Clinical Study Report

Drug Substance	Ticagtrelor
Study Code	D5130L00053
Edition Number	Version 1.0
Date	Nov. 30th, 2014

A Multicentre, Open-label, Randomized, 6-week, Phase IV Study of the Onset and Maintenance of the Antiplatelet Effect of Ticagrelor Compared with Clopidogrel with Aspirin as Background Therapy in Chinese Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)

Study dates:	First subject enrolled: 15/05/2013
	Last subject last visit: 18/03/2014
Phase of development:	Therapeutic use (IV)

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

SYNOPSIS

Drug Substance:	Ticagrelor	**STUDY SYNOPSIS**	
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A Multicentre, Open-label, Randomized, 6-week, Phase IV Study of the Onset and Maintenance of the Antiplatelet Effect of Ticagrelor Compared with Clopidogrel with Aspirin as Background Therapy in Chinese Patients with Non-ST or ST Elevation Acute Coronary Syndromes (ACS)

Study centre(s): There were 5 study centres in China, which participated this study.

Table 1 Study dates

Study dates		*Phase of development*
First subject enrolled	15/05/2013	Phase IV
Last subject completed	18/03/2014	

Publications

Under discussion

Study Objectives and criteria for evaluation

Primary objective

The primary objective was to test the hypothesis that the onset of the antiplatelet effect of 180mg-loading-dose ticagrelor is more rapid and greater than 600mg-loading-dose clopidogrel as evaluated by $P2Y_{12}$ reaction units (PRU) measured by Verify Now™ P2Y12 assay at 2 hours after first dose of study drug in Chinese patients with non-ST or ST elevation acute coronary syndromes (ACS).

Secondary objectives

To determine the effect on platelet aggregation of ticagrelor compared with clopidogrel by PRU measured by Verify NowTM P2Y12 assay at 0.5 hour, 8 hours, 24 hours and 6 weeks after first dose of study drugs.

Safety objectives

To assess the safety and tolerability of ticagrelor compared with clipidogrel in Chinese patients with ACS by evaluation of adverse events

Table 2 Objectives and variables

Objectives			***Variables***	
Priority	***Type***	***Description***	***Description***	***Method of assessment and derivation***
Primary	PD	The primary objective was to test the hypothesis that the onset of the antiplatelet effect of 180mg-loading-dose ticagrelor was more rapid and greater than 600mg-loading-dose clopidogrel as evaluated by PRU measured by Verify Now™ P2Y12 assay at 2 hours after first dose of study drug in Chinese patients with ACS.	The primary variable was the percentage inhibition of the $P2Y_{12}$ receptor at 2h after first dose of study drug as calculated by the baseline PRU value in the blood sample and PRU value in the blood sample at 2h following first dose of study drug determined on Verify Now™ $P2Y_{12}$, using the following formula: % inhibition of the $P2Y_{12}$ receptor = {1-[(PRU at 2h post treatment) / (PRU at baseline)]}×100%.	See SAP, Section 4.2.1
Secondary	PD	To determine the effect on platelet aggregation of ticagrelor compared with clopidogrel by PRU measured by Verify Now™ P2Y12 assay at 0.5 hour, 8 hours, 24 hours and 6 weeks after first dose of study drugs.	The secondary variables were the percentage inhibitions of the $P2Y_{12}$ receptor in the blood sample at 0.5h, 8h, 24h and 6w after first dose of study drug, as calculated by the baseline PRU value in the blood sample and PRU values in the blood sample at 0.5h, 8h, 24h and 6w following first dose of study drug determined on Verify Now™ $P2Y_{12}$.	See SAP, Section 4.2.2
Other	Safety	To assess the safety and tolerability of ticagrelor compared with clopidogrel in Chinese patients with ACS by evaluation of adverse	Safety variables included adverse events, laboratory tests, vital signs, ECG, physical examination, and pregnancy test.	See SAP, Section 4.2.3

Objectives			*Variables*	
Priority	***Type***	***Description***	***Description***	***Method of assessment and derivation***
		events. In addition, the safety data contributed to the life-cycle experience of exposure to ticagrelor.		

Note: Based on the SAP, the primary and secondary variables were described as the percentage inhibition of the $P2Y_{12}$ receptor in this clinical study report, while in the CSP, the pharmacodynamic variables were the PRU value.

