1.1 Synopsis of Clinical Study Report

Applicant of Drug Registration	AstraZeneca Pharmaceutical Company
Name of Study Drug:	Esomeprazole Sodium for intravenous administration

Title: A randomised, double-blind, double dummy, multicentre study to evaluate the efficacy and safety of esomeprazole 40 mg given i.v. or orally o.d. for 1 week to subjects with erosive reflux esophagitis, followed by 3 weeks' open oral treatment with esomeprazole 40 mg o.d.

Published thesis for the study: None

Study timeline: Start time(date of First Subject enrolled) 29 March, 2005
Complete time(date of Last Subject completed) 13 October, 2005

Objectives:

Primary Objective:

- To evaluate efficacy by assessment of healing rates after 4 weeks' treatment of erosive reflux esophagitis according to Los Angeles (LA) classification.

Secondary Objectives:

- To evaluate safety after 1 week's treatment with intravenous (i.v.) injection and oral esomeprazole administration, respectively.
- To evaluate safety after 4 weeks' treatment with esomeprazole.
- To evaluate rate of symptom resolution after 4 weeks' treatment of erosive reflux esophagitis.

Study design:

The study was carried out as a randomized, double-blind, double dummy, parallel, multicenter study. Subjects with erosive reflux esophagitis confirmed by Endoscopy examination, classified by the LA Classification system (graded A-D), will be randomised into treatments below:

• Esomeprazole powder for solution for injection, 40 mg / Placebo, dissolved in sodium chloride solution (9 mg/mL), given o.d. as a 3 minute injection for 1 week. or

- Esomeprazole 40 mg/Placebo tablet given orally o.d. for 1 week.

All subjects accepted open treatment period by esomeprazole tablet given orally o.d. from day 8 to day 28.

All adverse events (AEs), physical examination, laboratory measurements, blood pressure (BP), pulse and electrocardiogram (ECG) were assessed during study period.

Number of subjects(planned and analysed): estimated randomised 250 subjects, actually randomised 252 subjects.

Inclusion and exclusion criteria:

Inclusion criteria

Subjects are eligible for inclusion (enrolment) at Visit 1 if they fulfil the following criteria:

1. Subjects with erosive reflux oesophagitis, confirmed by endoscopy using the LA classification (A-D)
2. Adults aged 18 years or older
3. Subjects must be able to swallow
4. Subjects capable of providing written informed consent, willing and able to comply with all study procedures

Subjects are eligible for randomization at Visit 2 if they also fulfill the following criterion:

1. Women of child-bearing potential must have a negative pregnancy test

Exclusion criteria:
Subjects are not eligible for inclusion at Visit 1 if they fulfill any of the following criteria:

1. Subjects with any bleeding disorder or signs of gastrointestinal (GI) bleeding at the time of the baseline endoscopy (Visit 1)
2. Any significant "alarm symptoms" such as unintentional weight loss, hematemesis, melena, jaundice or any other sign indicating serious or malignant disease
3. Subjects with current or historical evidence of the following diseases/conditions:
   I) Zollinger-Ellison syndrome
   II) Primary oesophageal motility disorder(s) i.e. achalasia, scleroderma, oesophageal spasm
   III) Evidence of upper gastrointestinal malignancy at the screening endoscopy
   IV) Malignancy or clinically significant cardiovascular, pulmonary, renal, pancreatic or hepatic disease as judged by the investigator
   V) Unstable diabetes mellitus. Stable diabetics controlled on diet, oral agents or insulin are acceptable
   VI) Cerebral vascular disease, such as cerebral ischemia, infarction, haemorrhage

or embolus

4. Need for continuous concurrent therapy during the study period with:
   - Warfarin
   - Diazepam
   - Diphenylhydantoins, mephenytoin
   - Anticholinergics approved for treatment of GI disorders
   - Cisapride
   - NSAIDs (daily intake)
   - ASA (except for ≤165 mg daily for cardiovascular prophylaxis)
5. Complications related to GERD such as esophageal stricture and macroscopic Barrett´s esophagus
6. Contraindications to esomeprazole or other PPIs, including known or suspected hypersensitivity
7. Pregnancy or lactation. Woman of child-bearing potential must be either non-pregnant or postmenopausal or must use a reliable form of contraception during the study period, as judged by the investigator
8. Use of any other investigational compound or participation in another clinical trial within 28 days prior to start of study medication
9. Alcohol and/or drug abuse or any condition associated with poor compliance, including expected non-cooperation, as judged by the investigator
10. Previous participation in the study

Subjects are not eligible for randomization at Visit 2 if they fulfill any of the following criteria:

11. Subjects with clinically significant abnormal values in the laboratory measurements as judged by the investigator, other than those directly related to some concurrent and stable disease
12. Subjects with a positive pregnancy test
13. Subjects using a PPI for more than 10 days during the last 28 days. During the last 7 days before Visit 2 no use of PPI is allowed (antacids and H_2-receptor antagonists are allowed during this period)

Specification, batch no., usage and dosage of investigational product: powder of esomeprazole sodium for intravenous, 40mg/vial, Batch no.:H 1516-03-01-06, 40mg for solution in sodium chloride (9 mg/mL) for injection for 1 week.
Treatment period: Esomeprazole tablet, 40 mg/tablet, Batch no.: H 1365-01-02-04. 40mg given orally, o.d. for 3 weeks.

