AstraZeneca

Clinical Pharmacology Study Report

Drug Substance	Esomeprazole
Study Code	D961FC00001
Edition Number	1
Date	19 February 2008

A Phase I, Open, Randomized, Single-centre, 3-way Crossover Drug-drug Interaction Study of Esomeprazole Capsule 40 mg and Low-dose Acetylsalicylic Acid Tablet 325 mg after 5 days Repeated Oral Administration in Healthy Male and Female Subjects

Study dates: First subject enrolled: 9 May 2007
Last subject completed: 27 August 2007

Phase of development: Clinical Pharmacology (I)

This study was performed in compliance with Good Clinical Practice

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A Phase I, Open, Randomized, Single-centre, 3-way Crossover Drug-drug Interaction Study of Esomeprazole Capsule 40 mg and Low-dose Acetylsalicylic Acid Tablet 325 mg after 5 days Repeated Oral Administration in Healthy Male and Female Subjects

Study centre

The study was conducted at one centre: Quintiles AB, Phase I Services, Uppsala, Sweden.

Study dates		**Phase of development**
First subject enrolled	9 May 2007	Clinical pharmacology (I)
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Objectives

The primary objective of this study was to evaluate the effect of esomeprazole on low-dose acetylsalicylic acid (ASA) pharmacokinetics by assessment of area under the plasma concentration-time curve during a dosage interval (τ) at steady state (AUC_τ) and the observed maximum plasma concentration at steady state ($C_{ss,\,max}$) of ASA following repeated administration of low-dose ASA alone and in combination with esomeprazole.

The secondary objectives of the study were:

1. To evaluate the effect of low-dose ASA on esomeprazole pharmacokinetics by assessment of AUC_τ and $C_{ss,\,max}$ of esomeprazole following repeated administration of esomeprazole alone and in combination with low-dose ASA

2. To evaluate the effect of esomeprazole on the metabolite salicylic acid (SA) pharmacokinetics by assessment of AUC_τ and $C_{ss,\,max}$ of SA following repeated administration of low-dose ASA alone and in combination with esomeprazole

3. To evaluate the pharmacokinetics of esomeprazole, ASA and SA when given alone and in combination by assessment of area under the plasma concentration versus

time curve from time zero to the last quantifiable concentration (AUC_t), time to observed maximum plasma concentration (t_{max}) and terminal half life ($t_{½}$)

4. To evaluate the safety and tolerability of esomeprazole with and without low-dose ASA by assessment of adverse events, laboratory variables, blood pressure (BP) and pulse

5. To collect and store DNA samples for potential future research into genes which may influence drug response (pharmacokinetic profile, safety and tolerability) of esomeprazole and/or ASA and to provide CYP2C19 genotype as co-variate for pharmacokinetic analysis

Study design

The study was conducted as a single-centre (country: Sweden), open, randomized, three-way crossover drug-drug interaction study consisting of three treatment periods. In each treatment period healthy males and females received 5 days' repeated doses of esomeprazole 40 mg, every morning (omni mane (o.m.)), low-dose ASA 325 mg o.m. or esomeprazole 40 mg and low-dose ASA 325 mg given together o.m. Each treatment period was separated by a washout period of at least 13 days counted from the last day of dosing.

Target subject population and sample size

The aim was to include healthy male and female subjects between 20 and 50 years old with a body mass index (BMI) between 19 and 29 kg/m^2 and a weight between 50 and 95 kg. The goal was to have at least 48 evaluable subjects with a minimum of 25% of each gender. To achieve this, 55 subjects were randomized and 50 of those completed the whole study.

Investigational products and comparators: dosage, mode of administration and batch numbers

Esomeprazole 40 mg capsules
Five days' repeated oral administration, o.m. Batch No. H 1222-04-01-16

Acetylsalicylic acid 325 mg (Genuine Bayer® Aspirin)
Five days' repeated oral administration, o.m. Batch No. H 1917-01-02-01

Duration of treatment

Oral doses of the investigational products (IPs) were given once daily in the morning in three treatment periods. Each treatment period consisted of 5 days, and was separated by a washout period of at least 13 days, counted from the last day of dosing.

Variables

- **Pharmacokinetic**

  AUC_τ and $C_{ss,\,max}$ (primary variables and secondary variables)

  AUC_t, t_{max} and $t_{½}$ (secondary variables)

- **Safety**

  Adverse events (AEs), laboratory variables, BP and pulse (secondary variables)

Statistical methods

- **Pharmacokinetic**

The log-transformed variables AUC_τ and $C_{ss,\,max}$ were analyzed using a mixed model analysis of variance with fixed effects for sequence, period and treatment and a random effect for subject within sequence.

The effect of esomeprazole on low-dose ASA pharmacokinetics was tested using the ratio between AUC_τ for low-dose ASA in combination with esomeprazole and AUC_τ for low-dose ASA administered alone, and the corresponding ratio for $C_{ss,\,max}$. If the 90% confidence interval (CI) for the ratio of the true geometric mean was contained in the interval [0.80, 1.25], for both AUC_τ and $C_{ss,\,max}$, then no drug-drug interaction between low-dose ASA and esomeprazole was demonstrated.

AUC_t was analyzed and presented in the same way as AUC_τ and $C_{ss,\,max}$.

Descriptive statistics are given for all pharmacokinetic variables, presented for all subjects together as well as for each gender separately.

- **Safety**

AEs, laboratory variables, BP, pulse and electrocardiogram are presented descriptively.

