Observational Study Synopsis

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A Multi-Centre, Prospective Cohort, Non-Interventional Study about Evaluation on the Safety of Ticagrelor among Chinese ACS Patients

Sponsor:	AstraZeneca Investment (China) Co., Ltd.
Study dates:	First patient enrolled: May 28th, 2015 Last patient enrolled: March 22th, 2016
Phase of development:	Therapeutic use (IV)
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OBSERVATIONAL STUDY FINAL REPORT SUMMARY (CSR SYNOPSIS)

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Background/Rationale:

Ticagrelor is a direct-acting, oral, reversibly binding $P2Y_{12}$ receptor antagonist approved in China and a large number of other countries for the prevention of thrombotic cardiovascular events in patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG).

The PLATO (PLATelet inhibition and patient Outcomes, D5130C05262) study was an 18,624 patients, randomized, double-blind, parallel group, phase III, efficacy and safety study of ticagrelor compared to clopidogrel for prevention of vascular events in patients with ACS [1]. The study only included 416 ACS patients in China, in which 22 major bleeding events were reported. Due to drug intensive monitoring (DIM) requirement in China, safety evidence on ticagrelor among at least 3,000 Chinese ACS patients is needed.

The DAYU study (D5130C00087, NCT01870921) enrolled 2,004 ACS patients in China and the study report was completed on July 4, 2016. During 1 year follow up treatment with ticagrelor, the incidence of fatal/life-threatening and major bleeding events were 0.8% and 1.3%, respectively; serious adverse events (SAEs) other than bleeding were reported in 5.8% of the patients during treatment. The incidence of major CV events (cardiovascular death, MI, stroke) in DAYU was 4.2% during 1 year follow up. The safety profile in DAYU was generally consistent with the known safety profile of ticagrelor as described in the current approved prescribing information.

The YINGLONG study was initiated as part of DIM studies and was to evaluate safety and tolerability of ticagrelor, especially bleeding events and other SAEs during 1-year follow up in Chinese ACS patients.

Objectives

Primary objective
To describe the safety and tolerability of ticagrelor, by assessment of adverse events (AEs) (characteristics, reporting rate, severity, relationship and risk factors), especially bleeding events and other serious adverse events during 1-year follow up in Chinese ACS patients.

Secondary objectives

- To describe the incidence of major CV events (including CV death, MI, stroke) during 1-year follow up in Chinese ACS patients treated with ticagrelor
- To explore the incidence of fatal/life-threatening bleeding and major bleeding in different subgroup:
  - Male vs. female

  - Age <75years vs. age ≥75years
  - With GpIIb/IIIa inhibitors vs. without GpIIb/IIIa inhibitors
  - Patients with invasive therapy vs. patients with medically management therapy
- To observe the characteristics of the patients free of major CV events with ticagrelor
- To observe the treatment compliance with ticagrelor and reason for unplanned discontinuation among Chinese ACS patients

Methods:

The study was a multi-centre, prospective cohort, non-interventional study conducted in the department of cardiology from 19 tier-2 or 3 hospitals in China.

The study enrolled Chinese patients aged over 18, diagnosed with ACS and treated with at least one tablet of ticagrelor. The patients were followed up to 1 year. Major CV events and AEs were followed up from enrolment to the last visit. The treating doctor was in charge of prescribing or discontinuing ticagrelor (study drug) according to clinical practice. All eligible patients who were prescribed ticagrelor at the participating hospitals were enrolled until the quota of 1,000 patients had been reached. The interim analysis was conducted in Q4 2016, and the cut-off date for data was June 22, 2016. This is the final analysis of all collected data.

Inclusion/exclusion criteria

Key inclusion criteria:

1. Provision of informed consent prior to any study specific procedures
2. Chinese female or male aged at least 18 years old
3. Index event of non-ST or ST segment elevation ACS
4. At least one tablet of ticagrelor taken before enrolment

Key exclusion criteria:

1. Participation in another clinical study with an investigational product during the last 6 months
2. Previous enrolment in the present study
3. Allergy or any other contraindication to ticagrelor as described in ticagrelor China prescribing information (PI)

Statistical methods

All summaries were performed on the Safety Population (all patients who received at least one dose of ticagrelor, and for whom any post-dose data were available) unless otherwise stated. For continuous data, descriptive statistics were presented as number of patients (n), mean, SD, median, minimum and maximum unless otherwise specified. For categorical data, the frequency and percentage of patients in each category were presented.

Both the primary safety assessments of all AEs, bleeding events and SAEs, along with the secondary assessments were described using presentations of descriptive statistics. The incidence of major CV events (CV death, MI, stroke) and bleeding was estimated using Kaplan-Meier survival methodology on the Safety

Population. The association of patient characteristics with major CV events was explored via Cox proportional hazards model.

