AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor (AZD6140)
Study Code	D5130C00042
Date	18 March 2009

A Randomised, Double-blind, Two-way Crossover Study to Determine the Effects of Co-administration of AZD6140 and Nordette® (Combination of Levonorgestrel and Ethinyl Estradiol) After Multiple Oral Doses in Healthy Female Volunteers

Study dates: First healthy volunteer enrolled: 21 April 2008
Last healthy volunteer completed: 04 October 2008

Phase of development: Clinical pharmacology (I)

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

Study centre

SeaView Research, 3898 NW 7th Street, Miami, FL, USA

First healthy volunteer enrolled: 21 April 2008

Last healthy volunteer completed: 04 October 2008

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was:

To examine the effect of co-administration of ticagrelor (formerly AZD6140) and NORDETTE™ (ethinyl estradiol [EE]/levonorgestrel [LN]) on the pharmacokinetics (PK) of EE.

The secondary objectives of this study were:

- To characterise the PK of LN and the plasma levels of progesterone, 17-beta estradiol, luteinising hormone (LH), follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG) following concomitant administration of ticagrelor and EE/LN
- To characterise the PK of ticagrelor and AR-C124910XX following concomitant oral administration of ticagrelor and EE/LN
- To examine the safety and tolerability of ticagrelor when co-administered with EE/LN

Study design

This was a randomised, double-blind, 2-way crossover study conducted to determine the effect of co-administration of ticagrelor and EE/LN on the PK of EE and LN.

Target healthy volunteer population and sample size

Approximately 24 healthy female volunteers, 18 to 45 years of age, inclusive, were to be randomised to ensure that at least 16 healthy volunteers were evaluable for PK analysis. A sample size of 16 healthy volunteers would provide approximately 90% power that the 2-sided 90% confidence interval (CI) for the ratios of interest (EE maximum drug concentration in plasma [C_{max}] or area under the plasma concentration-time curve during the dosing interval [$AUC_{0-\tau,}$]) of EE/LN administered with ticagrelor to that of EE/LN alone would be completely contained within the pre-specified no effect (or interaction) range of 0.80 to 1.25.

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

Oral doses of 90 mg ticagrelor bd (Batch no. 07-010829AZ; formulation FDN334) or matching placebo (Batch no. HE202; formulation FDN322); and NORDETTE which contains ethinyl estradiol 0.03 mg/levonorgestrel 0.15 mg for the doses on Days 1 through 21 and EE/LN placebo for the doses on Days 22 through 28 (Batch no. 51285-0091-58).

Healthy volunteers were randomised to receive each of the following treatments in a randomised sequence (AB or BA):

- **Treatment A**: Ethinyl estradiol 0.03 mg/levonorgestrel 0.15 mg (NORDETTE) every day at approximately the same time in the morning and ticagrelor 90 mg administered bd for 21 days. On Cycle Days 22 to 28, volunteers took EE/LN placebo doses only.

- **Treatment B**: Ethinyl estradiol 0.03 mg/levonorgestrel 0.15 mg (NORDETTE) every day at approximately the same time in the morning, and ticagrelor-matching placebo administered bd for 21 days. On Cycle Days 22 to 28, volunteers took EE/LN placebo doses only.

Duration of treatment

The duration of healthy volunteer participation was approximately 142 days, including a screening phase of up to 30 days; a run-in phase lasting 2 cycles (28 days each) for volunteers not already on a stable dose (minimum of 2 months) of EE/LN; and two 28-day treatment periods (Cycles 1 and 2) which included 7-day washout (placebo) periods following each treatment. Final follow-up assessments were completed 5 to 6 days after Cycle 2.

Criteria for evaluation - pharmacokinetics (main variables)

Blood samples for the determination of EE and LN concentrations in plasma were obtained pre-dose on Days 1, 7, 14, and 21 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours following the morning dose on Day 21 of each treatment cycle (Cycles 1 and 2). The following PK parameters were assessed for EE (primary) and LN (secondary): $AUC_{0-\tau}$, C_{max}, trough drug concentration in plasma (C_{min}), time to reach maximum concentration (t_{max}).

