AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Esomeprazole
Study Code	D961FC00002
Edition Number	1
Date	04 November 2008

A Phase I, Open-label, Randomized, Single-center, 2-stage Group Sequential Design, 2-way Crossover Bioequivalence Study Comparing a Fixed-dose Combination Capsule of Esomeprazole 40 mg and Low-dose Acetylsalicylic Acid 325 mg with a Free Combination of Esomeprazole Capsule 40 mg and Low-dose Acetylsalicylic Acid Tablet 325 mg After Single Oral Administration in Healthy Male and Female Subjects

Study dates: First healthy volunteer/patient enrolled: 01 April 2008
Last healthy volunteer/patient completed: 18 May 2008

Phase of development: Clinical Pharmacology Phase 1

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study center

The study was conducted at one center: Bio-Kinetic Clinical Applications, Springfield, Missouri, United States.

Study dates		**Phase of development**
First subject enrolled	01 April 2008	Clinical pharmacology (I)
Last subject completed	18 May 2008	

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to investigate whether a fixed-dose combination capsule of esomeprazole 40 mg and low-dose ASA 325 mg was bioequivalent to a free combination of an esomeprazole capsule 40 mg and a low-dose ASA tablet 325 mg following single oral doses, by assessment of AUC and C_{max} for esomeprazole and ASA.

The secondary objectives of the study were:

1. To evaluate the pharmacokinetic properties of a fixed-dose combination capsule of esomeprazole 40 mg and low-dose ASA 325 mg and of a free combination of an esomeprazole capsule 40 mg and a low-dose ASA tablet 325 mg following single oral doses, by assessment AUC_t, t_{max}, and $t_{1/2}$ of esomeprazole and ASA, and by assessment of AUC, AUC_t, C_{max}, t_{max}, and $t_{1/2}$ of the metabolite, salicylic acid (SA).

2. To evaluate the safety and tolerability of esomeprazole in combination with low-dose ASA.

Study design

This was a Phase I, open-label, randomized, single-center, 2-stage group sequential design, 2-way crossover bioequivalence study comparing a fixed-dose combination capsule of esomeprazole 40 mg and low-dose ASA 325 mg with a free combination of an esomeprazole 40 mg capsule and a low-dose 325 mg ASA tablet after single oral administration in healthy male and female subjects. This study was conducted at a single center in the United States. The study was conducted in 2 stages (group sequential design). In both stages, subjects received the following 2 single-dose treatments in randomized order during 2 treatment periods:

Treatment A (test): Combination capsule of esomeprazole 40 mg and ASA 325 mg

Treatment B (reference): Esomeprazole 40 mg capsule + ASA 325 mg tablet

Target healthy volunteer population and sample size

The aim was to include healthy male and non-fertile female subjects between 20 and 50 years old with a body mass index (BMI) between 19 and 29 kg/m^2 and weight between 50 and 95 kg. The goal was to have a total of 42 evaluable subjects.

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

Esomeprazole/ASA – 40 mg/325 mg capsule
Single oral administration: H 1968-01-02-01

Esomeprazole – 40 mg capsule
Single oral administration: H 1222-04-01-17

ASA –325 mg tablet
Single oral administration: H 1917-01-01-01

Duration of treatment

The study had 2 treatment periods. Each period began with a single dose of study drug which was followed by a minimum washout period of 6 days.

Criteria for evaluation - pharmacokinetics (main variables)

Esomeprazole and ASA: AUC and C_{max} (primary variables).

Esomeprazole and ASA: AUC_t, t_{max}, and $t_{1/2}$ (secondary variables).

SA: AUC, AUC_t, C_{max}, t_{max}, and $t_{1/2}$ (secondary variables).

Criteria for evaluation - safety (main variables)

Adverse events (AEs), laboratory variables, physical examination, and vital signs (blood pressure and pulse).

Statistical methods

- Pharmacokinetics

Plasma concentrations and pharmacokinetic parameters of esomeprazole, ASA, and SA were listed and summarized by treatment using descriptive statistics. Geometric means and 95% confidence intervals (CI) were calculated for all pharmacokinetic parameters except t_{max}.

In this planned 2-stage group sequential design, crossover study, bioequivalence was assessed at each stage of the trial by assessment of AUC and C_{max} for esomeprazole and ASA. However, a decision on whether to proceed with the planned second stage of the study was made on the basis of results obtained from the analysis of pharmacokinetic data from the first stage.

At the end of each stage, AUC, AUC_t, and C_{max} for esomeprazole and ASA (for all subjects combined) were analyzed assuming log-normally distributed data. AUC, AUC_t, and C_{max} values for the fixed-dose combination capsule of 40 mg esomeprazole plus 325 mg ASA were compared to the AUC, AUC_t, and C_{max} values for the free combination of a 40 mg esomeprazole capsule and a 325 mg ASA tablet. The logarithmically transformed AUC, AUC_t, and C_{max} data were analyzed using a linear mixed-effect model including treatment, period, and sequence as fixed effects, and subject within sequence as a random effect. Based on these analyses, point estimates (least-squares means) were calculated. The linear contrasts subtracting the least-squares means of the free dose combination (reference) from the least-squares means of the fixed dose combination (test) were estimated and exponentiated to obtain estimates of the ratios of geometric least-squares means and the corresponding CI.