Results:

Patient population

This study enrolled 1,066 patients. 1,041 patients who provided any post-dose data after starting ticagrelor were included in the Safety Population. The median age was 61.0 years old, and the majority of patients [934 (89.7%)] were below 75 years old. 79.0% of patients were male and 21.0% of patients were female. The mean BMI of patients was 24.7 kg/m^2. Most of patients were Han ethnic. More patients had final diagnosis of index event with a STEMI (63.5%) than a NSTEMI (24.5%) or an UA (12.0%). The median time between hospitalization for index event and first dose was 0 day. Majority patients (647/1,041, 62.2%) took the first dose on the same day of hospitalization for the index event. The median number of days in hospital was 9.0 days. 93.5% of patients (973/1,041) completed 1-year follow-up.

Exposure

The mean exposure on study treatment was 246.37 days and a median exposure of 357 days. A total of 675 (64.8%) patients had > 6 months of exposure to study treatment; 47.1% of patients had > 1 year of exposure to study treatment; 0.5% of patients had > 13 months of exposure to study treatment.

Summary of safety results

Adverse events

AEs were reported in 403 (38.7%) patients during the treatment and in 443 (42.6%) patients during the study. AEs excluding bleedings were reported in 352 (33.8%) patients during treatment and in 395 (37.9%) patients during the study. During the treatment period, 141 (13.5%) patients reported AEs assessed by the investigator as causally related to ticagrelor. AEs that led to study drug discontinuation were reported in 41 (3.9%) patients. 272 (26.1%) patients reported AEs were mild in intensity during the treatment and 285 (27.4%) patients reported during the study. 82 (7.9%) patients reported AEs were moderate during the treatment and 94 (9.0%) patients reported during the study. 49 (4.7%) patients reported AEs were severe during the treatment and 64 (6.1%) reported during the study. The majority of the AEs were mild in intensity.

The 3 most commonly reported AEs including bleeding events during treatment by PT were dyspnoea [37 (3.6%) patients], petechiae [30 (2.9%) patients], and chest discomfort [28 (2.7%) patients]. When AEs of bleeding were excluded, the 3 most commonly reported AEs during treatment by PT were dyspnoea [37 (3.6%) patients], chest discomfort [28 (2.7%) patients], and unstable angina [24 (2.3%) patients].

Bleeding events

Bleeding AEs were reported in 107 (10.3%) patients during treatment and in 112 (10.8%) patients during the study. Most bleedings were considered of mild in intensity by the investigators. During the study, 11 (1.1%) patients experienced PLATO-defined major bleedings. 6 (0.6%) of those patients were classified as life-threatening/fatal bleedings, among which 1 (0.1%) was fatal (ICH). 5 (0.5%) of those patients

experienced other major bleeding events. 25 (2.4%) patients experienced PLATO-defined minor bleedings. 83 (8.0%) patients experienced PLATO-defined minimal bleedings.

11 (1.1%) patients reported major bleeding events within 12 months after exposure to ticagrelor with a KM estimated event rate (95% CI) of 1.6% (0.9%, 2.8%).

Rates of PLATO-defined fatal/life-threatening and major bleeding events were generally considered consistent across multiple patient subgroups with no specific finding. However, the small number of fatal/life-threatening or other major bleedings and the imbalance in size of some subgroups make it difficult to draw conclusions related to risk in a specific subgroup.

Deaths and serious adverse event

There were 21 (2.0%) deaths reported during the study [13 (1.2%) occurred during treatment and 8 (0.8%) post treatment]. Of these, 14 (1.3%) and 7 (0.7%) were categorized by the investigator as CV death and non-CV death, respectively. 1 death was assessed as causally related to ticagrelor by the investigator.

SAEs were reported in 117 (11.2%) patients during treatment and in 151 (14.5%) patients during the study. SAEs excluding bleedings were reported in 102 (9.8%) patients during treatment and in 133 (12.8%) patients during the study. During the treatment period, 18 (1.7%) patients reported SAEs assessed by the investigator as causally related to ticagrelor. SAEs that led to study drug discontinuation were reported in 21 (2.0%) patients.

The 3 most commonly reported SAEs during treatment with ticagrelor by PT were unstable angina [23 (2.2%) patients], coronary artery disease [13 (1.2%) patients], and AMI [9 (0.9 %) patients].

Summary of CV events

Major CV events (CV death, MI, and stroke) were reported in 37 (3.6%) patients within 1 year follow-up. CV deaths were reported in 14 (1.3%) patients. A total of 22 (2.1%) patients reported MI, including NSTEMI was reported in 11 (1.1%) patients, and STEMI was reported in 11 (1.1%) patients. Stroke was reported in 8 (0.8%) patients.

37 patients reported major CV events within 12 months after first exposure to ticagrelor, with a KM estimate event rate (95% CI) of 3.7% (2.7%, 5.1%).

Conclusion from the final analysis:

- This study provided the data of ticagrelor usage in Chinese ACS patients in the real world clinical practice. The duration of ticagrelor exposure was appropriate to assess the safety profile and bleeding risk.
- During 1 year follow-up, the incidence of PLATO-defined fatal/life-threatening and major bleeding events were 0.6% and 1.1%, respectively; SAEs excluding bleeding were reported in 9.8% of patients during treatment.
- The incidence of major CV events (CV death, MI, and stroke) in this study was 3.6% during 1 year follow-up.
- There were no new safety findings. The safety profile in YINGLONG study was consistent with the known safety profile of ticagrelor as described in the current approved prescribing information.