AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130L00012
Edition Number	Final Version v2.1
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A Randomized, Open Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease

Study dates: First patient enrolled: 17 April 2012
Last patient last visit: 10 May 2013

Phase of development: Therapeutic use (IV)

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

Study centre(s)

The study was conducted in 6 centres in the United States of America.

Publications

Clavijo LC, Maya J, Carlson G, Teng R, Caplan R, Price MJ. A Randomized, Open-label, Crossover, Multicenter Study of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease (CAD). Circulation 2013;128:A14467.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	PD	To compare the on-treatment platelet reactivity of ticagrelor versus clopidogrel at the 2-hour time point after a loading dose of each as measured by PRU using VerifyNow™ in Hispanic patients with stable CAD on chronic low dose ASA.	Inhibition of the $P2Y_{12}$ receptor at 2 hours after loading dose with ticagrelor compared with clopidogrel as measured by PRU from VerifyNow™ in Hispanic patients. The difference in LS means in PRU and associated 95% CI were compared between patients who received ticagrelor and those who received clopidogrel.
Secondary	PD	Compare the on-treatment platelet reactivity of ticagrelor versus clopidogrel at the 0.5- and 8-hour time points after a loading dose of each as measured by PRU using VerifyNow™ in Hispanic patients with stable CAD on chronic low-dose ASA.	Inhibition of the $P2Y_{12}$ receptor at 0.5 and 8 hours after loading dose with ticagrelor compared with clopidogrel as measured by PRU from VerifyNow™ in Hispanic patients.
Secondary	PD	Compare the on-treatment platelet reactivity of ticagrelor versus clopidogrel at the 2- and 8-hour time points on Day 7 and end of dosing interval (12 hours after last evening dose of ticagrelor and 24 hours after the last morning dose of clopidogrel) on Day 8 as measured by PRU using VerifyNow™ in Hispanic patients with stable CAD on chronic low-dose ASA.	Inhibition of the $P2Y_{12}$ receptor at 2 hours, 8 hours and end of dosing interval after 7 days of administration with ticagrelor compared with clopidogrel as measured by PRU from VerifyNow™ in Hispanic patients

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
			Percent reduction in platelet $P2Y_{12}$ receptor activity measured by VerifyNow™ on PRU, represented as percentage change from baseline (pre-treatment) where: % reduction from baseline = $\left(1 - \left[\frac{\text{PRU after study drug}}{\text{PRU at baseline}}\right]\right) \times 100\%$ Percentage IPA as measured by VerifyNow™ represented as the percentage change from BASE (on-treatment) - an independent measurement based on the rate and extent of platelet aggregation in the BASE channel.
Secondary	PK	To evaluate plasma concentration of ticagrelor and its active metabolite AR–C124910XX at times of the VerifyNow™ assessment	Ticagrelor and AR–C124910XX concentrations were reported. PK parameters were evaluated in a separate report.
Safety	Safety	To assess the safety of ticagrelor by assessment of AEs, physical examination and vital signs.	Safety endpoints, including AEs, physical examination findings, and vital signs. 12-lead ECG, clinical chemistry, haematology, urine/blood pregnancy test, and urinalysis were collected at screening only.
Exploratory	Genetic	To collect and store DNA for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to ticagrelor and clopidogrel.	The exploratory analysis may be conducted, and reported separately.

AE Adverse event; ASA Acetylsalicylic acid; CAD Coronary artery disease; CI Confidence interval; DNA Deoxyribonucleic acid; ECG Electrocardiogram; IPA Inhibition of platelet aggregation; LS Least squares; PD Pharmacodynamic; PK Pharmacokinetic; PRU $P2Y_{12}$ Reaction Units.

Study design

This was a multi-centre, randomised, open-label, multiple-dose, crossover study of the onset and repeated dose administration antiplatelet effect of ticagrelor compared with clopidogrel with chronic low-dose acetylsalicylic acid (ASA; 75 to 100 mg) as background therapy in Hispanic patients with stable coronary artery disease (CAD).

Patients were randomised to receive either Treatment A (clopidogrel 600 mg loading dose followed by 75 mg once daily [od] for 7, 8, or 9 days) followed by Treatment B (ticagrelor

180 mg loading dose followed by 90 mg twice daily [bd] for 7, 8, or 9 days) or Treatment B followed Treatment A, each separated by a washout period of 10 to 14 days.