Specification, batch no., usage and dosage of comparator: Esomeprazole tablet, 40 mg/tablet, Batch no.: H 1365-01-02-04. 40mg given orally, o.d. for 1 week.
Treatment period: Esomeprazole tablet, 40 mg/tablet, Batch no.: H 1365-01-02-04. 40mg given orally, o.d. for 3 weeks.

Criteria for evaluation:

Efficacy:

Primary variable: Healing rates of erosive reflux esophagitis according to Los

Angeles (LA) classification after esomeprazole 40 mg given i.v.for 1 week, followed by esomeprazole tablet given orally for 3 weeks or given treatment with esomeprazole 40 mg orally o.d. for 4 weeks.

Secondary variable: The rate of symptom resolutions after 4 weeks' treatment of erosive reflux esophagitis.

Safety:

Observe after treatment of Esomeprazole 40 mg qd given i.v or Esomeprazole tablet given orally:

- 1 week safety profiles
- 4 weeks safety profiles

Efficacy variables

Healing rates of erosive reflux esophagitis: The number and proportion of subjects who exhibit complete healing of erosive esophagitis (i.e. LA Classification Grade = Not Present) after 4 weeks' treatment.
Symptom disappeared rates of erosive reflux esophagitis: The number and proportion of subjects who's symptoms of erosive esophagitis disappear after 4 weeks' treatment.

Safety variables

To evaluate AEs, physical examination, BP and pulse, ECG, laboratory measurements after treatment. Analyze all AEs, Serious Adverse Event, AEs leading to discontinuation and severe AEs. Items of lab examination surpass twofold of normal range were judged as clinically significant abnormal values.

Statistical methods:

The number and percentage of subjects who exhibit complete healing of erosive esophagitis (i.e. LA Classification Grade = Not Present) after 4 weeks' treatment will be summarized and analyzed for both ITT and PP population. The healing rate and the associated 2-sided 95% confidence intervals will be calculated for each treatment group. The treatment difference in the healing rates and the associated 2-sided 95% CI for the treatment difference will also be calculated. The 95% CI of difference between two groups including 0 indicates that the healing rate is similar in two groups.

Safety endpoints will be summarized by treatment received in the safety population. Descriptive statistics for all AEs, physical examination, laboratory measurements, BP, pulse and ECG will be performed.

Results:

Total 292 patients were screened. 252 qualified patients were randomised into different treatments with given esomeprazole i.v. for 1 week, followed given esomeprazole orally for 3 weeks(n=126), or given esomeprazole orally for 4 weeks(n=126) . 252 subjects were entered into ITT analysis and safety analysis, 244 patients were entered into PP analysis.

Efficacy results:

Healing rate of erosive reflux esophagitis after 4 weeks treatment in esomeprazole i.v. for 1 week, followed given esomeprazole orally for 3 weeks (hereinafter as i.v group) was 78.6%(ITT) and 81.8%(PP); Healing rate in group with esomeprazole orally for 4 weeks (hereinafter as p.o. group) is 83.3%(ITT) and 83.7%(PP). There is no significant statistical differences between these two groups(table S1).

Table S1 Healing rates of Erosive Reflux Esophagitis after 4 weeks treatment

	Esomeprazole i.v	Esomeprazole p.o	Difference of healing rate	95%CI of difference	P*
ITT analysis	N=126	N=126			
Healing rate	99 (78.6%)	105(83.3%)	-4.8%	-14.4%-4.9%	0.3099
95%CI	(70.4%-85.4%)	(75.7%-89.4%)			
PP analysis	N=121	N=123			
Healing rate	99 (81.8%)	103(83.7%)	-1.9%	-11.4%-7.6%	0.6741
95%CI	(73.8%-88.2%)	(76.0%-89.8%)			

*P was calculated from Logistic analysis，considering treatment and center effect。

6 patients among 252 subjects were discontinued from the study, others were all accepted assessment of symptom of reflux esophagitis and Edoscopy examination. Actual evaluable patients is 246. Resolution rates of reflux esophagitis symptoms of two groups: chest pain in p.o.group is 88.9%, other symptoms such as heartburn, sour regurgitation, dysphagia are all above 93%.

Symptoms resolution rate

	Esomeprazole i.v		Esomeprazole p.o		Total	
	Positive number at baseline	Rate of disappeared	Positive number at baseline	Rate of disappeared	Positive number at baseline	Rate of resolution
GERD symptoms						
Heartburn	85	82(96.5%)	76	71(93.4%)	161	153(95.0%)
Regurgitation	92	91(98.9%)	90	84(93.3%)	182	175(96.2%)

Dysphagia	13	13(100 %)	19	18(94.7%)	32	31(96.9%)
Chest pain	30	29(96.7%)	36	32(88.9%)	66	61(92.4%)

Safety results：
In general, subjects show good tolerance to esomeprazole given orally or given in iv. Total incidence of AEs is 22.6%, including i.v. group of 15.1%, and p.o. group of 30.2%. Among those AEs, mild AEs accounted 89.5%, moderate AEs were 10.5%. No severe AE and Serious AE reported and no death reported. Subjects discontinued due to AE is 1.65%. AEs normally reported were hepatic enzyme elevations (5.6%), gastrointestinal symptoms, including diarrhea, abdominal pain (2.8%). In addition, AEs above 1% also included palpitation, dizzyness, headache, rash, gastric polyps and upper respiratory infection.

Report date: 13 January 2006