**Clinical Study Report Synopsis**

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|---|---|
| Drug Substance | AZD6140 |
| Study Code | D5130L00006 |
| Edition Number | Final Version 1.0 |
| Date | 3 November 2014 |
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# A 30-Day International, Randomised, Parallel-Group, Double-Blind, Placebo-Controlled Phase IV Study to Evaluate Efficacy and Safety of Pre-Hospital vs. In-Hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for PCI (ATLANTIC study)

**Study dates:** First patient enrolled: 12 Sep 2011
Last patient last visit: 14 Nov 2013

**Phase of development:** IV

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

## Study centres

This study was conducted in 112 investigational centres in 13 countries, and 102 ambulance services were involved.

## Publications

American Heart Journal, Volume 165, Issue 4 , Pages 515-522, April 2013, Gilles Montalescot, MD, PhD, Jens Flensted Lassen, MD, PhD, Christian W. Hamm, MD, PhD, et al.

The New England Journal of Medicine, DOI: Sep 1 2014, 371:1016-1027. Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction 2014, Gilles Montalescot, MD, PhD, Arnoud W. Van 't Hof, MD, PhD, Frédéric Lapostolle, M.D., PhD, et al.

## Objectives and criteria for evaluation

**Table S1 Objectives and outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Primary | Efficacy | To assess the efficacy of pre-hospital vs. in-hospital initiation of ticagrelor therapy by comparing the percentage of patients reaching the co-primary endpoint of TIMI flow grade 3 of MI culprit vessel at initial angiography or a ≥70% ST-segment elevation resolution pre- PCI | The co-primary endpoint was:<br>- the percentage of patients reaching TIMI flow grade 3 of MI culprit vessel at initial angiography, or<br>- the percentage of patients with ≥70% ST-segment elevation resolution pre PCI |
| Secondary | Efficacy | To compare the efficacy of pre-hospital vs. in-hospital initiation of ticagrelor therapy by assessing the following endpoints: | |
| | | 1. Composite of death, MI, stroke, urgent revascularisation and acute stent thrombosis during 30 days of study | Percentage of patients with composite of death, MI, stroke, urgent revascularisation, and acute stent thrombosis during 30 days of study |
| | | 2. Composite of death, MI, urgent revascularisation during 30 days of study | Percentage of patients with composite of death, MI, and urgent revascularisation during 30 days of study |

**Table S1 Objectives and outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| | | 3. Acute* stent thrombosis during 30 days of study | Percentage of patients with an acute stent thrombosis episode during 30 days of study |
| | | 4. Thrombotic bail-out with GPIIb/IIIa inhibitors at initial PCI | Percentage of patients receiving thrombotic bail-out with GPIIb/IIIa inhibitors at initial PCI |
| | | 5. Complete (≥70%) ST-segment elevation resolution at 60 minutes post-PCI | Percentage of patients with complete (≥70%) ST-segment elevation resolution at 60 minutes post-PCI |
| | | 6. cTFC at angiography, pre and post PCI | cTFC at angiography, pre and post PCI |
| | | 7. TMPG at angiography, pre and post PCI | Distribution of TMPG at angiography, pre and post PCI |
| | | 8. Time–relationship (from symptom onset to 1st dose intake) on each co-primary endpoint | Percentages of patients reaching TIMI flow grade 3 of MI culprit vessel at initial angiography and with ≥70% ST-segment elevation resolution pre-PCI by time from symptom onset to first dose intake |
| | | 9. Time–relationship (from 1st dose intake to ECG/angiography) on each co-primary endpoint | Percentage of patients with ≥70% ST-segment elevation resolution pre-PCI by time from first dose intake to ECG, and percentage of patients reaching TIMI flow grade 3 of MI culprit vessel by time from first dose to initial angiography |
| | | 10. TIMI flow grade 3 at end of procedure | Percentage of patients reaching TIMI flow grade 3 at end of procedure |
| Safety | Safety | 1. To assess the safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy using PLATO | <u>Bleeding events</u><br>1. Total number of patients with major life-threatening bleeding |

**Table S1 Objectives and outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| | | bleeding definition, within the first 48 h and during 30 days of study | events<br>2. Total number of patients with other major bleeding events<br>3. Total number of patients with minor or major bleeding events<br>The above endpoints were defined according to PLATO bleeding definition (excluded CABG-related bleeding), within the first 48 h and, during 30 days of study |
| | | 2. To assess the safety of pre-hospital vs. in-hospital initiation of ticagrelor therapy in term of adverse events within 30 days of study | <u>Other safety events</u><br>Adverse events, laboratory findings, physical examination, ECG evaluation, vital signs within 30 days of study |

