Clinical Study Report Synopsis

Drug Substance	Ticagrelor
Study Code	D5130L00013
Edition Number	Final
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A Randomized, Open Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in African American Patients with Stable Coronary Artery Disease

Study dates: First patient enrolled: 28 March 2012
Last patient last visit: 04 September 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 8 centres in the United States of America.

Publications

Waksman, R, Maya, J, Angiolillo, D.J, Carlson, G, Teng, R, Caplan, R. Ferdinand, K. CRT-99 Ticagrelor versus clopidogrel in African American patients with stable coronary artery disease: A randomized, open-label, multiple-dose, crossover study. J Am Coll Cardiol Intv. 2014:7(2_S):S6.

Waksman, R, Maya, J, Angiolillo, D.J, Carlson, G, Teng, R, Caplan, R, Ferdinand, K. Ticagrelor versus clopidogrel in African American patients with coronary artery disease and diabetes mellitus. J Am Coll Cardiol. 2014:63(12_S):A211.

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 African American 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 African American 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 African American 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 African American patients.
Secondary	PD	Compare on-treatment platelet reactivity of ticagrelor versus clopidogrel at the 2-hour, 8-hour timepoints 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 African American 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 the decrease in PRU from VerifyNow™ in African American patients.

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Secondary	PD		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 = $\left(1 - \left[\frac{\text{PRU after study drug}}{\text{PRU at baseline}}\right]\right) \times 100\%$
Secondary	PD		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.
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 P2Y12 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 African American 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 by 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 African American patients with stable CAD who were taking 75-100 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 to14 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 had been 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 50 patients were screened, and 34 enrolled (met all inclusion and no exclusion criteria) from 8 centres in the United States of America. Thirty patients completed 14 days of treatment and 31 patients completed a follow-up period. Three patients discontinued from the study during ticagrelor treatment and did not crossover to the clopidogrel treatment period. Of these, 1 patient (E0201105) experienced an AE of acute MI on Day 22 during the washout period following completion of ticagrelor treatment, and the remaining 2 patients (E0206109 and E0208004) withdrew on Day 7 and 11, respectively (withdrawal by patient). In addition, 1 patient (E0201102) experienced the AE of haemorrhoidal haemorrhage leading to discontinuation of treatment with ticagrelor but crossed over to and completed treatment with clopidogrel.

The mean (standard deviation [SD]) age of randomised patients was 62.3 (6.7) years. There were 12 patients (35.3%) who were ≥65 years old and 23 patients (67.6%) were male. The mean body mass index (BMI) was 32.3 kg/m^2 and 64.7% of all patients were obese (BMI >30 kg/m^2). In total, 22 patients (64.7%) had a borderline or abnormal baseline 12-lead electrocardiogram (ECG) reading.

There were 30 patients (88.2%) with relevant conditions other than cardiovascular disease. Of these, all 30 patients had current conditions while none had past conditions. There were 27 patients (79.4%) that had undergone a relevant surgery. The majority of patients had experienced a previous PCI (22 patients, 64.7%). All patients enrolled in the study (34 patients, 100.0%) reported the medical conditions of dyslipidaemia including hypercholesterolemia and hypertension. Type II diabetes mellitus was reported by half the patients in the study (17 patients, 50.0%)

Summary of pharmacodynamic results

Primary

The unadjusted mean (SD) PRU as measured by VerifyNow™ at 2 hours after loading dose was lower for ticagrelor treatment (26.6 [28.4]) compared with clopidogrel treatment (211.1 [76.4]). The LS mean difference in PRU between the 2 treatments (ticagrelor minus clopidogrel) was statistically significant (Difference: -183.6, 95% CI [-213.9, -153.3], $p<0.001$). This indicated the mean inhibition of $P2Y_{12}$ receptors at 2 hours after loading doses was greater with ticagrelor treatment compared with clopidogrel treatment.

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 (90.1% and 24.3% for ticagrelor and clopidogrel, respectively). This resulted in a statistically significant difference in LS means between treatment groups of 65.9 percentage points (95% CI [56.5, 75.3], 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 90.1% for patients who received ticagrelor compared with 25.6% for those who received clopidogrel. The difference between treatments in LS means was statistically significant (Difference: 64.5 percentage points, 95% CI [55.2, 73.9], 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: 157.3 and 26.3, clopidogrel: 277.9 and 192.6 for 0.5 hours and 8 hours, respectively). A statistically significant difference in LS means between treatments 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: 35.7 percentage points, 95% CI [22.2, 49.2], p<0.001; 8 hours: Difference: 60.9 percentage points, 95% CI [51.0, 70.8], p<0.001). Similarly, a statistically significant difference in LS means between treatments for percent IPA from BASE as measured by VerifyNow™ was observed at 0.5 hours (Difference: 32.4 percentage points, 95% CI [20.7, 44.2], p<0.001) and 8 hours post loading dose (Difference: 59.0 percentage points, 95% CI [48.2, 69.7], 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 African American 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: 22.9, clopidogrel: 157.8, Difference in LS means: -135.0, 95% CI [-160.4, -109.5], 8 hours: ticagrelor: 28.5, clopidogrel: 146.5, Difference in LS means: -118.1, 95% CI [-143.9, -92.2]). Statistically significant (p<0.001) differences between treatments 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 34 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 15.0 days (7.6 days for ticagrelor and 8.2 days for clopidogrel).

Seven patients experienced a total of 12 AEs with a higher incidence of subjects with AEs in the ticagrelor group (17.6%) than the clopidogrel group (6.5%). All AEs were mild or moderate in intensity, with no patients experiencing severe AEs in either group. The only AEs reported more than once were dyspnoea which was experienced by 2 patients in the ticagrelor group, and contusion which was reported twice for the one patient in the ticagrelor group.

There were no fatalities in this study. One serious AE (SAE) was reported during the study period, the SAE of acute myocardial infarction occurred during the washout period following ticagrelor. Three bleeding events were reported, two during treatment with ticagrelor (haemorrhoidal haemorrhage and epistaxis) and one after clopidogrel (vaginal haemorrhage). There was one AE that led to discontinuation of ticagrelor; the event of haemorrhoidal haemorrhage led to patient E0201102 discontinuing from ticagrelor treatment. Four patients (three during ticagrelor only and one during both ticagrelor and clopidogrel) had AEs that were considered by the investigator as related to treatment.

There were no notable findings or differences between ticagrelor treatment and clopidogrel treatment in laboratory results, vital sign parameters, and body weight.