Study design

This was a multicentre, open-label, randomized, 6-week, phase IV study of the onset and maintenance of the antiplatelet effect of Ticagrelor compared with Clopidogrel with Aspirin as background therapy in Chinese patients with non-ST or ST elevation acute coronary syndromes (ACS).

Target subjects population and sample size

The subject population were male and female patients aged 18 years and over, with a non- ST or ST segment elevation ACS (index event) and with high risk of secondary thrombotic events. The patients should not have used ticagrelor or clopidogrel within 2 weeks prior to Visit 1. Patients were randomised to treatment as soon as possible after presentation but at the latest within 24 hours of the onset of their index event.

Inclusion criteria

For inclusion in the study, subjects fulfilled the following criteria:

1. Provision of informed consent prior to any study specific procedures

2. Female or male aged at least 18 years

3. Females of child-bearing potential (i.e., females who were not chemically or surgically sterilised or females who were not post-menopause) must have a negative urine pregnancy test at enrolment and be willing to use reliable contraception.

4. Index event of non-ST or ST segment elevation ACS. The patient should be hospitalised for chest pain and potential ACS and the onset of the most recent cardiac ischaemic symptoms of the index event must occur within the 24 hours before randomisation and be documented by cardiac ischaemic symptoms[a] of ≥10 minutes duration at rest[b] and:

   Persistent ST segment elevation[c] ≥1mm (0.1mV) in 2 or more contiguous leads and primary PCI planned

or

New or presumed new left bundle branch block (LBBB) and primary PCI planned

or

Cardiac ischaemic symptoms[a] of ≥10 minutes duration at rest[b] and ST segment changes on ECG indicative of ischaemia:

Either

ST segment depression[d] ≥1mm (0.1mV) in 2 or more contiguous leads

or

Transient ST segment elevation[c] ≥1mm (0.1mV) in 2 or more contiguous leads

Patients should be enrolled and randomised as quickly as possible after presentation in order to maximise potential clinical benefits.

Definition of terms

a. Cardiac ischaemic symptoms: chest pain or discomfort or equivalent (eg, neck or jaw symptoms, dyspnoea believed to represent an angina pectoris equivalent) believed due to impaired coronary flow secondary to atherosclerotic disease. If symptoms were found not to be due to atherosclerosis related myocardial ischaemia before randomisation then the patient should not be randomised (eg, pericarditis, myocarditis, normal coronary arteries by angiography).

b. At rest: started spontaneously or with exercise but did not resolve with rest.

c. ST segment elevation not known to be pre-existing or due to a co-existing disorder (eg, acute pericarditis). Transient ST segment elevation <20 minutes is considered non ST elevation ACS and persistent elevation is considered ST elevation ACS.

d. ST segment depression: Transient or persistent ST segment depression which was not known to be pre-existing nor was as a result of a co-existing disorder (eg, left ventricular hypertrophy) or medication (eg, digoxin).

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Previous enrolment or randomisation in the present study

3. Participation in another clinical study with an investigational product during the last 30 days

4. Contraindication or other reason that clopidogrel or ticagrelor should not be administered (eg, hypersensitivity, active bleeding, moderate or severe liver disease, history of previous intracranial bleed, GI bleed within the past 6 months, major surgery within 30 days)

5. Index event is an acute complication of PCI

6. Patient has planned for an urgent CABG within 24 hours from the randomisation

7. Oral anticoagulation therapy or GP IIb/IIIa receptor antagonists therapy within 30 days prior to randomisation or cannot be stopped (ie, patient requires chronic therapy)

8. Ticagrelor or clopidogrel or other $P2Y_{12}$ inhibitors within 14 days prior to randomisation

9. Fibrinolytic therapy in the 24 hours prior to randomisation, or planned fibrinolytic treatment following randomisation (eg, for STEMI or pulmonary embolism)

10. Nonselective non-steroidal anti-inflammatory drugs (NSAIDs) and prostacyclins (PGI2) therapy that cannot be stopped

11. History of intolerance or allergy to ASA or clopidogrel or ticagrelor

12. Increased risk of bradycardic events (eg, no pacemaker and known sick sinus syndrome, second degree A-V block, third degree A-V block or previous documented syncope suspected to be due to bradycardia).

