Clinical Study Report Synopsis

Drug Substance	Esomeprazole 20 mg/ASA 81 mg
Study Code	D961FC00010
Edition Number	1
Date	FINAL 15 February 2012

An Open-label, Randomized, Single-center, 2-way Crossover Interaction Study, Evaluating the Effect of Esomeprazole 20 mg/Acetylsalicylic Acid 81 mg on the Pharmacodynamics and Pharmacokinetics of Clopidogrel on Days 1 and 9 in Healthy Volunteers

Study dates: First subject enrolled: 23 November 2010
Last subject last visit: 18 August 2011

Phase of development: Clinical pharmacology (I)

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

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S.1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the effect of esomeprazole 20 mg/acetylsalicylic acid 81 mg on the pharmacodynamics of clopidogrel by assessing maximal inhibition of platelet aggregation after 9 days of clopidogrel treatment relative to baseline	Maximal inhibition of platelet aggregation	Pharmacodynamic
Secondary	**Secondary**	
To assess the effect of esomeprazole 20 mg/acetylsalicylic acid 81 mg on the pharmacokinetics of the active metabolite of clopidogrel by assessing AUC, $AUC_{0\text{-last}}$, and $C_{ss,max}$ of the active metabolite of clopidogrel on Day 9	AUC, $AUC_{0\text{-last}}$, and $C_{ss,max}$	Pharmacokinetic
To assess the safety and tolerability of clopidogrel given alone and concomitantly with esomeprazole 20 mg/acetylsalicylic acid 81 mg by assessing adverse events, vital signs, laboratory variables, electrocardiogram, and physical examination	adverse events, vital signs, laboratory variables, electrocardiogram, and physical examination	Safety

Study design

The aim of this study was to assess whether there is a pharmacological interaction between esomeprazole 20 mg/ acetylsalicylic acid 81 mg (as a fixed dose combination) and clopidogrel. In this single-center, open-label, 2-way crossover study, volunteers were randomly assigned to 1 of 2 treatment sequences (AB or BA). During Treatment A, volunteers received clopidogrel 75 mg once daily for 9 days. During Treatment B, volunteers received clopidogrel 75 mg once daily for 4 days followed by esomeprazole 20

mg/acetylsalicylic acid 81 mg with clopidogrel 75 mg once daily for 5 days. There was a washout period of at least 14 days between each treatment.

Target subject population and sample size

Healthy males, aged between 18 and 45 years inclusive, and females aged between 18 and 55 years inclusive, with a body mass index between 19 and 30 kg/m^2 inclusive were screened for enrollment. There were 58 volunteers enrolled and randomly assigned to treatment sequence AB or BA.

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

Clopidogrel tablet 75 mg (batch number EL273) was administered orally as a tablet once daily with 240 mL of water. Esomeprazole 20 mg/acetylsalicylic acid 81 mg (batch number 10-002683AZ), as a fixed dose combination, was administered orally once daily as a capsule with clopidogrel tablet 75 mg once daily with 240 mL of water.

Duration of treatment

The total study duration for each healthy volunteer was approximately 2.5 months. This included a preentry visit within 28 days prior to randomization, 2 treatment periods of 9 days, a washout period of at least 14 days between the treatment periods (ie, between the last dose in Period 1 and the first dose in Period 2), and a follow-up visit 7 to 10 days after the last dose.

Statistical methods

The pharmacokinetic variables and maximal inhibition of platelet aggregation (mIPA) were analyzed using linear mixed models. The differences between the treatments in mIPA were assessed with 95% confidence intervals for the differences. The ratios of geometric least square means of AUC, $AUC_{(0\text{-last})}$, and $C_{ss,max}$ with corresponding 90% confidence interval were also calculated.

Pharmacokinetic, PD, and safety data were presented with descriptive statistics.

Subject population

There were 58 study participants who were randomly assigned to 1 of 2 dosing sequences, AB or BA. Fifty-six volunteers completed the study per protocol. One volunteer (E0001048) discontinued the study due to volunteer decision after receiving all doses of Treatment B only and 1 volunteer (E0001095) discontinued the study due to an adverse event after receiving all doses of Treatment B and 8 days of Treatment A.

Overall, there were 23 (39.7%) women and 35 (60.3%) men enrolled in the study. Fifty-seven (98.3%) volunteers were white and 1 volunteer (1.7%) was of other race. The mean age of all volunteers was 27±6 years (range from 20 to 52 years); mean height was 176±9 cm; mean

weight was 72.0±12.6 kg; and mean body mass index was 23.3±2.7 kg/m^2. Medical histories were unremarkable and the use of concomitant medications overall were minimal.

