AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Omeprazole/Esomeprazole
Study Code	D9612C00034
Edition Number	1
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An Open-label, Randomized, 4-treatment, 3-period, Crossover Interaction Study, Evaluating the Effect of Esomeprazole 40 mg, Omeprazole 80 mg, or Lansoprazole 60 mg on the Pharmacodynamics and the Pharmacokinetics of Clopidogrel in Healthy Volunteers

Study dates: First subject enrolled: 07 June 2010
Last subject last visit: 24 May 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 S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To assess the effect of esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg on the pharmacodynamic profile of clopidogrel by assessing maximum inhibition of platelet aggregation at Days 2, 6, 15, and 30 relative to baseline	maximum inhibition of platelet aggregation (mIPA)	Pharmacodynamic
Secondary	**Secondary**	
To assess the effect of esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg on the pharmacokinetic profile of clopidogrel active metabolite by assessing the AUC, $AUC_{(0-t)}$, and C_{max} after the loading dose of clopidogrel (Day 1); and $AUC_{(0-t),ss}$ and $C_{ss,max}$ at Days 5, 14, and 29	C_{max}, t_{max}, $AUC_{(0-t)}$, AUC	Pharmacokinetic
To evaluate safety and tolerability of clopidogrel given concomitantly with esomeprazole, omeprazole, or lansoprazole	adverse events, clinical laboratory results, physical examinations, electrocardiograms, and vital signs	Safety

Study design

This was an open-label, randomized, 4-treatment, 3-period, single-center crossover study designed to assess the pharmacodynamic and pharmacokinetic interaction between clopidogrel and esomeprazole, omeprazole, or lansoprazole. Each volunteer was randomly assigned to receive a sequence of clopidogrel alone and 2 of the proton pump inhibitors plus clopidogrel.

The reference treatment arm consisted of a clopidogrel loading dose of 300 mg administered on Day 1 and then clopidogrel 75 mg administered once daily for 28 days. The 3 test treatment arms had the same clopidogrel dosing used in the reference treatment arm coadministered with either esomeprazole 40 mg, omeprazole 80 mg, or lansoprazole 60 mg once daily for 29 days. The route of administration was oral. The treatment periods were separated by washout periods of at least 14 days. The randomization was performed as a partially balanced design with 18 sequences, including clopidogrel alone in all treatment sequences.

Target subject population and sample size

The target population was healthy males within age of 18 to 45 years of age and females within age of 18 to 55 years of age and body mass index (weight/height^2) between 18 kg/m^2 and 32 kg/m^2, inclusive.

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

All investigational product was administered via the oral route.

Treatment A – lansoprazole 60 mg (two 30-mg capsules, Lot Number 822302E21) once daily coadministered with clopidogrel (see Treatment D below) for 29 days

Treatment B – omeprazole 80 mg (two 40-mg capsules, Lot Numbers D015496 and D017530) once daily coadministered with clopidogrel (see Treatment D below) for 29 days

Treatment C – esomeprazole 40 mg (one 40-mg capsule, Lot Number E005792) once daily coadministered with clopidogrel (see Treatment D below) for 29 days

Treatment D – clopidogrel 300-mg loading dose (four 75-mg tablets, Lot Number OD57840) on Day 1 and then 75 mg (one 75-mg tablet, Lot Number OD57840) daily for 28 days

Duration of treatment

This study had 4 treatment arms with 3 treatment periods separated by a 14-day washout period. Volunteers were admitted to the clinic on Days -1, 4, 13, and 28 and released on Days 2, 6, 15, and 30 after the scheduled pharmacokinetic and pharmacodynamic assessments were obtained. The total study duration was approximately 146 days which included a 21-day pre-entry screening and a 7-day follow-up visit.

Statistical methods

Plasma concentrations of clopidogrel active metabolite and the derived pharmacokinetic parameters were summarized by treatment using descriptive statistics. Clopidogrel active metabolite has been shown to be only one of a pair of diastereomers (H3 and H4) of the Z configuration. Recent studies have shown that analysis specific for the H4 diastereomer of clopidogrel active metabolite is more accurate than analysis for combined H3 and H4 diastereomers because the H3 diastereomer of the Z configuration has been shown to have little biological activity. Samples were originally analyzed for clopidogrel active metabolite in human plasma using a validated method that merged the H3 and H4 diastereomers into a single chromatographic peak. The samples were analyzed again using a validated method that is specific for the H4 diastereomer. The H4 diastereomer is the primary focus of this report.

