Observational Study Report
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OBSERVATIONAL STUDY REPORT SYNOPSIS

A Post Marketing Surveillance(PMS) to evaluate the safety and efficacy of Brilinta Tablet(Ticagrelor)

Milestones:	Date of Fist Subject In: 30 Apr 2013 Date of Last Subject Last Visit: 20 Jul 2016
Phase of development:	Not Applicable – Observational study
Sponsor:	AstraZeneca

Objectives:

This study objective is to identify the following items through the post marketing surveillance(PMS) under routine clinical practice after marketing authorization of Brilinta Tablet(Ticagrelor)(hereafter " the study drug"): the occurrence of unrevealed serious adverse events (SAEs), current status of occurrence of adverse events (AEs), the factors that may influence safety and efficacy of the drug

Study design:

A Multicenter, Prospective, Observational, Regulatory Post Marketing Surveillance

Methods:

The investigator should consecutively record from the subjects who are first administered the study drug to the requested number of subjects in the CRF without omission. The enrolled subjects should be followed at least once. Efficacy follow-up will be conducted from administration start date of ticagrelor to administration end date of ticagrelor or final observation date. Safety follow-up will be conducted for all AEs occurred from administration start date of ticagrelor to 7days after administration end date of ticagrelor or 7days after final observation date.

Participating sites: The number of study sites is 50 across South Korea, including general hospitals and clinics running clinical practice of cardiology.

Study population:

Subjects of this PMS are patients with Acute Coronary Syndromes (Unstable angina, Non ST-segment Elevation Myocardial Infarction[NSTEMI] or ST-segment elevation myocardial infarction [STEMI]), including those who will received medication or Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Graft (CABG).

Inclusion Criteria:

- Patients with Acute Coronary Syndromes(Unstable angina, Non ST-segment Elevation Myocardial Infarction[NSTEMI] or ST-segment elevation myocardial infarction [STEMI] including patients managed medically, and those who are managed with PCI or CABG)
- Patients who are taking ticagrelor and Acetylsalicylic Acid (ASA) daily (75-150mg), or Patients who are taking ticagrelor only(In the case that the patients have contraindication with ASA. Contraindication should be recorded in accordance with on CRFs)

  Contraindications of ASA
  - Any hypersensitivity history to aspirin or other salicilates
  - Existing peptic ulcer disease
  - Concurrent or History of Aspirin-induced asthma (Asthma attack caused by Nonsteroidal anti-inflammatory drugs [NSAIDs])
  - Haemophilia
  - Severe liver disorders
  - Severe renal disorders
  - Severe heart failure
  - Patients who have bleeding tendency
  - Patients who are combined treated by Methotrexate 15 mg(15mg/week) for more than a week
  - Stage III Pregnant women (refer to the ASA PI)
- Patients who have signed the data release consent form prior to enrollment in this surveillance

Exclusion criteria:

- Patients with hypersensitivity to ingredients of this drug
- Patients with pathological hemorrhage(e.g. peptic ulcer, intracranial bleed) at the time of administration
- Patients with medical history of intracranial hemorrhage
- Patients with severe hepatic impairment
- Patients being administrated strong CYP3A4 inhibitors(e.g. ketoconazole, clarithromycin, nefazodone, ritonavir, atazanavir)
- Patients who are below the age of 18

Evaluations:

Safety endpoints: AE incidence

- Hemorrahage:
  - Major fatal/life-threatening hemorrhage

  - Other major hemorrhage
  - Minor hemorrhage
  - Minimal bleeds
- Other AE

Efficacy endpoints: Composite endpoint - Cardiovascular (CV) death, Myocardial infarction, Stroke

Statistical methods:

Subjects included in safety evaluation

All subjects who had received the study drug at least once and could be followed up were included in the safety evaluation. The following subjects were excluded from the safety evaluation in the order listed below.

(i) Subjects who consented before the contract date

(ii) Subjects who received the study drug before the contract date

(iii) Subjects who did not receive the study drug

(iv) Subjects who had received the study drug before

(v) Follow-up failure: (no verification of AE incidence)

(vi) Subjects with inclusion/exclusion criteria violation

(vii) Subjects with administration method/dose violation

Subjects included in efficacy evaluation

The following subjects were excluded from the efficacy evaluation in the order listed below.

