AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Esomeprazole
Study Code	D961FC00011
Edition Number	1
Date	02 February 2011

A Phase I, Open, Two-way Crossover, Drug-drug Interaction Study Evaluating the Effect of Esomeprazole on the Pharmacodynamics of Acetylsalicylic Acid after 5 Days of Treatment

Study dates: First subject enrolled: 01 September 2010
Last subject last visit: 03 November 2010

Phase of development: Clinical pharmacology (I)

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

Study center(s)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the effect of esomeprazole on low-dose aspirin PD using VerifyNow assay	ARUt/ARU0 - relative change in the VerifyNow Aspirin assay after 5 days of treatment, relative to baseline (Day 1) in healthy human volunteers	Pharmacodynamic
Secondary	**Secondary**	
To evaluate the effect of esomeprazole on low-dose aspirin PD by measuring change in TXB2 concentrations	TXBt/TXB0 - relative change in serum thromboxane B2 inhibition from baseline	Pharmacodynamic
To evaluate the safety and tolerability of esomeprazole taken concurrently with low-lose aspirin.	Adverse events, physical examination, pulse, blood pressure, and laboratory variables	Safety

Study design

This was a single center, open-label, 2-period crossover study designed to assess the pharmacodynamic interaction between aspirin and esomeprazole in healthy human volunteers. During the pre-screening period, in order to evaluate aspirin responders, volunteers received 81 mg of aspirin for 5 days. Volunteers who were confirmed as aspirin responders, using the VerifyNow Aspirin assay, were then assigned randomly to receive 81 mg of aspirin alone (Treatment A) for 5 days, followed by 20 mg of esomeprazole administered concurrently, as separate formulations, with 81 mg of aspirin (Treatment B) for 5 days, or vice versa. There was at least a 14-day washout period between treatments A and B. Based on a randomization schedule, volunteers were assigned to 1 of 2 sequences of dosing treatments (Sequence AB or Sequence BA).

Target subject population and sample size

Healthy males and females within the age of 18 to 75 years inclusive.

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

For the pre-screening period: Volunteers were administered a aspirin tablet 81 mg (chewable tablet; lot number 212280F), orally, once daily for 5 days with 240 mL of water. The aspirin tablets were swallowed whole with 240 mL of water.

For the 2-way crossover study: Treatment A was aspirin tablet 81 mg (chewable tablet; lot number 212280F) administered orally once daily for 5 days with 240 mL of water. Treatment B was a combination of separate formulations of a capsule of esomeprazole 20 mg (lot number E006999) and an aspirin tablet 81 mg (chewable tablet; lot number 212280F), administered orally once daily for 5 days with 240 mL of water. The aspirin tablets in the crossover period were swallowed whole with 240 mL of water.

Duration of treatment

The duration of the study was approximately 65 days. This included a 30-day enrollment/screening, an aspirin prescreen period (5 days of aspirin administration followed by a VerifyNow Asprin assay to screen aspirin non-responders), two 5-day treatment periods (6 overnight stays for each period including Day -1) separated by at least a 14-day washout period and a follow-up visit 7 to 10 days after the last dose administration.

Statistical methods

All pharmacodynamic analysis was performed using the pharmacodynamic population. Listings of pharmacodynamic blood sampling times were generated. Listings of pharmacodynamic variables were listed and summarized. For assessment of treatment differences the primary pharmacodynamic variable (ratio to baseline ARU) was log-transformed and analyzed using a linear mixed model with fixed effect for period, sequence and treatment, a random effect for volunteers within sequence and the log-transformed ARU at baseline as covariate. The least square mean difference in the pharmacodynamic variable between the treatments was calculated with 95% confidence intervals and antilog-transformed to generate a confidence interval for the ratio between the two treatment means.

In addition, treatment comparisons in inhibition were made using functions of the least-squares means estimated from the above mixed model. Inhibition was compared between treatments as both a ratio and a difference. The point estimates and 95% CI for the ratio and difference in inhibition were presented.

The secondary pharmacodynamic variable (serum thromboxane B2) was analyzed in an identical way.

Safety data were presented with descriptive statistics.