Abbreviations: CABG = coronary artery bypass graft; cTFC = corrected TIMI frame count; ECG = electrocardiogram; h = hour; MI = myocardial infarction; PCI = percutaneous coronary intervention; PLATO = a study of platelet inhibition and patient outcome; TIMI = thrombolysis in myocardial infarction; TMPG = TIMI myocardial perfusion grade; vs = versus

*:acute stent thrombosis replaced by definite stent thrombosis- see SAP.

## Study design

This was a 30-day, randomised, parallel-group, double-blind, placebo-controlled Phase IV, international, multi-centre study to evaluate the efficacy and safety of pre-hospital versus (vs.) in-hospital initiation of ticagrelor therapy in ST-elevation myocardial infarction (STEMI) patients planned for primary percutaneous coronary intervention (PCI).

## Target patient population and sample size

The study included men and women ≥18 years of age, with symptoms of acute myocardial infarction (MI) of more than 30 minutes but less than 6 hours (h) and new persistent ST-segment elevation ≥1 mm in 2 or more contiguous electrocardiogram (ECG) leads. This included patients (not pre-treated for their STEMI) in emergency rooms of non-PCI hospitals as well. The qualifying ECG and inclusion into the study were made solely by the ambulance personnel.

The sample size for the 2 co-primary endpoints was derived from the ST-segment elevation resolution hypothesis. However, the study was sufficiently powered for the 2 criteria. It was hypothesised that 15% of patients in the in-hospital group would achieve complete ST-segment elevation resolution versus 21% in the pre-hospital group (absolute difference of 6%). Taking into account a significance level of 2.5%, 779 evaluable patients were required in each treatment group to provide 80% power using a 2-group Chi-Square test of equal proportions. Assuming a 12% dropout for invaluable or missing ECG criteria, a total of 1770 patients were planned for randomisation and were required to for enrollment in the study to assess the ST-segment elevation resolution difference.

According to various studies, thrombolysis in myocardial infarction (TIMI) flow grade 3 at initial angiography ranges from 15% to 27%. Clinicians agree that a 30% to 35% relative difference between the 2 groups is clinically relevant. In order to hypothesise on the various degree of angiographic reperfusion expected, a table was created to show a range of hypothesis and the related sample size. A statistical difference was shown in the table created (presented in the study protocol). The dropout rate at initial angiography was assumed to be low (less than 8%).

Based on multiplicity procedures, the initial significance level was 2.5%, and the sample size calculation was based on a significance level of 2.5% and 80% power.

**Investigational product and comparator: dosage, mode of administration, and batch numbers**

The investigational product for this study was Ticagrelor (AZD6140) - 90 mg tablets.

During the double-blind period:

- Pre-hospital ticagrelor arm: Patients received a loading dose of 180 mg ticagrelor for the pre-hospital administration followed by placebo for in-hospital administration.
- In-hospital ticagrelor arm: Patients received a placebo for pre-hospital administration followed by 180 mg ticagrelor loading dose for in-hospital administration.

During 30 days active treatment period:

- After the loading dose, all patients received ticagrelor 90 mg (tablet), twice daily, orally, as a maintenance dose during 30 days.

**Duration of treatment**

The duration of treatment was 30 days (blind loading dose phase followed by maintenance period).

**Statistical methods**

Each co-primary endpoint was analysed separately using a logistic regression model with treatment as exploratory variable. For each endpoint the null hypothesis indicated no difference between the 2 groups. The alternative hypothesis was that there was a difference. A

correction procedure was used to adjust for multiplicity while maintaining an overall Type I error rate of 5%.

Secondary endpoints were examined with the use of an analysis identical to the one described for the co-primary endpoints.

The efficacy analysis was based on the modified intention-to-treat (mITT) analysis set (all randomised patients who received at least 1 dose of study medication).

The safety analysis included all randomised patients who received at least 1 dose of study drug.

Safety endpoints were analysed using descriptive methods.

**Patient population**

A total of 1862 consented patients were randomised into the pre-hospital ticagrelor arm (909 patients) or the in-hospital ticagrelor arm (953 patients). The demographic characteristics of the enrolled patients were as expected and similar across the 2 treatment arms.

