AstraZeneca

DRUG PRODUCT		**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE	Esomeprazole	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SH-QBE-0092		
VERSION NO.	1		
STUDY CODE	SH-QBE-0092		
DATE	7 November 2005		

A Single-centre, Open, Two-way Cross-over, Comparative Study of Esomeprazole 20 mg Once Daily and Rabeprazole 10 mg Once Daily Regarding 24-hour Intragastric pH Following Single and Repeated Oral Administration in Healthy Male and Female Subjects

STUDY CENTRE(S)

Singlecentre study

PUBLICATION (REFERENCE)

Röhss K, Wilder-Smith C, Jansson L, Naucler E. Esomeprazole 20mg provides more effective intragastric acid control than maintenance-dose rabeprazole, lansoprazole or pantoprazole in healthy volunteers. Clinical Drug Investigation 2004;24(1):1-7.

Röhss K, Claar-Nilsson C, Jansson L. Esomeprazole 20 mg provides more effective acid control than rabeprazole 10 mg following repeated drug administration. Scandinavian Journal of Gastroenterology 2002;37(Suppl 235):34, Abs 61.

STUDY PERIOD

- **DATE OF FIRST SUBJECT ENROLLED** 10 September, 2001
- **DATE OF LAST SUBJECT COMPLETED** 3 December, 2001

PHASE OF DEVELOPMENT

Therapeutic confirmatory

OBJECTIVES

The primary objective was to compare the percentage of time with intragastric pH>4 over the 24-hour period on Days 1 and 5 following repeated once daily administration of 20 mg esomeprazole and 10 mg rabeprazole in healthy male and female subjects.

The secondary objectives were:

- To compare the 24-hour median intragastric pH on Days 1 and 5 following repeated, once-daily administration of 20 mg esomeprazole and 10 mg rabeprazole in healthy male and female subjects.

- To evaluate the safety of esomeprazole by assessment of adverse events and laboratory variables.

STUDY DESIGN

Open, randomised, two-way cross-over study

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Healthy male and female subjects

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Esomeprazole capsule 20 mg administered om for 5 days.
Batch No. H 1189-04-01-06.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Rabeprazole (Pariet®) tablet 10 mg administered om for 5 days.
Batch No. H 1544-01-01-01.

DURATION OF TREATMENT

Two treatment periods of 5 days separated by a wash-out period of at least 14 days.

MAIN MEASUREMENTS AND VARIABLES:

- **PHARMACOKINETIC**

  This section is not applicable.

- **PHARMACODYNAMIC**

  The percentage of time with intragastric pH>4 over the 24-hour period following drug administration on Days 1 and 5.

  The 24-hour median intragastric pH during the 24-hour period following drug administration on Days 1 and 5.

- **SAFETY**

  Adverse events (AE) and laboratory screening.

METHODS FOR DATA EVALUATION

The Per Protocol (PP) population was used in the statistical analyses of the pharmacodynamic variables since this population is considered relevant for pharmacodynamic studies. Thus, data from subjects with major protocol deviations, eg, non-compliance with the study drug, were excluded from the statistical evaluation. Detailed criteria and identification of the PP population were determined before the data were unblinded. Missing values were not replaced in the statistical analyses. Thus, subjects with data available from only one treatment period were excluded from the Analysis of Variance (ANOVA).

The safety population, defined as subjects who received at least one dose of any study drug and for whom post-dose data were available, was used for the evaluation of the safety variables.

Pharmacodynamic statistical evaluation

The percentage of time with intragastric pH>4 during the 24-hour period following drug administration on Days 1 and 5 was analysed using a mixed model ANOVA with fixed effects for period, sequence and treatment and a random effect for subject within sequence. The estimated mean for each treatment and the estimated mean treatment difference were estimated with a symmetric 95% confidence interval (CI). Each CI was based on Student's t-distribution. The sums of squares of the residuals in the linear model were used to estimate the variance. The p-values for each comparison were calculated. Days 1 and 5 were analysed separately.

The 24-hour median pH was analysed in the same way as above.

Descriptive statistics for the percentage of time with pH>4 over the 24-hour period and the median 24-hour pH were also calculated for the total group as well as for males and females separately.

Demographic variables, age, height, weight and body mass index (BMI), are presented descriptively.

Safety variables

Adverse Events (AE) and laboratory variables are presented descriptively.

SUBJECTS

	Total
No. enrolled	54
No. randomised and treated	36
Males/Females	19/17
Mean age (range)	26 (20-41)
No. analysed for pharmacodynamics	30
No. analysed for safety	
Esomeprazole	33
Rabeprazole	35
No. completed	32

SUMMARY

- **PHARMACODYNAMIC RESULTS**

The estimated mean differences in percentage of time with intragastric pH>4 on Days 1 and 5, between esomeprazole and rabeprazole, were minus 4.1 percentage points and 8.2 percentage points respectively. The corresponding values for the estimated mean of the 24-hour median intragastric pH were minus 0.2 percentage points and 0.3 percentage points, respectively. The differences on Day 1 were not statistically significant whereas all differences on Day 5 were significant.

- **SAFETY RESULTS**

Oral administration of esomeprazole 20 mg or rabeprazole 10 mg od for 5 days in healthy male and female subjects was well tolerated. AEs were reported at a similar frequency during both treatment periods. There were no Serious Adverse Events (SAEs). Two subjects discontinued taking the study drug due to AE and one due to personal reasons. One subject discontinued during wash-out period between the treatments due to AE.