AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130C00079
Edition Number	1
Date	

A open label, randomized, cross-over and potential parallel, single dose study of ticagrelor 180 mg and acetylsalicylic acid (ASA) in healthy volunteers followed by autologous *in vivo* platelet transfusion to determine the effects of platelet supplementation on the reversibility of platelet inhibition

Study dates: First subject enrolled: 26 December 2012
Last subject last visit: 6 April 2014

Phase of development: Clinical pharmacology (I)

Principal Investigator:

Sponsor's Responsible Medical Officer:

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

Study centre

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	Pharmacodynamics	To evaluate the effect of autologous platelet transfusions in healthy volunteers at 24 and 48 hours (and potentially 12 hours)[a] after a loading dose of ticagrelor on platelet inhibition as measured by LTA	Percent of inhibition of ADP-induced platelet aggregation assessed by LTA
Secondary	Pharmacodynamics	To potentially evaluate the effect of autologous platelet transfusions in healthy volunteers at either 12, 24 or 48 hours after a loading dose of clopidogrel on platelet inhibition as measured by LTA[a]	Percent of inhibition of ADP-induced platelet aggregation assessed by LTA
Secondary	Pharmacodynamics	To evaluate the effect of autologous platelet transfusions in healthy volunteers at 24 and 48 hours (and potentially 12 hours) after a loading dose of ticagrelor on platelet inhibition as measured by VerifyNow™	Platelet reactivity as measured by PRU using VerifyNow™
Secondary	Pharmacodynamics	To potentially evaluate the effect of autologous platelet transfusions in healthy volunteers at either 12, 24 or 48 hours after a loading dose of clopidogrel on platelet inhibition as measured by VerifyNow™	Platelet reactivity as measured by PRU using VerifyNow™
Secondary	Pharmacodynamics	To evaluate the durability of restoration of platelet aggregation following platelet transfusion	Percent of inhibition of ADP-induced platelet aggregation assessed by LTA and platelet reactivity as measured by PRU using VerifyNow™

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Safety	Safety	To describe the safety and tolerability of ticagrelor administered as a loading dose prior to an autologous platelet transfusion.	Vital signs (blood pressure and pulse rate), electrocardiogram, laboratory safety data (clinical chemistry, hematology, complete blood count, and urinalysis), physical examination and adverse events

ADP: Adenosine diphosphate; LTA: Light transmission aggregometry; PRU: $P2Y_{12}$ Reaction Unit

[a] If the 24 hour and 48 hour cohorts were both successful, a platelet transfusion at 12 hours after the loading dose of ticagrelor (Day 1) in a single treatment, without crossing over to a non transfusion period, hence a parallel group, was to be performed.

Study design

This was an open label, randomized, cross-over study of 180 mg ticagrelor administered in healthy volunteers followed by autologous *in vivo* platelet transfusion to determine the effects of platelet supplementation on the reversibility of platelet inhibition. The study was to be conducted at a single study center in approximately 48 healthy male and female (of nonchildbearing potential) volunteers aged 18 to 50 years (inclusive).

The study consisted of 2 treatments each for Cohort 1 (platelet transfusion at 24 hours) and Cohort 2 (platelet transfusion at 48 hours).

After completion of Cohort 1 and Cohort 2, a decision was to be made regarding the continuation of the study and the subsequent cohorts to be initiated according to the results observed from Cohort 1 and Cohort 2.

Treatment A: platelet apheresis on Day -2 followed by a ticagrelor 180 mg loading dose on Day 1 for Cohort 1; and platelet apheresis on Day -1 followed by a ticagrelor 180 mg loading dose on Day 1 for Cohort 2, respectively. Background acetylsalicylic acid (ASA) treatment (81 mg once daily) commenced immediately after platelet apheresis on the relevant day, based on the randomization scheme and treatment group, up to and including the day prior to the platelet transfusion.

Treatment B: ticagrelor 180 mg loading dose on Day 1. Background ASA treatment (81 mg once daily) commenced on the relevant day, based on the randomization scheme and treatment group, up to and including the day prior to the randomized platelet transfusion from Treatment A.