(i) Subjects excluded from the safety evaluation

(ii) Efficacy evaluation (occurrence of severe cardiovascular disease after the onset of acute coronary artery syndrome) not recorded

(iii) Subjects who were administered with the study drug for less than 3 months (90 days)

Analysis methods of safety endpoints

Safety analysis was conducted for subjects included in the safety evaluation and AEs were coded using WHO-ART 092.

Among subjects in the safety evaluation, the number of subjects experiencing AEs and the number of events were counted. Then the AE incidence was calculated and the 95% CI was estimated. Regarding AEs by demographical data of subjects in the safety evaluation, the number of subjects experiencing AEs and the number of events were counted. Then AE incidence was calculated and 95% CI was estimated. They were analyzed using Chi-square test or Fisher's exact test.

Analysis methods of efficacy endpoints

Efficacy analysis was conducted for subjects included in the efficacy evaluation. The incidence of composite endpoint ‡ was analyzed for the efficacy population using the Kaplan-Meier

method, and the Kaplan-Meier estimates were calculated for median time to incident occurrence, CI, and incidence. The Kaplan-Meier curve according to observation period was presented. The incidence of composite endpoint ‡ according to demographic data was analyzed using the Kaplan-Meier method. The Kaplan-Meier estimates were calculated for median time to incident occurrence, CI, and incidence, and the Kaplan-Meier curve according to observation period was presented for factors showing statistically significant differences in the Kaplan-Meier analysis. The influence of background factors and treatment factors on incidence was analyzed using the Cox proportional hazard regression model and variables were selected using Stepwise. Intercepts were included in the model, with the criteria for inclusion being 5% significance level and the criteria for exclusion being 10% significance level.

‡Composite endpoint: First incidence of CV death, Myocardial infarction, or Stroke

Results:

Overall participation status

From July 2011 to August 2016, CRFs were retrieved from a total of 3,347 subjects by 138 investigators at 50 centers. Among the subjects whose CRFs were retrieved, a total of 3,073 subjects were included in the safety evaluation, excluding 5 subjects who consented before the contract date, 7 who received the study drug before the contract date, 4 who did not receive the study drug, 2 who had received the study drug before, 37 who were lost to follow-up, 56 with inclusion/exclusion criteria violation, and 163 with administration method/dose violation. Of these, the subjects for the efficacy evaluation were 2,310, excluding 763 subjects who received the study drug for less than 3 months (90 days).

Descriptive data

Gender: Among the 3,073 subjects, 75.20% (2,311/3,073 subjects) was male and 24.80% (762/3,073 subjects) was female.

Age: The mean age of the subjects was 61.41±11.77 years, ranging from 23 to 95 years. Looking at age group distribution, 29.97% (921/3,073 subjects) were in the '55 to 64 years' group, followed by 25.25% (776/3,073 subjects) in the '65 to 74 years' group, 21.90% (673/3,073 subjects) in the '45 to 54 years' group, 15.10% (464/3,073 subjects) in the '75 years and above' group, and 7.78% (239/3,073 subjects) in the 'below 45 years' group.

Geriatric: Classifying geriatric subjects as those aged '65 years and above', 40.35% (1,240/3,073 subjects) of the subjects were found to be geriatric.

Height: The mean height of the subjects was 164.98±8.50 cm, ranging from 122.00 to 189.30 cm.

Weight: The mean weight of the subjects was 67.15±11.46 kg, ranging from 35.00 to 115.00 kg.

BMI: The mean BMI of the subjects was 24.59±3.15 kg/m^2, ranging from 15.15 to 41.42 kg/m^2. Looking at BMI group distribution, 95.23% (2,653/2,786 subjects) of subjects had BMIs 'Under 30 kg/m^2', while 4.77% (133/2,786 subjects) had BMIs of '30 kg/m^2 and above'.

Smoking: In total, 53.86% (1,655/3,073 subjects) of subjects were 'Nonsmoking' while 38.56% (1,185/3,073 subjects) were 'Smoking', and 7.58% (233/3,073 subjects) were 'Smoking history (less than a year after quitting smoking)'.

Pregnant and breast feeding women: There was no pregnant or breast feeding woman in the female subjects.