Target patient population and sample size

The target patient population for this study was self-identified Hispanic patients with stable CAD who were taking 75 to 100 mg ASA daily treatment. Patients enrolled into the study had to have either stable angina pectoris (current or history of) with objective evidence of CAD, a previous myocardial infarction (MI) or previous revascularisation history (ie, percutaneous coronary intervention [PCI] or coronary artery bypass graft).

The primary outcome of this study was the comparison of ticagrelor with clopidogrel in $P2Y_{12}$ receptor inhibition at 2 hours post loading dose, as measured by P2Y12 Reaction Units (PRUs) using VerifyNow™. A sample size of 12 completed patients was required to provide 90% power to detect a difference of 100 PRUs between ticagrelor and clopidogrel at 2 hours post loading dose, assuming a standard deviation of 93 PRUs, correlation of 0.5 between paired observations, and a two-sided alpha level of 0.05. Based on a need to enrol a cohort of sufficient size for clinical credibility and to evaluate $P2Y_{12}$ receptor inhibition at secondary time points (other than the primary 2 hour post loading dose) and to collect potential adverse events (AEs), it was planned that 34 patients would be enrolled in order to ensure 28 patients were evaluable. This would provide more than 99% power to detect the anticipated primary outcome effect.

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

The dosage for the active ticagrelor treatment was a 180 mg loading dose followed by 90 mg bd maintenance dose for 7, 8, or 9 days. For the clopidogrel comparator, a 600 mg loading dose followed by 75 mg od maintenance dose for 7, 8, or 9 days was used.

Two batches of ticagrelor and one batch of clopidogrel were used in this study. Individual batch numbers and further information are included in the clinical study report.

Duration of treatment

This study consisted of 2 treatment periods. During each period, patients received one of the 2 possible treatments for 7 to 9 days. There was a 10 to 14 day washout period between the 2 treatments. The study duration for each patient was up to 11 weeks.

Statistical methods

The primary analysis of the difference between ticagrelor and clopidogrel in PRU at 2 hours was analysed using a mixed effect model with fixed effects for period (I/II), treatment sequence (AB/BA), treatment (A/B), and a random effect for patient within sequence. The primary analysis specified in the protocol included pre-dose PRU as a covariate. Pre-dose PRU was included in a sensitivity analysis. Treatment level means were estimated using least squares (LS) means and 2-sided 95% confidence intervals (CIs). Tests were evaluated with a 2-sided alpha level of 0.05. Residual plots were used to assess the distribution assumptions

underlying the analysis. If the assumptions were violated, a Wilcoxon signed rank test was to be used.

Secondary analyses of PRUs at other time points were analysed with similar mixed effects models. Safety was evaluated using descriptive statistics.

Patient population

A total of 53 patients were screened, and 40 enrolled (met all inclusion and no exclusion criteria) from 6 centres in the United States of America. Of these, 38 patients completed 14 days of treatment and 39 patients completed a follow-up visit. One patient discontinued from the study (withdrew consent) during ticagrelor treatment (last study dose on Day 2, discontinuation from study on Day 4) and did not crossover to the clopidogrel treatment period.

The mean (standard deviation [SD]) age of patients in randomised patients was 63.8 (8.8) years. There were 18 patients (45%) who were ≥65 years old and 28 patients (70.0%) were male. The mean body mass index (BMI) was 30 kg/m^2 and 43.6% of all patients were obese (BMI >30 kg/m^2). In total, 27 patients (67.5%) had a borderline or abnormal baseline 12-lead electrocardiogram reading.

There were 34 patients (85.0%) with relevant conditions other than cardiovascular disease. Of these, 30 patients had current conditions while 4 patients had past conditions. There were 33 patients (82.5%) that had undergone a relevant surgery. The majority of patients had experienced a previous PCI (32 patients, 80.0%) or a MI (26 patients, 65.0%). The following medical conditions were ongoing in the majority of patients: dyslipidaemia including hypercholesterolaemia (39 patients, 97.5%), hypertension (38 patients, 95.0%), and Type II diabetes mellitus (21 patients, 52.5%).

Summary of pharmacodynamic results

Primary

The unadjusted mean (SD) PRU as measured by VerifyNow™ at 2 hours after loading dose was lower for ticagrelor (34.1 [31.6]) compared with clopidogrel (201.3 [87.5]). The LS mean difference in PRU between the 2 treatment groups (ticagrelor minus clopidogrel) was statistically significant (Difference: -167.2, 95% CI [-197.0, -137.4], p<0.001). This indicated the mean inhibition of $P2Y_{12}$ receptors at 2 hours after loading doses was greater in the ticagrelor treatment group compared with the clopidogrel treatment group.