Both pharmacodynamic and pharmacokinetic variables were analyzed using a linear mixed-effect analysis of variance model with fixed effect for period, sequence, site, and treatment and a random effect for volunteer within sequence. The clopidogrel alone treatment was the reference for the 3 test interaction treatment arms.

Safety data were summarized using descriptive statistics.

Subject population

The volunteer population consisted of 108 healthy volunteers, 63 (58.3%) male and 45 (41.7%) female volunteers with a mean age of 30 years. Of the 108 enrolled volunteers, 87 (80.6%) of them completed all planned study treatments (ie, all 3 dosing periods per protocol) and 21 (19.4%) volunteers were discontinued from the study. Two volunteers discontinued due to eligibility criteria not being fulfilled (positive drug screens). One volunteer discontinued due to severe noncompliance to the protocol (chewed the investigational product instead of swallowing it whole). Eight volunteers discontinued due to volunteer decision. Three volunteers discontinued due to other reasons (2 volunteers became pregnant and 1 volunteer was discontinued due to Sponsor decision [missed dosing on Days 4 and 5 of Period 2]). One volunteer discontinued due to lost to follow-up. One volunteer discontinued due to a serious adverse event of schizophrenia and 5 volunteers were discontinued due to nonserious adverse events.

All 108 volunteers enrolled in the study were analyzed for safety. Of the 108 volunteers enrolled, 101 volunteers were included in the pharmacokinetic and pharmacodynamic analyses.

Summary of pharmacokinetic results

A single dose of lansoprazole, omeprazole, or esomeprazole did not affect exposure to the active metabolite of clopidogrel (H4) on Day 1. The 90% confidence interval of the geometric mean ratio for active metabolite (H4) AUC, $AUC_{(0-t)}$, and C_{max} comparing each proton pump inhibitor + clopidogrel (test) to clopidogrel alone (reference) was contained within the equivalence limits of 80% to 125% on Day 1.

Lansoprazole, omeprazole, and esomeprazole coadministration decreased overall exposure [$AUC_{(0-t)}$] to the active metabolite of clopidogrel (H4) on average 24%, 41%, and 38%, respectively, on Day 5. Lansoprazole, omeprazole, and esomeprazole coadministration decreased maximum exposure (C_{max}) to the active metabolite of clopidogrel (H4) on average 27%, 46%, and 46%, respectively, on Day 5. The lower limit of the 90% confidence interval of the geometric mean ratio for active metabolite (H4) $AUC_{(0-t)}$, and C_{max} comparing each proton pump inhibitor + clopidogrel (test) to clopidogrel alone (reference) fell below the lower bounds of the equivalence limits of 80% to 125% on Day 5.

Lansoprazole, omeprazole, and esomeprazole coadministration decreased overall exposure [$AUC_{(0-t)}$] to the active metabolite of clopidogrel (H4) on average 24%, 46%, and 39%, respectively, on Day 14. Lansoprazole, omeprazole, and esomeprazole coadministration decreased maximum exposure (C_{max}) to the active metabolite of clopidogrel (H4) on average 29%, 51%, and 43%, respectively, on Day 14. The lower limit of the 90% confidence interval of the geometric mean ratio for active metabolite (H4) $AUC_{(0-t)}$, and C_{max} comparing each proton pump inhibitor + clopidogrel (test) to clopidogrel alone (reference) fell below the lower bounds of the equivalence limits of 80% to 125% on Day 14.

Lansoprazole, omeprazole, and esomeprazole coadministration decreased overall exposure [$AUC_{(0-t)}$] to the active metabolite of clopidogrel (H4) on average 17%, 45%, and 35%, respectively, on Day 29. Lansoprazole, omeprazole, and esomeprazole coadministration decreased maximum exposure (C_{max}) to the active metabolite of clopidogrel (H4) on average 18%, 49%, and 37%, respectively, on Day 29. The lower limit of the 90% confidence interval of the geometric mean ratio for active metabolite (H4) $AUC_{(0-t)}$, and C_{max} comparing each proton pump inhibitor + clopidogrel (test) to clopidogrel alone (reference) fell below the lower bounds of the equivalence limits of 80% to 125% on Day 29.