Renal and hepatic disorders: It was found that 2.99% (92/3,073 subjects) of subjects had renal disorders, while 2.83% (87/3,073 subjects) had hepatic disorders.

Long-term use: Classifying patients who had been administered with the study drug for 180 days or longer as long-term users, 16.21% (498/3,073 subjects) were long-term use subjects.

Disease duration: The mean disease duration for acute coronary artery syndrome was 57.94±367.23 days, ranging from 1 to 5,001 day(s) among the subjects. Looking at disease duration distribution, 63.70% (1,927/3,025 subjects) of subjects had a disease duration of '< 2 days', followed by 19.31% (584/3,025 subjects) with '≥ 2 ~ < 4 days' and 16.99% (514/3,025 subjects) with '≥ 4 days'. The mean disease duration for subjects who did not receive the loading dose (first dose: single dose, 2 tablets (180 mg)) due to 'already receiving other antiplatelet agent' was 90.48±475.75 days, ranging from 1 to 4,885 day(s) among the subjects. Looking at disease duration distribution, 56.17% (173/308 subjects) had a disease duration of '≥ 2 ~ < 4 days ', followed by 35.71% (110/308 subjects) with '≥ 4 days ' and 8.12% (25/308 subjects) with '< 2 days'.

Total administration period: The mean administration period was 110.92±64.92 days, ranging from 1 to 668 day(s). Looking at administration period distribution, 58.97% (1,812/3,073 subjects) received the study drug for '≥ 3 months ~ < 6 months', 16.21% (498/3,073 subjects) for '≥ 6 months ', and 12.33% (379/3,073 subjects) for '< 1 month'.

Safety data

During this observation period, 2,926 AEs were reported from 1,540 subjects among 3,073 in the safety population, resulting in a 50.11% incidence. Analyzing AEs by SOC, 'RESPIRATORY SYSTEM DISORDERS' occurred in 21.71% (667/3,073 subjects), followed by 'BODY AS A WHOLE - GENERAL DISORDERS' in 13.28% (408/3,073 subjects) and 'PLATELET, BLEEDING & CLOTTING DISORDERS' in 11.71% (360/3,073 subjects). Looking at specific symptoms, the most frequent was 'DYSPNOEA' in 15.55% (478/3,073 subjects), followed by 'CHEST PAIN' in 7.84% (241/3,073 subjects) and 'BRUISE' in 5.30% (163/3,073 subjects).

Of these, there were 1,133 cases from 765 (24.89%) subjects with ADRs whose causality to the study medication could not be ruled out. Analyzing ADRs by SOC, 'RESPIRATORY SYSTEM DISORDERS' occurred in 11.65% (358/3,073 subjects), followed by 'PLATELET, BLEEDING & CLOTTING DISORDERS' in 9.47% (291/3,073 subjects) and 'BODY AS A WHOLE - GENERAL DISORDERS' in 3.55% (109/3,073 subjects). Looking at specific symptoms, the most frequent was 'DYSPNOEA' in 9.96% (306/3,073 subjects), followed by 'BRUISE' in 4.52% (139/3,073 subjects) and 'CHEST PAIN' in 2.38% (73/3,073 subjects).

During this surveillance period, 168 SAEs were reported in 150 subjects (4.88%), with 40 SADRs in 39 subjects (1.27%), 1,549 unexpected AEs in 1,000 subjects (32.54%), and 397 unexpected ADRs in 280 subjects (9.11%). In addition, 119 unexpected SAEs were reported in 112 subjects (3.64%), and 15 unexpected SADRs were reported in 15 subjects (0.49%).

Analyzing the incidences of bleeding that occurred during this surveillance period according to bleeding type, 'Minimal bleeds' occurred in 8.72% (268/3,073 subjects), followed by 'Minor hemorrhage' in 2.99% (92/3,073 subjects) and 'Other major hemorrhage' in 0.72% (22/3,073 subjects).

Efficacy data

The evaluation criteria for efficacy was the 'composite endpoint' which was defined as the first occurrence of CV death, Myocardial infarction, or Stroke, which are severe cardiovascular diseases that occur after the onset of acute coronary artery syndrome. The number of occurrences of the 'composite endpoint' was investigated.