Summary of efficacy results

Not applicable.

Summary of pharmacodynamic results

The treatment comparison of Day 10 maximal inhibition of platelet aggregation is presented in Table S.2 below. The LS mean inhibtion of platelet aggregation was 49.6% following the administration of clopidogrel with esomeprazole/ASA and 49.7% following the administration of clopidogrel alone. This represents an absolute LS mean treatment difference of -0.104% (p=0.9572) with 95% CI of (–3.99, 3.78,). These results show there was no statistically significant change in mIPA after administration of clopidogrel with esomeprazole/ASA compared to clopidogrel administered alone.

The 95% confidence interval for the mean difference in maximal inhibition of platelet aggregation after administration of clopidogrel with esomeprazole/ acetylsalicylic acid and clopidogrel alone was narrow and included 0%. These results show there was no statistically significant change in the maximal inhibition of platelet aggregation after administration of clopidogrel with esomeprazole/ acetylsalicylic acid compared to clopidogrel administered alone.

Table S.2 Statistical comparison of maximal inhibition of platelet aggregation, mIPA (%), on Day 10

Treatment	n	LS mean	95% CI	Pair	Pairwise comparison mean difference (95% CI)	p-value
A	56	49.7	(44.4, 55.0)			
B	58	49.6	(44.4, 54.9)	B - A	-0.104 (-3.99, 3.78)	0.9572

LS least square; CI confidence interval.
Treatment A: Once daily administration of clopidogrel 75 mg for 9 days;
Treatment B: Once daily administration of clopidogrel 75 mg for 4 days followed by once daily administration of clopidogrel 75 mg with esomeprazole 20 mg/ASA 81 mg for 5 days.

There was no consistent trend for a decrease or an increase in the arithmetic mean maximal inhibition of platelet aggregation among the genotype groups when clopidogrel was administered with esomeprazole/ acetylsalicylic acid compared to when clopidogrel was administered alone.

Summary of pharmacokinetic results

The results of the statistical comparisons between treatments showed that administration of esomeprazole/ acetylsalicylic acid with clopidogrel reduced overall and maximum active metabolite of clopidogrel exposure by almost 40% compared to clopidogrel alone. The upper limit of the 90% confidence intervals for AUC, $AUC_{0\text{-last}}$, and $C_{ss,max}$ LS mean ratios were well below 80% demonstrating concomitant esomeprazole administration reduced exposure to the active metabolite of clopidogrel. Statistical comparisons of AMC exposure parameters [AUC, $AUC_{0\text{-last}}$, and $C_{ss,max}$] between treatments are presented in Table S.3 below.

Table S.3 Statistical comparison of key AMC pharmacokinetic parameters

Parameter (units)	Treatment	N	Geometric LS Mean	Pair	Ratio	
					Percent	90% CI
AUC	A	50	12.00			
(ng·h/mL)	B	49	7.44	B/A	62.04	58.09, 66.25
$AUC_{0\text{-last}}$	A	56	12.23			
(ng·h/mL)	B	58	7.51	B/A	61.45	58.24, 64.85
$C_{ss,max}$	A	56	12.40			
(ng/mL)	B	58	7.55	B/A	60.85	55.87, 66.27

AMC active metabolite of clopidogrel; LS least-squares; CI confidence intervals.
Treatment A: Once daily oral administration of clopidogrel 75 mg for 9 days;
Treatment B: Once daily oral administration of clopidogrel 75 mg for 4 days followed by once daily oral administration of clopidogrel 75 mg with esomeprazole 20 mg/ASA 81 mg for 5 days.

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of safety results

In this population of healthy male and female volunteers, esomeprazole 20 mg/ASA 81 mg administered concomitantly with clopidogrel 75 mg was well tolerated. There were no deaths or serious adverse events reported during the study. One volunteer was discontinued from the study due to an adverse event of moderate urticaria. Adverse events occurred more frequently during treatment with clopidogrel plus esomeprazole/ASA than during clopidogrel alone (58.6% versus 42.1%, respectively), mainly reflecting known adverse drug reactions to Axanum. There were no clinically important changes in clinical laboratory values, vital signs, electrocardiograms, or physical examination. The safety results in this study are consistent with the safety profile of Axanum and did not raise any safety concerns.