13. Patient requires dialysis

14. Platelet count less than $100X10^9/L$

15. Haemoglobin (Hb) level less than 100g/L

16. Killip class ≥ 3 at baseline

17. Recent (within 30 days of dosing) blood donation

18. Pregnancy or lactation

19. Concomitant oral or intravenous therapy (see examples below) with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers within 14 days of study treatment or cannot be stopped for the course of the study.

Strong inhibitors: ketoconazole, itraconazole, voriconazole, telithromycin, clarithromycin, nefazadone, ritonavir, saquinavir, nelfinavir, indinavir, atanazavir, over 1 litre daily of grapefruit juice.

Substrates with narrow therapeutic index: cyclosporine, quinidine.

Strong inducers: rifampin/rifampicin, phenytoin, carbamazepine.

The sponsor should be consulted for enrolment with any concomitant medicines which are suspected of undergoing strong drug-drug interaction

20. Any other condition which in the opinion of the investigator, may either put the patient at risk or influence the result of the study (eg, cardiogenic shock or severe haemodynamic instability, active cancer, risk for non-compliance, risk for being lost to follow up)

Procedures for withdrawal of incorrectly enrolled subjects see Section 5.3 of Clinical Study Protocol (CSP).

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

Investigational product, dosage and mode of administration

Ticagrelor: 90mg tablet. Patients received a loading dose of 180mg ticagrelor tablets (two 90mg tablets) taken orally, followed by 90mg of ticagrelor 12 hours after the first dose. The third dose of ticagrelor was given to patients after the blood sample had been obtained 24 hours after the first dose. Thereafter, the patients took 90mg of ticagrelor orally bd. The total study period was 6 weeks.

Comparator, dosage and mode of administration

Clopidogrel: 75mg tablet. Patients received a loading dose of 600mg clopidogrel tablets (eight 75mg tablets) taken orally. The second dose of clopidogrel had been given to patients after the blood sample had been obtained 24 hours after the first dose. Thereafter, the patients took 75mg of clopidogrel orally od. The total study period was 6 weeks.

Batch numbers: Please see Section 5.4.1.

Duration of treatment

Patients were randomised to treatment no later than 24 hours after the most recent symptoms of the onset of their index event; there was no run-in period. The duration of study treatment for an individual patient was 6 weeks.

Statistical methods

Platelet $P2Y_{12}$ receptor blockade at 2 hours after the first dose was analysed by the Wilcoxon rank sum test. ANOVA and Analysis of covariance (ANCOVA) were used as the sensitivity

analysis. ANCOVA included fitting fixed effect term for treatment group, and platelet aggregation at baseline (Visit 1) as covariates. Least square means and two-sided 95% confidence intervals for the primary comparisons of interest (ticagrelor versus clopidogrel) were calculated.

The full analysis set (FAS) was the primary analysis set for the analysis of platelet $P2Y_{12}$ receptor blockade at 2 hours after the first dose. Platelet $P2Y_{12}$ receptor blockade at 2 hours after the first dose was analyzed for the per protocol set (PPS) as well.

All analyses and summaries for secondary PD variables were based on PPS.

Results

Subject population

There were a total of 60 randomized subjects, in which 29 subjects were treated with ticagrelor (test drug) and 31 subjects were treated with clopidogrel (control drug). The median age for ticagrelor group was 57 yrs vs 61 yrs in clopidogrel group. A total of 10 patients were female patients (2 in ticagrelor group vs. 8 in clopidogrel group) and 47 male patients (26 in ticagrelor group vs. 21 in clopidogrel group).

A total of 57 subjects entered FAS, including 28 (96.55%) subjects in ticagrelor group and 29 (93.55%) subjects in clopidogrel group. A total of 53 subjects entered PPS, including 26 (89.66%) subjects in ticagrelor group and 27(87.10%) subjects in clopidogrel group. A total of 51 patients completed the study, with 26/29(89.66%) and 25/31 (80.65%) patients in ticagrelor and clopidogrel groups, respectively.