Median time from randomisation to angiography was 48 minutes, and the median time between the pre- and in-hospital loading doses was 31 minutes. Approximately half the patients in each treatment arm received morphine for the index event and/or PCI.

**Table S2 Patient population and disposition**

| | **Statistic or Category** | **Ticagrelor Pre-Hosp** | **Ticagrelor In-Hosp** | **Total** |
|---|---|---|---|---|
| N randomized | | 909 | 953 | 1862 |
| N (%) of patients who | completed | 844 (92.85%) | 897 (94.12%) | 1741 (93.5%) |
| | discontinued | 65 (71.5%) | 56 (58.8%) | 121 (6.5%) |
| Patients in the full analysis set | | 909 | 953 | 1862 |
| Patients in the safety analysis set | | 908 | 950 | 1858 |
| Patients included in the mITT analysis set | | 906 | 952 | 1858 |

| | | **Randomised Treatment** | | |
|---|---|---|---|---|
| **Characteristic** | **Statistic or Category** | **Ticagrelor Pre-Hosp** | **Ticagrelor In-Hosp** | **Total** |
| **Disposition** | | | | |
| Age (years) | Mean | 60.6 (12.38) | 61.0 (12.49) | 60.8 |
| | Range | 29 to 95 | 26 to 95 | |
| Sex | Male | 736 (81.0%) | 757 (79.4%) | 1493 (80.2%) |

**Table S2 Patient population and disposition**

| | Statistic or Category | Ticagrelor Pre-Hosp | Ticagrelor In-Hosp | Total |
|---|---|---|---|---|
| | Female | 173 (19.0%) | 196 (20.6%) | 369 (19.8%) |
| BMI Group (kg/m$^2$) | <30 kg/m$^2$ | 702 (77.2%) | 747 (78.4%) | 1449 (77.8%) |
| | ≥30 kg/m$^2$ | 177 (19.5%) | 178 (18.7%) | 355 (19.1%) |
| | Unknown | 30 (3.3%) | 28 (2.9%) | 58 (3.1%) |
| **CV Risk Factor, n (%)** | | | | |
| Hypertension | | 384 (42.2) | 411 (43.1) | 795 (42.7) |
| Dyslipidaemia | | 316 (34.8) | 337 (35.4) | 653 (35.1) |
| Diabetes mellitus | | 115 (12.7) | 138 (14.5) | 253 (13.6) |
| **TIMI Risk Score Group, n (%)** | | | | |
| | 0-2 | 552 (60.7) | 573 (60.1) | 1125 (60.4) |
| | 3-6 | 337 (37.1) | 365 (38.3) | 702 (37.7) |
| | >6 | 20 (2.2) | 15 (1.6) | 35 (1.9) |

Abbreviations: BMI = body mass index; Hosp = hospital; Max = maximum; min = minimum; SD = standard deviation

**Summary of efficacy results**

There were no statistically significant differences between the pre- and in-hospital ticagrelor arms for the co-primary efficacy variables TIMI flow grade 3 of the MI culprit vessel at initial angiography and ST-segment elevation resolution ≥70% pre-PCI.

A total of 143 patients (17.4%) in the pre-hospital treatment arm and 145 patients (16.9%) in the in-hospital ticagrelor arm had TIMI flow grade 3 of the MI culprit vessel at initial angiography.

A total of 102 patients (13.2%) in the pre-hospital treatment arm and 102 patients (12.4%) in the in-hospital treatment arm had ST-segment elevation resolution ≥70% pre-PCI.

When analysed by pre-specified patient subgroups, there was a statistically significant difference favouring the in-hospital ticagrelor arm for the TIMI flow grade 3 endpoint in patients with the highest Killip Classification pre-PCI >I ($p = 0.0257$ compared with patients in the pre-hospital ticagrelor arm). For the ST-segment elevation resolution ≥70% endpoint, there was a statistically significant difference favouring the pre-hospital ticagrelor arm in patients who did not receive morphine for the index event/PCI ($p = 0.0249$ compared with patients in the in-hospital ticagrelor arm).

Among the secondary variables, no statistically significant difference was observed between the 2 treatment arms in the composite endpoint of death, MI, stroke, urgent revascularisation, or definite early stent thrombosis, or in the composite endpoint of death, MI, or urgent revascularisation during the 30-day study period.