Summary of pharmacodynamic results

Primary PD variable

Lansoprazole coadministration significantly reduced the mean mIPA compared to clopidogrel alone by 6.5%, 8.2%, 10.7%, and 6.3% on Days 2, 6, 15, and 30, respectively. Expressed in relative terms, the difference between the least-squares mean for clopidogrel + lansoprazole and clopidogrel alone represents a 15.9%, 15.0%, 20.5%, and 13.5% loss of the inhibitory effect of clopidogrel therapy on Days 2, 6, 15, and 30, respectively.

Omeprazole coadministration reduced mean mIPA compared to clopidogrel alone by 2.4%, 17.3%, 16.4%, and 15.6% on Days 2, 6, 15, and 30, respectively. These reductions were statistically significant with the exception of Day 2. Expressed in relative terms, the difference between the least-squares mean for clopidogrel + omeprazole and clopidogrel alone represents a 6.1%, 31.6%, 31.5%, and 33.1% loss of the inhibitory effect of clopidogrel therapy on Days 2, 6, 15, and 30, respectively.

Esomeprazole coadministration reduced mean mIPA compared to clopidogrel alone by 0.4%, 10.9%, 17.1%, and 12.9% on Days 2, 6, 15, and 30, respectively. These reductions were

statistically significant with the exception of Day 2. Expressed in relative terms, the difference between the least-squares mean for clopidogrel + esomeprazole and clopidogrel alone represents a 1.2%, 19.9%, 32.8%, and 27.2% loss of the inhibitory effect of clopidogrel therapy on Days 2, 6, 15, and 30, respectively.

A secondary pharmacodynamic analysis was performed to examine mIPA which excluded low responders. A low responder was defined as a volunteer with a mIPA response of 25% or less at Day 2 while receiving clopidogrel alone. Twenty-four subjects enrolled in this study were classified as low responders to clopidogrel. The results excluding these 24 low responders were similar to the primary pharmacodynamic analysis.

Summary of pharmcokinetic/pharmacodynamic relationships

Not applicable

Summary of pharmacogenetic results

Not applicable

Summary of safety results

In this population of healthy male and female volunteers, all 4 study treatments were well tolerated. There were no deaths during the study. There were 2 serious adverse events in 2 volunteers (miscarriage [volunteer was withdrawn from the study 11 days prior to the miscarriage due to pregnancy] and schizophrenia [volunteer was withdrawn from the study], both events occurred during clopidogrel alone treatment) assessed by the Investigator as not related to investigational product. Five volunteers discontinued due to nonserious adverse events; urticaria, 2 events (lansoprazole/clopidogrel and clopidogrel alone treatments), rectal bleeding (lansoprazole/clopidogrel treatment), inflammatory arthritis (esomeprazole/clopidogrel treatment), dizziness (clopidogrel alone treatment), supraventricular tachycardia (clopidogrel alone treatment), tremor (clopidogrel alone treatment), and anxiety (clopidogrel alone treatment). Investigational product was discontinued for one volunteer due to an adverse event of pyrexia (lansoprazole/clopidogrel treatment), but the volunteer remained in the study (only the last dose in Period 3 was not administered).

Following the first dose of investigational product, adverse events were reported for 88 (81.5%) volunteers. The number of volunteers experiencing adverse events was similar across the treatment groups. Adverse events were reported for 38 (57.6%) volunteers during lansoprazole/clopidogrel treatment, 30 (46.9%) volunteers during omeprazole/clopidogrel treatment, 30 (46.2%) volunteers during esomeprazole/clopidogrel treatment, and 47 (46.5%) volunteers during clopidogrel alone treatment.

Most adverse events were reported with similar frequency between the treatment groups or were experienced by only 1 or 2 volunteers in a treatment group. The most frequently reported adverse events overall were headache (29/108 volunteers, 26.9%) and ecchymosis (21/108 volunteers, 19.4%).

Fourteen (13.0%) volunteers reported adverse events that were assessed by the Investigator as moderate in intensity and 2 (1.9%) volunteers reported severe adverse events (kidney stones and schizophrenia [both 75 mg clopidogrel alone treatment]).

There were no clinically relevant changes in clinical laboratory, vital sign, electrocardiogram, body weight, or physical examination findings.