Subject population

The first subject was enrolled on 9 May 2007 and the last subject completed the study on 27 August 2007. Of the 89 subjects who were screened, 55 were randomized, 54 completed at least 1 treatment period according to protocol (Per Protocol population) and 50 subjects completed the whole study. All 55 randomized subjects were included in the Safety population, 51 subjects were included in the analysis of the effect of esomeprazole on ASA/SA pharmacokinetics and 52 subjects in the analysis of the effect of ASA on esomeprazole pharmacokinetics.

Five (5) subjects discontinued the study prematurely: 1 subject due to incorrect enrolment, 1 subject for taking disallowed concomitant medication (ibuprofen), and 3 subjects due to AEs. The AEs which led to discontinuation were multiple skin haematomas in 1 subject, allergic rhinitis, conjunctivitis, pharyngitis and itching gum in 1 subject and suspected pericarditis in 1 subject.

The Safety population consisted of 17 caucasian males and 38 caucasian females with a mean age of 27.1 years and a mean BMI of 23 kg/m^2.

Summary of pharmacokinetic results

As the results in Table S 1 show, no pharmacokinetic interaction between esomeprazole and ASA was detected. The 90% CI for the geometric mean ratio of AUC_t and $C_{ss,max}$ of esomeprazole, ASA and SA after administration of esomeprazole in combination with ASA versus esomeprazole or ASA alone were contained in the pre-defined "no interaction" limits of 80 to 125%.

The ratio of AUC_t of esomeprazole, ASA and SA, respectively, after administration of esomeprazole and ASA given alone and in combination, did not indicate any pharmacokinetic interaction.

Mean $t_{½}$ of esomeprazole was 1.42 hours, both after administration of esomeprazole alone and in combination with ASA. Median t_{max} of esomeprazole was comparable after administration of esomeprazole alone (2.25 hours) and in combination with ASA (2.50 hours).

Mean $t_{½}$ of ASA was comparable after administration of ASA alone (0.40 hour) and in combination with esomeprazole (0.36 hour). Median t_{max} of ASA was 0.50 hour, both after administration of ASA alone and in combination with esomeprazole. Mean $t_{½}$ of SA was 1.98 hours after administration of ASA alone and 1.97 hours after ASA in combination with esomeprazole and median t_{max} was 1.75 hours, both after administration of ASA alone and in combination with esomeprazole.

The estimatated geometric mean ratios and 90% CIs for the comparisons of AUC_τ, AUC_t and $C_{ss,max}$ of esomeprazole, ASA and SA after administration of esomeprazole and ASA alone and in combination are presented in Table S 1.

Table S 1 Estimated ratios of geometric means with 90% CI for pharmacokinetic variables of esomeprazole, ASA and SA following repeated oral administration of esomeprazole capsule 40 mg o.m. (A) or ASA 325 mg o.m. (B) or a combination of esomeprazole capsule 40 mg o.m. and ASA 325 mg o.m. (C). Per Protocol population

					90 % CI	
Variabel	**Ratio**		**Number of subjects**	**Estimate**	**lower**	**upper**
Esomeprazole	Esomeprazole with ASA/ Esomeprazole alone (C/A)	AUC_τ	52	0.93	0.89	0.98
	Esomeprazole with ASA/ Esomeprazole alone (C/A)	AUC_t	52	0.93	0.89	0.98
	Esomeprazole with ASA/ Esomeprazole alone (C/A)	$C_{ss,\ max}$	52	0.96	0.91	1.01
ASA	ASA with esomeprazole/ ASA alone (C/B)	AUC_τ	49	1.04	1.00	1.09
	ASA with esomeprazole/ ASA alone (C/B)	AUC_t	51	1.04	1.00	1.09
	ASA with esomeprazole/ ASA alone (C/B)	$C_{ss,\ max}$	51	1.12	1.03	1.22
SA	ASA with esomeprazole/ ASA alone (C/B)	AUC_τ	51	0.99	0.95	1.02
	ASA with esomeprazole/ ASA alone (C/B)	AUC_t	51	0.99	0.95	1.02
	ASA with esomeprazole/ ASA alone (C/B)	$C_{ss,\ max}$	51	1.02	0.98	1.06

Data derived from Appendix 12.2.6.3

Summary of pharmacogenetic results

According to the genotyping results, all subjects except 1, were extensive CYP2C19 metabolizers. One (1) subject was classified as a poor CYP2C19 metabolizer.

As only one subject was classified as a poor CYP2C19 metabolizer, no conclusion could be drawn regarding metabolizer status and exposure to esomeprazole.

Summary of safety results

In total, 171 AEs were reported by 46 subjects in the study. Most AEs were evenly distributed between the treatments, however, fewer subjects reported headaches during administration of low-dose ASA (given alone or in combination with esomeprazole) than during administration of esomeprazole alone which may be due to the pharmacodynamic effects of ASA.

Two (2) post-study SAEs were reported by 1 subject. Both SAEs, pyelonephritis and renal abscess, started 17 days after the last dose and were not considered related to study treatment.

Three (3) subjects discontinued due to AEs. The AEs which led to discontinuation were allergic rhinitis, conjunctivitis, pharyngitis and itching gum in 1 subject, chest discomfort/dyspnoea in 1 subject and multiple skin haematomas in 1 subject. Of these AEs, only the skin haematomas were considered as possibly related to study treatment.

The most common AEs during active treatment were headache, flatulence, fatigue, nasopharyngitis, abdominal pain and nausea.

There were no clinically significant changes in laboratory safety values or vital signs from pre-entry to follow-up.