During each treatment period healthy volunteers received a loading dose of 180 mg of ticagrelor with background ASA. The healthy volunteers had platelet apheresis and platelet transfusion performed during 1 of the 2 treatment periods based on the randomization scheme.

Cohort 1: the platelet transfusion was performed 24 hours after receiving the 180 mg ticagrelor loading dose. Healthy volunteers received ASA background treatment once on

Day -2 immediately after completion of the platelet apheresis, on Day -1, and again on Day 1 when ticagrelor was administered.

Cohort 2: the platelet transfusion was performed 48 hours after receiving the 180 mg ticagrelor loading dose. Healthy volunteers received ASA background treatment once on Day -1 immediately after completion of the platelet apheresis, and again on Day 1 when ticagrelor was administered, as well as once on Day 2.

The definition of success for each cohort was:

- A decrease (at 5% significance level) in inhibition of platelet aggregation (IPA) (light transmission aggregometry [LTA]) measured 12 hours after transfusion between Treatment A and Treatment B. The definition of success for each cohort was based on the final extent of aggregation.

The results reported for this study revealed that Cohort 1 was unsuccessful and Cohort 2 was successful. Therefore, it was decided to initiate Cohort 3b, which was the final cohort in this study. Eligible healthy volunteers in Cohort 3b received 2 treatments.

Treatment C: 600 mg clopidogrel loading dose with platelet apheresis and transfusion at 48 hours.

Treatment D: 600 mg clopidogrel loading dose with no platelet apheresis and transfusion.

The ASA background treatment for the clopidogrel cohort was to be identical to that for the ticagrelor administration for the same transfusion timing, ie, 48 hours.

Target subject population and sample size

Healthy male and/or female volunteers aged 18 to 50 years, inclusive, with a platelet count >200 x 10^9/L at screening and at admission. Healthy volunteers with adenosine diphosphate (ADP)-induced platelet aggregation <60% prior to platelet apheresis were not included.

Planned:	Up to 48 healthy volunteers
Randomized:	44 healthy volunteers
Treated:	44 healthy volunteers
Completed study:	36 healthy volunteers

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

Each healthy volunteer was administered 180 mg ticagrelor (2 x 90 mg tablets; batch number AM0071) or 600 mg clopidogrel (2 x 300 mg tablets; batch number: 1A006), orally, as a single administration on Day 1 of each treatment period, based on the randomization scheme

and cohort assignment. Background ASA (81 mg once daily; batch number NAA0T3N) was administered as a chewable tablet from either Day -2 (Cohort 1) or Day -1 (Cohorts 2 and 3b).

Duration of treatment

The study duration for each healthy volunteer was to be approximately 9 weeks, comprising 4 visits. Each healthy volunteer participated in 2 treatment periods. The 180 mg loading dose administrations of ticagrelor were separated by a washout period of at least 14 days.

Statistical methods

To assess the effect of platelet transfusion on inhibition of platelet aggregation–final aggregation (IPA-FA) (LTA), inhibition of platelet aggregation–maximum aggregation (IPA-MA) (LTA), and $P2Y_{12}$ Reaction Unit (PRU) (VerifyNow™), 12 hour post-transfusion values were compared by cohort (Cohorts 1, 2, and 3b). Comparisons between the platelet transfusion treatment (test) and the without platelet transfusion treatment (reference) were performed by cohort for Cohorts 1, 2, and 3b. For each cohort, IPA-FA, IPA-MA, and PRU were analyzed using a mixed effects model with sequence, period, and treatment as fixed effects and healthy volunteer nested within sequence as a random effect. Least squares means and associated 95% confidence intervals (CIs) were calculated and presented. Also, the difference between platelet transfusion and without transfusion treatments and associated 95% CIs were calculated and presented. To be included in these analyses, healthy volunteers were required to have valid data in both study periods.

Additional analyses were also performed as described in Section 5.7.1.3.

Safety analyses

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized by cohort, treatment, and time point using descriptive statistics (n, mean, SD, minimum, median, maximum). Categorical variables were summarized by cohort, treatment, and time point in frequency tables (frequency and proportion). Safety variables (eg, clinical laboratory values and vital signs) were reported to the same precision as the source data. Derived variables were reported using similar precision to those from which they were derived (eg, QTc derived from QT interval).