For Treatment A only (ticagrelor + EE/LN), blood samples for PK analysis of ticagrelor and its active metabolite AR-C124910XX were obtained pre-dose on Days 1, 7, 14, and 21 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours following the morning dose on Day 21 of each treatment cycle (Cycles 1 and 2). The following PK parameters were assessed: $AUC_{0-\tau}$, C_{max}, C_{min}, and t_{max}. Metabolite to parent C_{max} and $AUC_{0-\tau}$ ratios were also estimated.

Criteria for evaluation - pharmacodynamics (main variables)

Pharmacodynamics were assessed via pre-dose morning plasma levels of endogenous hormones (progesterone, 17-beta estradiol, LH, FSH, and SHBG) on Days 1, 7, 14, and 21 of Cycles 1 and 2.

Criteria for evaluation - safety (main variables)

Safety was assessed based on adverse events (AEs), vital signs (heart rate and blood pressure), electrocardiograms (ECGs), clinical laboratory parameters (haematology, clinical chemistry, and urinalysis), and physical examinations.

Statistical methods

Pharmacokinetics

The PK parameters $AUC_{0-\tau}$, C_{min}, and C_{max} for EE and LN were log-transformed before analysis. They were analysed using an analysis of variance (ANOVA) model with fixed effects for sequence, period and treatment, and a random effect for volunteer within sequence. Estimates of the primary contrast and 2-sided 90% confidence intervals (CIs) were constructed. Estimates of treatment effect and CIs were exponentially back-transformed to provide point and interval estimates in the linear scale.

For EE and LN, it was concluded that there is no interaction if the 90% CI was contained completely within 80% to 125% for the ratios:

$AUC_{0-\tau}$ (ticagrelor + oral contraceptive [OC]) / $AUC_{0-\tau}$ (placebo + OC)

C_{max} (ticagrelor + OC) / C_{max} (placebo + OC)

C_{min} (ticagrelor + OC) / C_{min} (placebo + OC)

Pharmacodynamics

Endogenous hormone plasma concentrations, including progesterone, 17-beta estradiol, LH, FSH, and SHBG were summarised by treatment and protocol-scheduled time, and reported as descriptive statistics. Mean plasma concentration time plots and individual plasma concentration time plots were produced for each compound by treatment.

The concentration (CONC) of endogenous hormones on Days 1, 7, 14, and 21 for each cycle were analysed using a repeated-measures model with fixed effects for sequence, period, treatment, and a random effect for volunteer-within-sequence, and AR(1) as the covariance structure for the plasma concentrations of a volunteer within a period. Least square (LS) means with 95% CI of treatment effect and contrast between the 2 treatments (ticagrelor + EE/LN versus placebo + EE/LN) on each protocol-scheduled day were estimated and reported. The analysis was conducted for progesterone, 17-beta estradiol, LH, FSH, and SHBG, respectively.

The contrasts included as follows on each protocol-scheduled Days 1, 7, 14, and 21:

$CONC_{progesterone}$ (ticagrelor + OC) - $CONC_{progesterone}$ (placebo + OC)

$CONC_{17\text{-}beta}$ (ticagrelor + OC) - $CONC_{17\text{-}beta}$ (placebo + OC)

$CONC_{LH}$ (ticagrelor + OC) - $CONC_{LH}$ (placebo + OC)

$CONC_{FSH}$ (ticagrelor + OC) - $CONC_{FSH}$ (placebo + OC)

$CONC_{SHBG}$ (ticagrelor + OC) - $CONC_{SHBG}$ (placebo + OC)

Safety

Safety and tolerability data (AEs, vital signs, ECGs, clinical laboratory, and physical examinations) were summarised descriptively by treatment and presented in tabular and/or graphical form. No formal statistical analysis was performed.

