AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	esomeprazole	REFERRING TO PART	
DOCUMENT NO.	01	OF THE DOSSIER	
VERSION NO.	1		
STUDY CODE	SH-QBE-0067		
DATE	15 February, 2002		

Maintenance treatment of patients with healed reflux esophagitis, comparing remission rates during 6 months with esomeprazole 20 mg q.d. and lansoprazole 15 mg q.d. - A randomised, double-blind multi-centre study- METROPOLE

STUDY CENTRE(S)

Multi-centre study including Belgium with 14 centres, Denmark 7, France 14, Germany 20, Hungary 6, Iceland 4, Ireland 4, Italy 10, Norway 15, Portugal 8, Spain 10, Switzerland 7, UK 24 and South Africa 5 centres.

PUBLICATION (REFERENCE)

Not applicable

STUDY PERIOD

- **DATE OF FIRST PATIENT ENROLLED** May 9, 2000
- **DATE OF LAST PATIENT COMPLETED** August 28, 2001

PHASE OF DEVELOPMENT

Phase IIIB

OBJECTIVES

The primary objective was:
The comparison of symptomatic and/or endoscopic remission rates during 6 months' treatment with esomeprazole 20 mg q.d. (E20) and lansoprazole 15 mg q.d. (L15), after initial healing of reflux esophagitis.

The secondary objectives were:
The comparison of endoscopic remission rates during 6 months' treatment with E20 and L15, after initial healing of reflux esophagitis.

The assessment of healing rates and symptom resolution after 4 and 8 weeks after 40 mg esomeprazole q.d. (E40).

The assessment of symptoms in the two treatment groups after 1, 3 and 6 months.

The assessment of safety and tolerability.

Additional Objectives
The assessment of QoL in the two treatment groups. Measurements were only made in those countries with validated questionnaires.

STUDY DESIGN

Randomised, double-blind, international multi-centre study, parallel grouped with double-dummy design.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients with endoscopically verified reflux esophagitis, classified according to the Los Angeles Classification, were enrolled in the healing phase after giving their signed informed consent. Asymptomatic patients with endoscopically verified healed reflux esophagitis, classified according to the Los Angeles Classification, were randomised to the maintenance phase after the initial 4-8 week healing phase.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Healing medication
Esomeprazole 40 mg capsule, 40 mg q.d. Per oral. Batch no H 1222-04-01-09.

Investigational product
Esomeprazole 20 mg capsule, 20 mg q.d. Per oral. Batch no H 1189-04-01-06.
Placebo capsule, Per oral. Batch no H 0459-06-03-07.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Lansoprazole 15 mg capsule, 15 mg q.d. per oral. Batch no H 1460-02-01-01 and H 1460-02-01-02
Placebo capsule, Per oral. Batch no H 1480-01-01-01.

DURATION OF TREATMENT

Healing phase 4-8 weeks' treatment with E40.
Maintenance phase 6 months' treatment with E20 or L15.

MAIN VARIABLE(S):

- **EFFICACY**

The primary variable was time to relapse, defined as reflux esophagitis grade A-D, and/or unwillingness to continue in the study due to reflux symptoms.

A secondary variable was time to endoscopic relapse, defined as reflux esophagitis grade A-D.

- **SAFETY**

Adverse events (AEs), Laboratory assessments.

STATISTICAL METHODS

The two treatment groups were compared regarding time to relapse, the primary variable, using Life Table methods for graphic presentation and a log rank test for statistical inference. The secondary variable, time to endoscopic relapse, was analysed with the same methods.

Healing rates and symptom resolution after 4 and 8 weeks were described using frequency tables.

The severity of symptoms after 1, 3 and 6 months was also presented in a frequency table.

The number of patients by outcome of the Overall treatment effect (OTE) questionnaire was presented using frequency tables. The difference between the two treatment groups was analysed regarding the proportion of patients feeling better and given together with 95% confidence intervals.

The mean scores for each dimension of the Quality of Life in Reflux and Dyspepsia (QOLRAD) questionnaire were presented by descriptive statistics. The treatment groups were compared for each dimension by an analysis of variance (ANOVA) with the corresponding baseline dimensions used as a covariate.