The result of the efficacy evaluation was that the composite endpoint occurred in 9 subjects (0.39%) out of 2,310 subjects in the efficacy population, with 4 cases of 'Myocardial infarction' and 5 cases of 'Stroke'.

The mean disease duration for acute coronary artery syndrome in the efficacy population was 62.38±383.51 days, ranging from 1 to 5,001 day(s) among the subjects. Looking at disease duration distribution, 61.26% (1,393/2,274 subjects) of subjects had a disease duration of '< 2 days', followed by 20.14% (458/2,274 subjects) with '≥ 2 ~ < 4 days' and 18.60% (423/2,274 subjects) with '≥ 4 days'.

The mean disease duration for subjects who did not receive the loading dose (first dose: single dose, 2 tablets (180 mg)) due to 'already receiving other antiplatelet agent' was 68.72±394.24 days, ranging from 1 to 4,565 day(s) among the subjects. Looking at disease duration distribution, 54.76% (138/252 subjects) had a disease duration of '≥ 2 ~ < 4 days', followed by 37.30% (94/252 subjects) with '≥ 4 days' and 7.94% (20/252 subjects) with '< 2 days'.

Conclusion:

This study was conducted from July 2011 to August 2016 by continuously enrolling subjects, beginning with those who started taking Brilinta Tablets from the contract date until the requested number was reached. A total of 138 investigators from 50 centers took part. CRFs were collected from 3,347 subjects, with safety evaluation being conducted in 3,073 subjects and efficacy evaluation in 2,310 subjects.

During this surveillance period, 2,926 AEs were reported from 1,540 subjects among 3,073 in the safety population, resulting in a 50.11% incidence. In total, 168 SAEs were reported in 150 subjects (4.88%), 1,549 unexpected AEs were reported in 1,000 subjects (32.54%), and 119 unexpected SAEs were reported in 112 subjects (3.64%).

The result of the efficacy evaluation was that the composite endpoint occurred in 9 subjects (0.39%) out of 2,310 subjects in the efficacy population, with 4 cases of 'Myocardial infarction' and 5 cases of 'Stroke'.

The ADRs of dyspnea and bruising which occurred frequently in this study were frequently reported AEs after study drug administration, which are found in the label information for Brilinta Tablets. Analyzing AE incidence according to demographic data, as well as AE incidence among special subject groups, AE incidences showed statistically significant differences according to the 13 factors of gender ($p=0.0003$), age ($p=0.0117$), smoking ($p=0.0418$), specific diagnosis for acute coronary artery syndrome ($p<0.0001$), disease duration ($p=0.0022$), past medical history ($p<0.0001$), total administration period of study drug ($p=0.0005$), administration of study drug loading dose ($p=0.0282$), mean daily dose of study drug ($p=0.0007$), concomitant medications ($p=0.0016$), geriatric patient ($p=0.0010$), renal disorders ($p=0.0063$), and long-term use ($p=0.0040$). In relation to this, it was found in the label information for Brilinta Tablets that administration to patients with moderate to severe renal disorders and patients aged 75 and above were to be conducted with caution, due to increased creatinine. Furthermore, it is stated in the label information that the PLATO study results showed no difference in risk of hemorrhage for age, gender, body weight, race, geographical area, concurrent disease, concomitant medications, and medical history.

However, as the surveillance was a non-intervention study, which depended on information collected from actual clinical settings, so there were limitations. Benefits of drug use are usually shown in single result, but risks appear in a complex form of side effects. For this reason, to identify and evaluate AEs, patient interview must be conducted, but considering the real-world medical practices in Korea, it is very difficult for medical professionals to take time to confirm safety profile of individual drugs. Therefore, it should be admitted that the surveillance results may be affected to a certain extent by various limitations associated with PMS and domestic medical practices.

In conclusion, the PMS study results showed no specific trend comparing to previously reported AE incidence and no specific matter that may affect the safety and efficacy. Therefore, the administration of Brilinta Tablet concomitantly with aspirin to reduce the incidence of thrombotic cardiovascular incidents (CV death, Myocardial infarction, Stroke) in adult patients with acute coronary artery syndrome is deemed safe and effective. The study drug will continue to be observed through future surveillance, spontaneous reports, and research reports.