AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor (AZD6140)
Study Code	D5130C00050
Date	17 March 2009

A Randomised, Double-Blind, Two-Period Crossover Study to Assess the Effect of AZD6140 on Uric Acid Levels in Healthy Male Volunteers

Study dates: First healthy volunteer enrolled: 27 May 2008
Last healthy volunteer completed: 8 July 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

The study was conducted in the United States at SeaView Research, Inc., Miami, FL. The first healthy volunteer was enrolled on 27 May 2008.

Publications

There were none at the time of writing this report.

Objectives

The primary objective of this study was to examine the effect of ticagrelor (formerly known as AZD6140) administration on serum uric acid levels and urinary uric acid excretion in healthy male volunteers under conditions of dietary control.

The secondary objectives of the study were

- To examine the effect of ticagrelor administration on precursors (hypoxanthine and xanthine) in uric acid catabolism pathway
- To examine the pharmacokinetics (PK) of ticagrelor and AR-C124910XX (the active metabolite)
- To examine the effect of ticagrelor administration on 6β-hydroxyl cortisol and cortisol levels in urine
- To evaluate safety and tolerability of ticagrelor by assessment of adverse events (AEs), laboratory variables, pulse, and blood pressure (BP)

Study design

This was a double-blind, placebo-controlled, randomised, 2-period, 2-way crossover study. There were 2 treatments (ticagrelor 90 mg twice daily for 5 days and matching placebo twice daily for 5 days).

Target healthy volunteer population and sample size

Approximately 24 healthy male volunteers, 18 to 45 years of age, and with normal serum uric acid at screening, were randomised to ensure that at least 18 volunteers were evaluable.

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

Ticagrelor was provided in 90-mg tablets (Batch 07-010829AZ), and matching placebo tablets (Batch HE202) were provided, both for twice-daily oral administration.

Duration of study

The duration of study clinic confinement was 24 days, not including the Screening Period that started 4 to 21 days before the study, or the time from the end of the final period's study

procedures to the Follow-up Visit (4 to 7 days after discharge). Each study period consisted of a 4-day run-in, 5-day ticagrelor administration (Days 1 to 5), and 3-day follow-up observation (to Day 8); the 2 periods were run sequentially, which allowed a 7-day washout period between the 2 treatments.

Criteria for evaluation - pharmacodynamics and pharmacokinetics (main variables)

Pharmacodynamics (PD) variables of ticagrelor and AR-C124910XX included serum uric acid, renal clearance of uric acid, the amount of uric acid excreted in urine, fractional excretion of uric acid, serum hypoxanthine and xanthine levels, and ratio of 6β-hydroxyl cortisol/cortisol. In addition, the following laboratory data were collected: blood electrolyte panel (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, and creatinine) and urinary levels of uric acid, sodium, potassium, creatinine, and protein.

PK parameters of ticagrelor and AR-C124910XX, including maximum plasma concentration during the dosing interval (C_{max}), time to reach maximum concentration (t_{max}), and area under the plasma concentration-time curve during the dosing interval (AUC_{τ}), were calculated.

Criteria for evaluation - safety (main variables)

Data were collected regarding AEs, clinical laboratory results, vital signs (pulse and BP), and electrocardiograms (ECGs).

Criteria for evaluation - pharmacogenetics (main variables)

An optional blood sample for pharmacogenetic analysis was taken.

Statistical methods

Baseline for PD parameters was defined as the last PD sample taken before the first dose administration for each period. PD parameters were analysed using a repeated measures analysis of covariance model with fixed effects of treatment, period, sequence, protocol time of PD sampling, protocol time of PD sampling and treatment interaction, and baseline creatinine clearance, with a random effect of volunteer within sequence. The least squares (LS) means of PD parameters with 95% confidence intervals (CIs) were calculated by time point. Two–sided 95% CIs were constructed for the LS mean difference between treatments (ticagrelor–placebo) for the same time point, and for the LS mean difference between the same time points of Day 5 (ticagrelor-placebo)-Day 1 (ticagrelor-placebo). Mean and individual PD time plots by treatment were produced. No adjustments for multiple comparisons were made.

Ticagrelor and AR-C124910XX plasma concentrations were summarised using descriptive statistics by time points. Geometric mean and individual plasma concentration time plots were produced. Descriptive statistics were used to summarise all PK parameters.

Safety and tolerability data were listed and summarised descriptively. All AE data were listed and summarised using the Medical Dictionary for Regulatory Activities (Version 11.0).

Volunteer population

Twenty-four healthy volunteers between the ages of 22 and 45 were randomised and completed the study. All volunteers were male (100%) and most were white (79.2%). All volunteers received at least 1 dose of investigational product and were included in the PK, PD, and safety analysis sets.

Summary of pharmacokinetic results

During this study, each volunteer received ticagrelor 90 mg twice daily for 5 days. The area under the concentration versus time curve ($AUC_{[0-12]}$ and $AUC_{[0-24]}$) and C_{max} of ticagrelor and AR-C124910XX were comparable in this study with the results from previous studies in healthy populations.

Summary of pharmacodynamic results

- Compared with placebo, a modest 3.6% (5.459 compared to 5.653 mg/dL) mean elevation of serum uric acid was observed 8 hours after the first dose of ticagrelor, and the increased mean serum uric acid concentration (compared to placebo) was maintained until 36 hours after the final dose of ticagrelor. Serum uric acid levels returned to baseline 60 hours post-dose.

- Compared with placebo, mean increases of 25% (9.5201 compared to 11.9391 μM) and 20% (2.3039 compared to 2.7701 μM) in serum hypoxanthine and xanthine, respectively, were observed following the multiple doses of ticagrelor.

- Compared with placebo, the amount of uric acid excreted in urine (0 to 24 hours) was higher by a mean of 7.0% (619.33 compared to 662.77 mg) after the initiation of administration of ticagrelor. Following multiple doses of ticagrelor 90 mg, and 24 hours after the last dose of ticagrelor, the amount of uric acid excreted in urine (0 to 24 hours) was higher by a mean of 2.5% (670.96 compared to 687.53 mg).

- Compared with placebo, 24 hours following the last dose of ticagrelor, renal clearance of uric acid (12 to 24 hours) was higher by a mean 19% (6.71 compared to 7.98 mL/min).

- The mean 6β-hydroxyl cortisol/cortisol ratios were not statistically significantly altered after administration of ticagrelor on Days 1 or 5.

Summary of pharmacokinetic/pharmacodynamic relationships

No clear relationship was observed between changes in ticagrelor or AR-C124910XX plasma concentrations and response in the parameters examined: serum uric acid, xanthine, and hypoxanthine levels.

Summary of pharmacogenetic results

Blood samples were collected for pharmacogenetic analysis according to the clinical study protocol and may be analyzed and reported at a later date.

Summary of safety results

Twice-daily doses of ticagrelor 90 mg for 5 days were generally well tolerated in healthy volunteers. There were no deaths, serious AEs, or AEs leading to discontinuation. There was 1 other significant AE of conjunctival haemorrhage reported in a volunteer receiving ticagrelor. Of the 24 volunteers, 5 volunteers had AEs while receiving ticagrelor, and 2 volunteers had AEs while receiving placebo (1 volunteer had AEs in both treatments). Headache was the only AE that occurred in more than 1 volunteer (1 while receiving ticagrelor and 1 while receiving placebo). All AEs were mild in intensity except for 1 moderate-intensity rash. No clinically meaningful findings were observed based on haematology, clinical chemistry, urinalysis, ECGs, vital signs, and physical examination results.