Subject population

There were 37 volunteers enrolled in the study, 32 (86.5%) participants were randomized to the cross-over period, and 30 (81.1%) individuals completed the study. There were

7 volunteers (18.9%) who were withdrawn from the study prior to completion: 2 due to an adverse event; 1 by subject decision; 2 due to protocol non-compliance (lost to follow-up); 1 due to a low platelet count (protocol deviation); 1 due to Investigator decision. All 37 volunteers enrolled were included in the safety analysis. Twenty-nine (96.7%) of the 30 completing volunteers were included in the PD analysis set. Volunteer E0001008 was not included in the PD analysis because the volunteer had an ARU > 549 in the pre-screening period. There were 10 women (27%) and 27 men (73%); 35 volunteers were white (94.6%), 2 volunteers were black (5.4%). The mean age at screening was 48 ±16 years (range from 19 to 75 years), and twenty three (62.6%) of the 37 volunteers were at least 50 years old. Medical histories were unremarkable and the use of concomitant medications during the study was minimal.

Summary of efficacy results (Not applicable)

Summary of pharmacokinetic results (Not applicable)

Summary of pharmacodynamic results

Twenty-nine volunteers completed both treatments without important protocol deviations and were included in the pharmacodynamic analysis. The statistical comparison of ratio to baseline aspirin reaction unit values between treatments is presented in Table below:

Table Primary statistical comparison of ratio to baseline platelet aggregation with aspirin alone vs aspirin + esomeprazole

Treatment [a]	n	Geometric LS Mean	95% CI	Pair	Ratio	95% CI
A	29	0.7004	(0.6796, 0.7219)			
B	29	0.7142	(0.6929, 0.7360)	B/A	1.0196	(0.99, 1.05)

Note(s): CI confidence interval LS least-squares
Estimates are based on a linear mixed model with fixed effects for period, sequence and treatment, a random effect for subject within sequence and the log-transformed baseline value as covariate.
Dependent variable is log-transformed ratio to baseline (Day 6/Day 1)
[a] Treatment A: 1 tablet, aspirin 81 mg;
Treatment B: 1 capsule, esomeprazole 20 mg + 1 tablet, aspirin 81 mg.

The ratio of Day 6 to baseline values of VerifyNow ARU were very similar between the two treatments. There is no evidence that antiplatelet activity of aspirin is changed with coadministration of esomeprazole, as measured by ratio-to-baseline ARU.

The statistical comparisons of ratio to baseline thromboxane B2 concentrations between treatments is presented in Table below:

Table **Primary statistical comparison of ratio-to-baseline serum TXB2 concentrations with aspirin alone vs aspirin + esomeprazole**

Treatment [a]	n	Geometric LS Mean	95% CI	Pair	Ratio	95% CI
A	29	0.0041	(0.0032, 0.0052)			
B	29	0.0044	(0.0034, 0.0056)	B/A	1.0628	(0.8757, 1.2898)

Note(s): CI confidence interval LS least-squares
Estimates are based on a linear mixed model with fixed effects for period, sequence and treatment, a random effect for subject within sequence and the log-transformed baseline value as covariate.
Dependent variable is log-transformed ratio to baseline (Day 6/Day 1)
[a] Treatment A: 1 tablet, aspirin 81 mg;
Treatment B: 1 capsule, esomeprazole 20 mg + 1 tablet, aspirin 81 mg.

Aspirin administered alone or with esomeprazole reduced serum TXB2 by more than 99.5%. The lower bounds of the 95% confidence intervals for both treatments excluded 99%. There is no evidence that aspirin-induced suppression of TXB2 formation is altered by coadministration of esomeprazole.

Summary of pharmacokinetic/pharmacodynamic relationships (Not applicable)

Summary of pharmacogenetic results (Not applicable)

Summary of safety results

All 37 volunteers enrolled in the study were included in the safety analysis. There were no deaths or serious adverse events reported during the study. Two volunteers were discontinued due to an adverse event, two due to protocol non-compliance (lost to follow-up), one due to volunteer decision, one volunteer was withdrawn by the Investigator following elevated urine glucose levels, and one volunteer was withdrawn following a protocol deviation related to platelet count. The most frequent adverse events were gastrointestinal events, with 4 adverse events occurring in 3 volunteers. These gastrointestinal adverse events were deemed by the Investigator as mild and related to study drug. Three (75%) of these adverse events occurred during Treatment A, and 1 (25%) during Treatment B.

Overall, adverse events occurred more frequently during the aspirin pre-screening period and the aspirin only Treatment A period. There were 8 (73.7%) adverse events reported during these aspirin only periods (aspirin pre-screen and aspirin only Treatment A), compared to 3 (27.3%) adverse events that occurred during the esomeprazole + aspirin Treatment B period.

There were no clinically important changes in hematology, clinical laboratory, vital signs, electrocardiograms, or physical examination findings during the study.