Since this was a group sequential design, the confidence levels at each stage were adjusted and set to 94% in order to compensate for the multiple analyses and to assure that the actual overall confidence level for the procedure was 90%.

- Safety

Adverse events, laboratory variables, vitals, and ECGs are presented descriptively.

Subject population

The first subject was enrolled on 1 April 2008 and the last subject completed the study on 18 May 2008. Forty-nine subjects were enrolled, randomized, and received treatment. Three subjects voluntarily discontinued from the study. However, since all subjects received treatment, they were included in both the PK and the safety analyses.

The safety population consisted of 20 healthy white males and 29 healthy white females with a mean age of 28.0 years and a mean BMI of 24.1 kg/m^2.

Summary of pharmacokinetic results

Key PK parameters for esomeprazole, ASA, and SA, and the results of statistical comparisons between treatments are summarized in Table 1.

Table 1 Summary and Results of Statistical Comparisons of Key Esomeprazole, Acetylsalicylic Acid, and Salicylic Acid Pharmacokinetic Parameters

	Treatment A (N = 46)		Treatment B (N = 46)		Statistical Comparison (Treatment A/B) [a]	
Parameter	**GLS Mean**	**95% CI**	**GLS Mean**	**95% CI**	**Ratio**	**94% CI**
Esomeprazole						
AUC (µmol*h/L)	5.327	(4.456, 6.368)	5.513	(4.612, 6.591)	96.6	(90.0, 103.8)
AUC_t (µmol*h/L)	5.249	(4.385, 6.284)	5.440	(4.544, 6.512)	96.5	(89.8, 103.7)
C_{max} (µmol/L)	2.821	(2.456, 3.240)	2.845	(2.477, 3.268)	99.1	(90.2, 108.9)
t_{max} (h) [b]	3.00	(1.25, 4.00)	3.00	(1.25, 5.00)	NA	NA
Acetylsalicylic Acid						
AUC (µmol*h/L)	24.14	(22.55, 25.84)	23.24	(21.71, 24.88)	103.9	(99.6, 108.3)
AUC_t (µmol*h/L)	23.42	(21.84, 25.12)	22.63	(21.09, 24.27)	103.5	(99.2, 108.0)
C_{max} (µmol/L)	17.20	(15.53, 19.06)	16.89	(15.24, 18.71)	101.9	(91.7, 113.2)
t_{max} (h) [b]	0.75	(0.33, 2.25)	0.50	(0.33, 3.00)	NA	NA
Salicylic Acid						
AUC (µmol*h/L)	653.1	(606.2, 703.7)	661.5	(613.9, 712.6)	98.7	(95.5, 102.1)
AUC_t (µmol*h/L)	629.4	(585.4, 676.8)	636.2	(591.6, 684.1)	98.9	(95.8, 102.2)
C_{max} (µmol/L)	121.3	(114.3, 128.7)	127.2	(119.9, 134.9)	95.4	(91.9, 99.0)
t_{max} (h) [b]	2.25	(1.50, 3.50)	2.13	(1.25, 4.00)	NA	NA

Treatment A = Esomeprazole 40 mg and low-dose ASA 325 mg combination capsule given as a single dose.
Treatment B = Esomeprazole 40 mg capsule + low-dose ASA 325 mg tablet, given as a single dose.

a) Results presented are GLS mean ratios and 94% CIs.
b) Data presented for this parameter are median (minimum, maximum). Number of subjects summarized for this parameter are 47 for Treatment A and 48 for Treatment B.

Note: Results are based on a linear mixed effect model with terms for treatment, sequence, and period as fixed effects and subject within sequence as a random effect. For each parameter, subjects had to have values for both treatments to be included in the analysis.
CI – confidence interval; N – number of subjects and number of observations; NA – not applicable;
GLS - geometric least-squares.
Source: Tables 11.2.4, 11.2.5, 11.2.6, and 11.2.7.

Treatment A (combination capsule of esomeprazole and ASA) was found to be bioequivalent to Treatment B (esomeprazole capsule + ASA tablet) for both the primary PK variables (AUC, and C_{max} of esopreprazole and ASA) and for the secondary exposure-related PK variables (ie, AUC_t of esopreprazole and ASA, and AUC, AUC_t, and C_{max} of SA). Geometric least-squares

mean ratios for all the parameters were within a range of 95.4 to 103.9% and CIs were within the 80 to 125% acceptance range for bioequivalence.

No real differences were observed in t_{max} between treatments for any of the analytes.

Summary of safety results

In this population of healthy male and female subjects, both treatments (the combination capsule of esomeprazole 40 mg and ASA 325 mg and esomeprazole 40 mg capsule plus ASA 325 mg tablet) were well tolerated. A total of 20 AEs, 1 of which was predose, were reported by 13 subjects in the study. Subjects in both treatment groups (Treatment A: combination capsule of esomeprazole 40 mg and ASA 325 mg; Treatment B: esomeprazole 40 mg capsule plus ASA 325 mg tablet) experienced AEs; however, subjects in the Treatment B dose group reported the most AEs.

No deaths, SAEs, or discontinuations due to AEs were reported during study conduct. There were no other significant adverse events reported during the study.

The most common AEs during active treatment were headache and dizziness, reported by 6 (12.2%) and 5 (10.2%) subjects, respectively.

There were no significant changes in laboratory safety values, vital signs, ECG findings, or physical examination findings during study conduct.

Date of the report

04 November 2008