Analysis Populations

	Ticagrelor (N=29)	***Clopidogrel (N=31)***	***Total (N=60)***
Randomization	29	31	60
Treated	29 (100.00%)	31 (100.00%)	60 (100.00%)
FAS	28 (96.55%)	29 (93.55%)	57 (95.00%)
PPS	26 (89.66%)	27 (87.10%)	53 (88.33%)
Patients Completed Treatment	26 (89.66%)	25 (80.65%)	51 (85.00%)

The most common reason for prematurely withdrawal (including permanent discontinuation) was due to the need to use GP IIb/IIIa receptor antagonist therapies with 1(3.45%) and 3(9.68%) patient in the ticagrelor group and clopidogrel group, respectively. There was only one subject who had been discontinued from the study due to an adverse event (DAE) in the ticagrelor group, which was upper GI bleeding.

In summary, except gender where females in clopidogrel group were about 4 times as many as in ticagrelor group, ticagrelor group and clopidogrel group were basically balanced with

respect to age, and weight, and subjects' baseline characteristics including baseline diagnostic information, specific/other relevant medical and surgical history, ACS index event, local cardiac biomarker measurements for index event, TIMI risk score, Killip classification, nicotine use and pregnancy, and operations, and time between ACS index events and admission to hospital, and use of concomitant medications, and thus had strong comparability. The overall rates of compliance were similar between the 2 treatment groups and were sufficient to support the objectives of the study. Sufficient numbers of patients were randomised and evaluable to meet protocol-defined power for assessing the study objectives.

Summary of efficacy results

Not applicable.

Summary of pharmacokinetic results

Not applicable.

Summary of pharmacodynamics results

Onset and Maintenance with Mean $P2Y_{12}$ Inhibition Rate

For the primary PD variable (primary end point), in FAS, and in terms of onset of $P2Y_{12}$ receptor inhibition, the mean $P2Y_{12}$ inhibition rate at 2 hours after loading dose was greater with ticagrelor than with clopidogrel (48.2% vs. 9.78%, *P*=0.0021), which is statisitically significant at the 5% level, in PPS analysis, the mean $P2Y_{12}$ inhibition rate at 2 hours after loading dose was significantly (6.15 fold) higher with ticagrelor than with clopidogrel (51.57% vs. 8.38%, *P* <0.0001). The result of PPS was consistent with that of FAS.

For the secondary PD variables, in PPS, the mean $P2Y_{12}$ inhibition rate at 0.5 hour after loading dose showed no significant difference between the ticagrelor group and the clopidogrel group (8.23% vs. -3.91%, P value of Wilcoxon rank sum test =0.0828), while in FAS, there was a significant difference of the mean $P2Y_{12}$ inhibition rate after the loading dose between the ticagrelor group and the clopidogrel group (7.95% vs. -4.45%, the P value of Wilcoxon rank sum test =0.0396). Despite the PPS analysis not being significantly different, the trend was similar to FAS.

For the secondary PD variables, in PPS, the mean $P2Y_{12}$ inhibition rate at 8 hours and 24 hours after loading dose were significantly higher with ticagrelor than with clopidogrel (67.91% vs. 25.38%, P < 0.0001 at 8 hours, and 79.25% vs. 28.76%, P < 0.0001 at 24 hours). The result of FAS was consistent with those of PPS.

During maintenance phase from 24 hours through 6 weeks, in PPS, significantly higher potency of antiplatelet aggregation with ticagrelor than with clopidogrel persisted in terms of the $P2Y_{12}$ inhibition rate (83.78% vs. 24.22% at 6 weeks, P < 0.00001).

By 24 hours after loading dose (in PPS, see Table 49), the maximum value of PRU in ticagrelor was 197.00, meaning that 100% of patients on ticagrelor had their PRU below 240, whereas it had not been found in any protocol-specified time point throughout the study that

100% of patients on clopidogrel had their PRU below 240. Even the lowest maximum value of the range of PRU over time for clopidogrel was 302 (still >240).