Sensitivity analyses were consistent with the primary analysis.

Secondary

There was a larger mean percent reduction from baseline in PRU activity at 2 hours after loading dose as measured by VerifyNow™ for patients who received ticagrelor compared with clopidogrel (86.3% and 28.7% for ticagrelor and clopidogrel, respectively). This resulted in a statistically significant difference in LS means between treatment groups of 57.6

percentage points (95% CI [48.4, 66.8], p<0.001). In addition, the LS mean percent inhibition of platelet aggregation (IPA) from BASE at 2 hours after loading dose as measured by VerifyNow™ was 87.9% for patients who received ticagrelor compared with 29.2% for those who received clopidogrel. The difference between treatment groups in LS means was statistically significant (Difference: 58.7 percentage points, 95% CI [49.9, 67.5], p<0.001).

The unadjusted mean PRU as measured by VerifyNow™ at all other time points was smaller in the ticagrelor group compared with clopidogrel and all secondary endpoints showed a statistically significant benefit of ticagrelor compared with clopidogrel in platelet function.

Greater receptor inhibition at 0.5 hours and 8 hours post loading dose was observed for ticagrelor compared with clopidogrel as indicated by the mean PRU activity as measured by VerifyNow™ (ticagrelor: 134.6 and 34.0, clopidogrel: 266.6 and 202.8 for 0.5 hours and 8 hours, respectively). A statistically significant difference in LS means between treatment groups for percent reduction from baseline in platelet $P2Y_{12}$ receptor activity as measured by VerifyNow™ was observed at both time points (0.5 hours: Difference: 48.2 percentage points, 95% CI [35.4, 61.0], p<0.001; 8 hours: Difference: 58.2 percentage points, 95% CI [46.0, 70.4], p<0.001). Similarly, a statistically significant difference in LS means between treatment groups for percent IPA from BASE as measured by VerifyNow™ was observed at 0.5 hours (Difference: 42.6 percentage points, 95% CI [29.1, 56.0], p<0.001) and 8 hours post loading dose (Difference: 54.8 percentage points, 95% CI [44.5, 65.0], p<0.001). The 0.5-hour secondary time point result demonstrated that ticagrelor (90 mg bd) has a faster onset of platelet inhibition than clopidogrel (75 mg od) in Hispanic patients with CAD on chronic low dose ASA.

At 2- and 8-hour time points on Day 7, after multiple doses of ticagrelor and clopidogrel, a statistically significant decrease (p<0.001) in LS mean PRU as measured by VerifyNow™ was observed for ticagrelor compared with clopidogrel (2 hours: ticagrelor: 28.5, clopidogrel: 179.0, Difference in LS means: -150.5, 95% CI [-176.9, -124.1], 8 hours: ticagrelor: 38.7, clopidogrel: 178.9, Difference in LS means: -140.2, 95% CI [-168.4, -111.9]). Statistically significant (p<0.001) differences between treatment groups in the percent reduction from baseline and percentage inhibition from BASE as measured by VerifyNow™ were also observed at these time points. A similar pattern of statistically significant treatment differences was observed at the end of dosing interval on Day 8, indicating a larger inhibitory effect of ticagrelor than clopidogrel across the maintenance dosing interval.

Summary of safety results

A total of 40 patients received at least 1 dose of study drug and were included in the safety analysis set. The mean duration of treatment across all patients was 15.6 days (7.8 days for ticagrelor and 7.9 days for clopidogrel), with a mean cumulative dose of 1498.5 mg for ticagrelor and 1151.9 mg for clopidogrel.

Eleven patients experienced a total of 19 AEs with a slightly higher incidence of AEs in the clopidogrel group (15.4%) than the ticagrelor group (12.5%). The majority of AEs were mild in intensity, with 1 patient in each treatment group experiencing a moderate AE and no

patients experiencing severe AEs. The most frequently occurring AEs overall were headache (7.5%), dyspnoea and fall (5.0% each).

There were no fatalities, no other serious AEs during the study period, no bleeding events, and no AEs that led to discontinuation of study medication. Three patients (all within the ticagrelor group) had AEs that were assessed by the investigator as having reasonable possibility of being caused by the investigational product.

As the majority of patients were diabetic, many had abnormal high glucose values at Screening (67.5% and 69.2% for ticagrelor and clopidogrel, respectively). All other laboratory values falling outside of the normal range occurred in a maximum of 6 patients in any treatment group.

There were no notable findings or differences between treatment groups in vital sign parameters, and body weight.