The primary variable was analysed using both an intention to treat (ITT) and a per protocol (PP) approach. Secondary variables were analysed using an ITT approach only.

PATIENTS

Healing phase	E40
No. planned	1350
No. enrolled and treated	1391
Males/Females	833/558
Mean age (range)	49.1 (17-85)
No. analysed for efficacy (APT)	1385
No. completed	1312

Maintenance phase	E20	L15	Total
No. planned	500	500	1000
No. randomised and treated	619	617	1236
Males/Females	390/229	361/256	751/485
Mean age (range)	49.3 (18-85)	49.2 (19-84)	49.3 (18-85)
No. analysed for efficacy (ITT)	615	609	1224
Completed 6 months	522	489	1011

SUMMARY

- **EFFICACY RESULTS**

During the study 248 patients experienced relapse, and 224 of these were endoscopic relapses, as shown in Table 1. The log rank test showed a statistically significant difference between E20 and L15 ($p<0.0001$). The cumulative life table rate was 83% for E20 and 74% for L15, for both the ITT and the PP population (Figure 1).

Table 1. Number (%) of patients by outcome, ITT.

	E 20	L 15	All
Total	615(100.0%)	609(100.0%)	1224(100.0%)
No relapse	464(75.4%)	420(69.0%)	884(72.2%)
Relapse	97(15.8%)	151(24.8%)	248(20.3%)
Endoscopic relapse	89(14.5%)	135(22.2%)	224(18.3%)
Unwillingness to continue due to reflux symptoms	8(1.3%)	16(2.6%)	24(2.0%)
Discontinued or missing data, no relapse	54(8.8%)	38(6.2%)	92(7.5%)

The log rank test for time to endoscopic relapse showed a statistically significant difference between E20 and L15 ($p=0.0002$). The corresponding life table rate was 84% for E20 and 76% for L15.

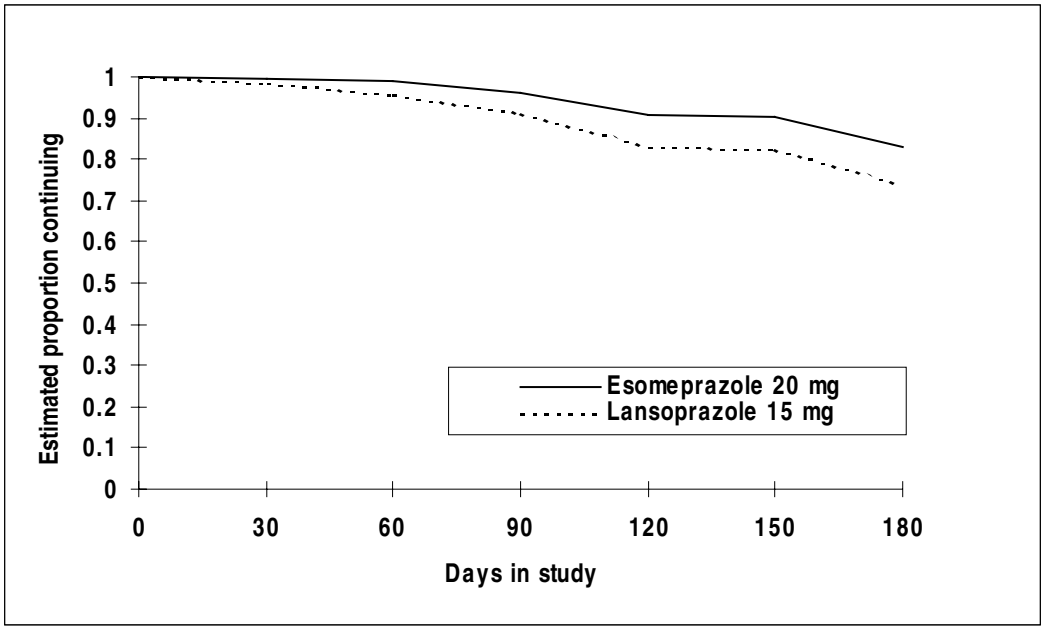

Figure 1. Time to relapse, ITT.

- **SAFETY RESULTS**

No findings raised any concerns about the safety of the drugs in the doses studied.