Subject population

In total, 44 healthy volunteers were randomized to the study and all healthy volunteers (100.0%) received treatment (ie, 15 healthy volunteers in Cohort 1, 13 healthy volunteers in Cohort 2, and 16 healthy volunteers in Cohort 3b). Overall, 39 (88.6%) of the healthy volunteers completed treatment, while 36 (81.8%) of the healthy volunteers completed the study.

All of the randomized healthy volunteers were eligible for inclusion in the study according to the inclusion and exclusion criteria.

All healthy volunteers enrolled in Cohort 3b carried 2 functional (*1) alleles (CYP2C19 *1/*1 or *1/*17). There were no healthy volunteers with CYP2C19 *17/*17.

Summary of pharmacodynamic results

One autologous platelet transfusion performed 24 hours (Cohort 1) after a loading dose of ticagrelor (180 mg) resulted in no differences in IPA (final or maximum extent by LTA) or PRU. A statistically significant increase (30.6) in PRU was observed at 72 hours, but the 72 hour post-transfusion PRU values were similar to their respective pre-ticagrelor dosing values (baseline).

One autologous platelet transfusion performed 48 hours (Cohort 2) after a loading dose of ticagrelor (180 mg) resulted in no differences in IPA (final or maximum extent) or PRU at most times post-transfusion, while small, but statistically significant differences in IPA and/or PRU were observed at pre-transfusion (12.8% absolute difference in IPA-final extent and 20 in PRU), 12, and 24 hours post-transfusion (<25% absolute difference in IPA and <28 in PRU). However, the pre-transfusion differences observed in IPA or PRU estimates were statistically significant, suggesting that the differences in IPA and/or PRU seen at 12 or 24 hours post-transfusion from Cohort 2 could mostly be due to the pre-transfusion differences, thereby confounding the interpretation of results for IPA final extent.

Although there were statistically significant differences in IPA or PRU at some time points post-transfusion compared with pre-transfusion, the effects did not appear consistent across all platelet aggregation parameters. Therefore, it is unlikely to be of clinical benefit in reversing the antiplatelet effects of ticagrelor based on the biomarkers IPA and PRU.

One autologous platelet transfusion performed 48 hours after a loading dose of clopidgorel (600 mg in Cohort 3b) resulted in small, but statistically significant decreases in IPA (<19% absolute difference) at 24, 36, and 48 hours post-transfusion for final extent and at 36 and 48 hours for maximum extent. Small increases in PRU (≤43) were observed at 12, 24, and 36 hours. Whether the small effect on the biomarkers would be clinically beneficial remains to be determined.

Summary of safety results

A total of 44 healthy volunteers were randomized into 3 cohorts. Treatment A (180 mg ticagrelor with platelet apheresis and transfusion) and Treatment B (ticagrelor with no platelet apheresis and transfusion) were administered in Cohort 1 and Cohort 2 and Treatment C (600 mg clopidogrel with platelet apheresis and transfusion) and Treatment D (600 mg clopidogrel with no platelet apheresis and transfusion) were administered in Cohort 3b.

No deaths, serious adverse events (SAEs) or discontinuations due to adverse events (AEs) were reported during the study. Adverse events were reported in all cohorts and on all treatments. At least 1 AE was reported by 9 healthy volunteers (60.0%) in Cohort 1, 3 healthy volunteers (23.1%) in Cohort 2, and 6 healthy volunteers (37.5%) in Cohort 3b. All AEs, by PT, were reported for only 1 or 2 healthy volunteers. Two healthy volunteers (1 each in Cohort 1 and Cohort 3b) reported AEs which were considered to be related to the

investigational products. Most of the AEs were considered to be mild in severity by the Investigator and no severe AEs were reported during the study in any cohort.

Variation in mean and median clinical laboratory evaluations and vital signs was observed, however no trend was demonstrated over time, between cohorts or between treatments. Abnormal electrocardiogram values were reported, but none were considered to be clinically significant by the Investigator. Except for a pretreatment AE of mild ecchymosis for a healthy volunteer in Cohort 3b, there were no changes in physical examinations compared to baseline reported during the study which were considered to be clinically significant by the Investigator.

Conclusions