Definite stent thrombosis was reduced in the pre-hospital ticagrelor arm compared with the in-hospital arm within the first 24 h of the index PCI and during the 30-day study period. No patients in the pre-hospital ticagrelor arm and eight patients (0.8%) in the in-hospital had definite stent thrombosis in the first 24 h (nominal p = 0.008). Two patients (0.2%) in the pre-hospital ticagrelor arm and 11 patients (1.2%) in the in-hospital ticagrelor arm had a definite stent thrombosis during the 30-day study period while on treatment (nominal p = 0.0307).

Overall deaths occurred in 3.3% of patients of pre-hospital ticagrelor arm and 2% of in-hospital ticagrelor arm during the 30 day study period.

The ST-segment elevation resolution ≥70% 1 h post-PCI was numerically in favour of the pre-hospital ticagrelor arm (57.5%) compared with the in-hospital ticagrelor arm (52.5%) (nominal p = 0.0547).

The percentage of patients with TIMI flow grade 3 post –PCI was respectively 82.2% and 80.4% in the pre-hospital and in hospital ticagrelor arms.

The thrombolytic use with GPIIb/IIIa was 8.6% in the pre-hospital ticagrelor arm and 10.5% in the in-hospital ticagrelor arm, but did not reach significance.

**Summary of safety results**

At least 1 dose of the study medication was administered in 908 patients (99.9%) in the pre-hospital ticagrelor arm and 950 patients (99.7%) in the in-hospital ticagrelor arm.

There were no statistically significant differences between the treatment arms in adjudicated non- coronary artery bypass graft (CABG) related major or minor bleeding events within 48 h of first dose or after 48 h post first dose. Non-CABG related major adjudicated bleeding events were reported in 16 patients (1.8%) in the pre-hospital ticagrelor arm and in 15 patients (1.6%) in the in-hospital ticagrelor arm within the first 48hours and 1.2% in both arms during the 30-day study period. Fatal non-CABG-related major adjudicated bleeding events were reported in 3 patients (0.3%) in the pre-hospital ticagrelor arm and in 3 patients (0.3%) in the in-hospital ticagrelor arm during the 30-day study period.

There were no statistically significant differences between the treatment arms in CABG-related major or minor bleeding events within 48 h of first dose or after 48 h post first dose. No fatal CABG-related bleeding events were reported in either treatment arm.

There were no statistically significant differences between the 2 arms in PCI-related major or minor bleeding events within 48 h of first dose or after 48 h post first dose.

Overall, the incidence of bleeding was low whatever the group, the time period within 48 h of first dose or after 48 h post first dose.

The occurrence of adverse events (AEs), serious adverse events (SAEs), or permanent discontinuation of study medication due to AEs (DAEs) was comparable between the

2 treatment arms when on treatment and no clinically significant differences between the treatment groups were observed.

Including bleeding events, 60.9% of patients in the pre-hospital ticagrelor arm and 59.3% in the in-hospital ticagrelor arm reported at least 1 AE while on treatment. Permanent discontinuations of study medication due to AEs (excluding bleeding events) were noted in 5.4% of patients in the pre-hospital ticagrelor arm and 3.9% of patients in the in-hospital ticagrelor arm.

Including bleeding events, on-treatment SAEs were reported in 15.4% of patients in the pre-hospital ticagrelor arm and 15.1% in the in-hospital ticagrelor arm. Of these, SAEs considered to be related to the study treatment were reported in 2% of the patients in the pre-hospital ticagrelor arm and 1.5% of patients in the in-hospital ticagrelor arm. SAEs leading to death were reported in 2.9% of patients in the pre-hospital ticagrelor arm and 1.7% of patients in the in-hospital ticagrelor arm. Post-treatment SAEs were reported in 1.3% of patients in the pre-hospital ticagrelor arm and 0.6% of patients in the in-hospital ticagrelor arm. In three of these patients, all in the pre-hospital ticagrelor arm (0.3%), the SAE led to death.

Most common SAEs leading to death were cardiogenic shock, cardiac arrest, mechanical complication and heart failure. Death due to spontaneous bleeding was reported only in 2 patients (0.2%) each in the 2 treatment arms during the 30-day treatment period.

While on-treatment, the incidence of dyspnoea was higher in the in-hospital ticagrelor arm (9.3%) compared with the pre-hospital ticagrelor arm (7.4%). These were considered to be SAEs in 0.2% of patients in the pre-hospital ticagrelor arm and 0.1% of patients in the in-hospital ticagrelor arm.

No clinically significant differences in the haematology, clinical chemistry, vital signs, ECG evaluations, or physical examination results were observed between the 2 treatment groups.