjects who	completed	78 (98.7%)	81 (100%)	83 (96.5%)	242 (98.4%)
	discontinued	1 (1.3%)	0 (0.0%)	3 (3.5%)	4 (1.6%)
N analysed for ITT/Safety		79	81	86	246
N analysed for PP		74	75	75	224

[a] Refers to treatment during the 1-week period of randomised treatment (all three treatments were followed by 3 weeks of open treatment with oral esomeprazole 40 mg).

[b] Other comprised of mixed race (33%), Malay (1%) and coloured (5%).

The proportion of subjects who had important protocol deviations leading to exclusion from the per protocol analysis was generally similar across treatment groups. Overall, the treatment groups were comparable in terms of demographic characteristics and baseline values.

Efficacy results

The healing rates of erosive reflux esophagitis after 4 weeks' treatment are given in Tables S2 and S3.

Table S2 Healing rates of erosive reflux esophagitis after 4 weeks' treatment, ITT/Safety population

	Esomeprazole 40 mg once daily		
	3-min injection	**30-min infusion**	**oral**
Estimated healing rate	79.7%(63/79)	80.2%(65/81)	82.6%(71/86)
95% CI	69.2%-88.0%	69.9%-88.3%	72.9%-89.9%

Table S3 Difference in healing rate after 4 weeks' treatment, ITT/Safety population

	Estimate	**95% CI**	
		lower	**upper**
3-min injection - oral	-2.8%	-14.8%	9.1%
30-min infusion - oral	-2.3%	-14.1%	9.5%

The observed healing rates of approximately 80% in each treatment group agree well with earlier findings for oral 4-week treatment with esomeprazole 40 mg od in similar populations of subjects with erosive reflux esophagitis and do not indicate any true difference between the three treatment regimens studied.

Thus, it can be assumed that a 1-week iv treatment (injection or infusion) followed by 3 weeks of oral treatment with esomeprazole 40 mg is similar to 4 weeks of oral esomeprazole 40 mg treatment as regards healing of erosive reflux esophagitis. The healing rates were similar in all treatment groups.

Safety results

A summary of adverse events in each category during 1 week's treatment is given in Table S4.

Table S4 Number of subjects who had an adverse event and total number of adverse events in any category during 1 week's treatment (safety population)

Category of adverse events	Esomeprazole 40 mg once daily		
	3-min injection	30-min infusion	oral
	n=79	n=81	n=86
	N of subjects who had an adverse event in each category[a]		
Any adverse events	29	28	29
Serious adverse events	0	0	1
Discontinuations of study treatment due to adverse events	0	0	1
Other significant adverse event	0	0	0
Severe adverse events	1	1	4
	Total number of adverse events		
Any adverse events[b]	44	51	52
Serious adverse events[b]	0	0	1
Discontinuations adverse events[b]	0	0	2
Other significant adverse event[b]	0	0	0
Severe adverse events	1	1	5

[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] Events are counted by preferred term, ie, for subjects with multiple events falling under the same preferred term, only 1 occurrence of the event is counted.

In this safety study, iv treatment with esomeprazole 40 mg administrated as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole 40 mg in subjects with erosive reflux esophagitis. The AE patterns were similar among the 3 treatment groups. Headache and flatulence were the most commonly reported AEs. The safety evaluation of serious adverse events (SAEs), discontinuations due to AEs or the other safety parameters, including ophthalmic examination have not raised any safety concerns. No clinically relevant trends in the laboratory values were observed and no clinically relevant changes in vital signs, ECG and physical examination were found. When evaluating the individual safety data and the grouped safety data separately, no safety concerns were raised.

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