In the PPS analysis, with respect to percentage of patients whose PRU was less than 240 (a cut-off threshold level for high residual platelet reactivity (HRPR)) (See Table 50), there were 19 (35.8%) patients whose baseline PRU <240 (with 10 (38.5%) patients in ticagrelor group vs. 9 (33.3%) patients in clopidogrel groups). The percentage of patients whose PRU was less than 240 at 0.5 hour was similar [10 (38.5%) vs. 10 (37.0%), p=1.000] after a loading dose of ticagrelor and clopidogrel, respectively. There was no statistical difference between ticagrelor group and clopidogrel group, while there was a statistical difference between the two study groups at 2 hours , 8 hours, 24 hours, and 6 weeks after loading, respectively,[19 (73.1%) vs. 11 (40.7%)), P=0.0267], [21 (87.5%) vs. 16 (59.3%)), P=0.0309], [25 (100.0%) vs. 19 (70.4%), P=0.0044], [24 (100.0%) vs. 18 (72.0%), P=0.0096]. At 2 hours, 8 hours, 24 hours and 6 weeks after loading in the ticagrelor group, less than 50% of patients had HRPR, while in the clopidogrel group, this was observed only at 8 hours, 24 hours and 6 weeks after loading.

In the PPS analysis, the maximum median value of the $P2Y_{12}$ inhibition rate of the $P2Y_{12}$ receptor in the ticagrelor group was statistically significantly (2.49 fold) higher than that in the clopidogrel group (96.94 % vs. 39.01%, Wilcoxon rank sum test p<0.0001). (See Table 51).

Summary of pharmacokinetic/pharmacodynamic relationships

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

Key safety findings for this study were as follows:

- All 60 randomized patients entered safety set (SS).
- The mean duration of exposure of patients with PLATO dosing regimen was 37.1days and 37.8 days in the ticagrelor group and clopidogrel group, respectively.
- There were a total of 25 patients that experienced at least 1 AE with 44.8% (13/29) and 38.7% (12/31) in the ticagrelor group and the clopidogrel group, respectively. The proportions of patients experiencing at least 1 AE were similar between the 2 treatment groups.
- Individual AEs were similar in frequency and type among the treatment groups.
- The most frequent AEs by PT for ticagrelor were hypertensive heart disease (10.34%, 3/29) and hyperuricemia (10.34%, 3/29), respectively, as well as abnormal hepatic function and back pain (6.90%, 2/29), respectively, while the

most frequent AEs by PT for clopidogrel were hypertensive heart disease, arrhythmia, abnormal hepatic function, and hyperuricemia (each was 6.45%, 2/31, respectively).

- There were only two patients who experienced adverse drug reaction (ADR) in this study, the one (patient #E1305008) in the ticagrelor group experienced an upper gastrointestinal hemorrhage of severe intensity, and the other patient (#E1301010) in the clopidogrel group experienced abnormal hepatic function of mild n intensity, respectively. Both patients recovered.

- There were only 2 serious adverse events (SAEs) reported in this study, in which one SAE (patient #E1305008) was an upper GI hemorrhage that occurred in the ticagrelor group, and judged to be ticagrelor related by the investigator. The other (patient #E1303012) was diagnosed as abnormal hepatic function in the clopidogrel group, which was not judged to be related to clopidogrel by investigator. Both subjects recovered.

- There were no deaths reported in this study.

- There were no clinically significant changes in clinical laboratory evaluations, other than hepatic function as above.

- There were no clinically significant findings relating to vital signs, physical findings, ECGs. However, there were a few types of abnormal laboratory finding without associated clinical symptoms, e.g. increased blood creatinine (149.2 umol/L) occurred in ticagrelor group, and 14 patients experienced abnormal liver function tests with increased ALT, AST, and/or TBIL (changed from “normal before treatment” to become “abnormal after treatment”), with 7 patients in each treatment group.

- Of note, in this study, bleeding-related AEs, dyspnoea and hyperuricemia were classified as Other Significant AEs (OAEs). There was only one case of bleeding-related AE, which was upper GI bleeding of severe intensity (also a SAE) in this study. There was one case of dyspnea which occurred in the clopidogrel group, no dyspnea occurred in the ticagrelor group. A total of 4 cases of hyperuricemia occurred in the study with 3 (10.34%, 3/29) patients in the ticagrelor group and 1 (3.2%, 1/31) patient in the clopidogrel group.

- No thrombotic AEs were reported during the study. There was only one patient (#E1305008) who discontinued study drug due to AE (DAE) with severe upper gastrointestinal hemorrhage that occurred in the ticagrelor group, which was also the only case of bleeding-related AE in this study.

Date of report

Nov. 30th, 2014