Subject population

A total of 26 healthy female volunteers between the ages of 19 and 43 years were enrolled in the study and randomized to treatment sequence. The majority of volunteers were Caucasian (76.9%). All 26 volunteers received at least 1 dose of ticagrelor or ticagrelor placebo and were therefore included in the safety analysis set. Due to protocol noncompliance/violations that resulted in the early discontinuation of 4 volunteers, 3 volunteers did not receive ticagrelor and were therefore excluded from the ticagrelor PK analysis set, and all 4 volunteers were excluded from the PK analysis set for EE/LN and the PD analysis set due to a lack of PK and PD outcomes in one or both treatment cycles. Therefore, the ticagrelor PK analysis set consisted of 23 (88%) volunteers; the EE/LN PK analysis set consisted of 22 (85%) volunteers; and the PD analysis set consisted of 22 (85%) volunteers. Twenty-two volunteers completed the study.

Summary of pharmacokinetic results

A 20% to 30% increase in EE exposure was observed when EE/LN was co-administered with ticagrelor compared to that for placebo + EE/LN (90 % CIs of 0.961 to 1.504 for C_{min}, 1.181 to 1.443 for C_{max}, and 1.028 to 1.401 for $AUC_{0\text{-}\tau}$). Median t_{max} values were similar between the 2 treatment groups (1.0 hour for ticagrelor + EE/LN versus 1.1 hour for placebo + EE/LN).

The PK of LN was not affected when EE/LN was co-administered with ticagrelor; 90% CIs for the geometric mean ratios were within 80% and 125% for C_{max} (1.016 to 1.162), for C_{min} (0.943 to 1.0960), and for $AUC_{0\text{-}\tau}$ (0.968 to 1.099).

Following co-administration of ticagrelor and EE/LN, ticagrelor was rapidly absorbed with a median t_{max} of approximately 1.5 hours (range, 1 to 4 hours). Mean C_{max} and $AUC_{0\text{-}\tau}$ values were 1032.5 ng/mL and 5487.0 ng·h/mL, respectively. The exposure to AR-C124910XX was approximately 29% that of ticagrelor in terms of C_{max} and 36% in terms of $AUC_{0\text{-}\tau}$ with a

slightly longer time to peak concentrations as compared to ticagrelor (median t_{max} of 2 hours; range, 1.5 to 4 hours). A rise in C_{min} of ticagrelor and AR-C124910XX was observed on Day 21. This may be due to the CYP3A4 variability during the menstrual cycle, ie, the CYP3A4 activity may be the lowest during the luteal phase.

Summary of pharmacodynamic results

There were no statistically significant differences in endogenous hormone values between the 2 treatment groups. Furthermore, progesterone levels remained low during the luteal phase for both treatment groups, suggesting that ovulation did not occur and that contraceptive efficacy was maintained when ticagrelor was co-administered with EE/LN.

Summary of pharmacogenetic results

The genetic component of the study served to generate data for use in future retrospective analyses. Therefore, results of genetic analyses will not form part of the clinical study report for this study.

Summary of safety results

Repeated oral administration of ticagrelor and EE/LN were well tolerated over two 21-day treatment cycles. The number of volunteers with AEs was similar during treatment with ticagrelor + EE/LN and placebo + EE/LN (5/23, 22% and 5/26, 19%, respectively), as was the number of volunteers with treatment-related AEs (4/23, 17% and 3/26, 12%, respectively). Vessel puncture site haematoma (2 volunteers, placebo + EE/LN) and genital haemorrhage (2 volunteers, ticagrelor + EE/LN) were the only AEs that occurred in more than a single volunteer. All AEs were considered to be of mild intensity with the exception of 1 AE of back pain following treatment with placebo + EE/LN that was moderate in intensity. All AEs were resolved at the end of the study with the exception of iron deficiency anemia and contusion. There were no deaths, serious AEs, or discontinuations due to AEs. There were no clinically significant changes in laboratory values, vital signs, or ECG parameters.