AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130C00074
Edition Number	1
Date	6 November 2012

A Single-center, Open-label, Randomized, 3-Treatment, 3-Period Cross-over Study to Investigate the Potential Effect of Cyclosporine on the Pharmacokinetics, Safety, and Tolerability of Ticagrelor and the Effect of Ticagrelor on the Pharmacokinetics, Safety, and Tolerability of Cyclosporine Administered Concomitantly in Healthy Male Subjects

Study dates:	First subject enrolled: 17 January 2012
	Last subject last visit: 22 June 2012
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 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	Pharmacokinetic	To investigate the effect of cyclosporine on the pharmacokinetics of ticagrelor in healthy male volunteers	Plasma: ticagrelor and AR-C124910XX C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$ AR-C124910XX:ticagrelor ratios: C_{max}, $AUC_{(0-t)}$, AUC
		To investigate the effect of ticagrelor on the pharmacokinetics of cyclosporine in healthy male volunteers	Whole blood: cyclosporine C_{max}, t_{max}, $AUC_{(0-t)}$, AUC, $t_{1/2}$
Secondary	Safety	To assess the safety and tolerability of coadministration of ticagrelor and cyclosporine in healthy male volunteers by assessment of adverse events, safety laboratory variables, physical examination, electrocardiogram, and vital signs	Adverse events, laboratory variables, vital signs, physical examination, and electrocardiogram
Exploratory[a]	Biomarker	To collect plasma samples for possible biomarker research	Not applicable

[a] Results from the exploratory analyses, if performed, will be reported separately from the Clinical Study Report.

AUC: Area under the concentration-time curve in sampled matrix from zero to infinity; $AUC_{(0-t)}$: Area under the concentration-time curve from zero to the last quantifiable concentration in sampled matrix; C_{max}: Maximum concentration in sampled matrix; CSP: Clinical Study Protocol; $t_{1/2}$: Terminal half-life; t_{max}: Time to maximum concentration in sampled matrix.

Study design

This was a single-center, open-label, randomized, cross-over study with 3 treatments administered at 3 visits to investigate the potential pharmacokinetic (PK) interaction of 600 mg cyclosporine and 180 mg ticagrelor. All healthy volunteers were to receive 3 treatments: Treatment A (a single oral dose of 600 mg cyclosporine + a single oral dose of 180 mg ticagrelor), Treatment B (a single oral dose of 600 mg cyclosporine), and Treatment C (a single 180 mg ticagrelor dose) in a cross-over design. A total of 26 healthy male volunteers were randomized to receive the treatments in 1 of 6 sequences, separated by a washout period of at least 14 days between doses.

Target subject population and sample size

Healthy male volunteers aged 18 to 45 years (inclusive) with a body mass index (BMI) of 18 to 30 kg/m^2 (inclusive) were to be randomized in this study.

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

Table S2 Details of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer	Batch number
Ticagrelor	90 mg tablets	AstraZeneca	11-003127AZ
Cyclosporine	100 mg capsules	Novartis	F4147 F4149

Duration of treatment

Three single doses at 3 visits separated by a washout period of at least 14 days between doses

Statistical methods

Plasma concentrations of ticagrelor and the metabolite AR-C124910XX and their derived PK parameters were summarized by treatment by using appropriate descriptive statistics.

For statistical comparisons between treatments, the PK parameters for ticagrelor, AR-C124910XX, and cyclosporine were natural log-transformed prior to analysis. The natural log-transformed AUC and C_{max} data were separately analyzed using a mixed effects model with terms for treatment, period, and sequence as fixed effects and healthy volunteer nested within sequence as a random effect. The estimated least squares means and intrasubject variability from the mixed effects model were used to construct 90% CIs for the difference in means on the log scale between the 2 treatments. The treatment effect and its corresponding 90% CIs were back-transformed using antilogarithms to its original scale and reported as ratio of treatments (ticagrelor + cyclosporine / ticagrelor alone or ticagrelor + cyclosporine / cyclosporine alone).

Safety variables were summarized using descriptive statistics.

Subject population

All healthy volunteers were eligible to be included and randomized in this study. Of the 26 healthy volunteers randomized, 21 healthy volunteers received all the planned investigational product administrations and 20 healthy volunteers completed the study. One healthy volunteer was withdrawn due to an adverse event (AE), 1 healthy volunteer was withdrawn by the sponsor, 1 healthy volunteer withdrew consent, and 3 healthy volunteers were lost to follow-up.

Summary of pharmacokinetic results

Geometric mean AUC [AUC and $AUC_{(0-t)}$] and C_{max} for ticagrelor were approximately 2.8-fold and 2.3-fold higher in the presence of cyclosporine, when compared to when ticagrelor was given alone. Geometric mean AUC [AUC and $AUC_{(0-t)}$] for AR-C124910XX was approximately 33% higher and C_{max} was 17% lower for AR-124910XX in the presence of cyclosporine, when compared to when ticagrelor was given alone. The parameters t_{max} and $t_{1/2}$ were similar between treatments for both ticagrelor and AR-C124910XX. Generally, all PK parameters for cyclosporine were similar when cyclosporine was given alone or when coadministered with ticagrelor.

Summary of safety results

Ticagrelor + cyclosporine were administered to 24 healthy volunteers, cyclosporine alone to 25 healthy volunteers, and ticagrelor alone to 24 healthy volunteers.

No deaths or serious adverse events (SAEs) were reported. One healthy volunteer was prematurely withdrawn from the study due to mild vomiting, considered to be related to cyclosporine by the Investigator. This event was reported 51 minutes after cyclosporine alone. At least 1 AE was reported for 23 healthy volunteers (88.5%): 15 healthy volunteers (62.5%) after ticagrelor + cyclosporine, 17 healthy volunteers (68.0%) after cyclosporine alone, and 6 healthy volunteers (25.0%) after ticagrelor alone.

The highest incidence of healthy volunteers with at least 1 AE was reported after cyclosporine alone (17 healthy volunteers [68.0%]) and the highest incidence of healthy volunteers with at least 1 AE considered related to any treatment was reported after cyclosporine alone (16 healthy volunteers [64.0%]). The most frequently reported AEs were feeling hot (all considered related to the treatment) and nausea (most considered related to the treatment), all reported after either ticagrelor + cyclosporine or cyclosporine alone. Most of the AEs were mild (1 AE of moderate severity, viral infection) and most of the AEs had resolved at the time of database lock.

No relevant measurements or changes in any laboratory parameters, vital signs, ECG, or physical examination findings were reported.