2. TACW Synopsis

Clinical Study Report Synopsis: Study H7T-MC-TACW

Title of Study: Effectiveness of Prasugrel versus Clopidogrel in Subjects with High Platelet Reactivity on Clopidogrel Following Elective Percutaneous Coronary Intervention with Implantation of Drug-Eluting Stents

Number of Investigators: This multicenter study included 30 principal investigators.

Study Centers: This study was conducted at 30 study centers in 2 countries.

Publications Based on the Study: None at this time.

Length of Study:	**Phase of Development:** 2
Date of first subject visit: 06 July 2009 Date of last subject visit: 19 April 2011	

Objectives:

Primary Outcome Measure: The primary objective was to estimate the relative risk of the composite endpoint of Clinical Events Committee (CEC) adjudicated CV death or MI through 6 months of maintenance treatment with prasugrel plus aspirin compared with clopidogrel plus aspirin after loading with 600 mg clopidogrel and successful elective PCI with placement of at least 1 DES in subjects with high platelet reactivity as assessed by the VerifyNow™ device (P2Y12 reaction units [PRU] >208) after a MD (75-mg) of clopidogrel. The cut-point was chosen according to the putative upper tertile (PRU >208) of platelet reactivity after loading with clopidogrel. The intent of this study was to demonstrate that prasugrel is superior to clopidogrel in preventing the composite endpoint in this population. Two-sided 95% confidence intervals (CIs) for the hazard ratio (HR) were planned to be calculated with the corresponding p-value; however, due to early termination of the study and the low event rate, the hazard ratio was not calculated for the primary objective.

Secondary Outcome Measures:

The secondary efficacy objectives were to compare prasugrel with clopidogrel with respect to risk of the following CEC adjudicated events through 6 months:

- Definite or probable stent thrombosis according to Academic Research Consortium (ARC) criteria.
- CV death, MI, or urgent target vessel revascularization (UTVR).
- CV death, MI, or stroke.
- CV death, MI, stroke, or rehospitalization for cardiac ischemic events.
- All-cause death or MI.
- All-cause death, MI, or UTVR.
- All-cause death, MI, stroke or rehospitalization for cardiac ischemic events.

Safety objectives:

- To evaluate the incidence of non-coronary artery bypass graft (non-coronary artery bypass graft [CABG]) surgery-related Thrombolysis in Myocardial Infarction Study Group (TIMI) major bleeding in subjects receiving prasugrel or clopidogrel
- To evaluate the incidence of life-threatening bleeding (a subset of non-CABG-related TIMI major bleeding) in subjects receiving prasugrel or clopidogrel.
- To evaluate the incidence of non-CABG-related TIMI major or TIMI minor bleeding in subjects receiving prasugrel or clopidogrel.
- To evaluate the overall safety and tolerability based on clinical findings, laboratory values, and the occurrence of treatment-emergent adverse events (TEAEs) in subjects receiving prasugrel or clopidogrel.
- Other safety analyses included, but were not limited to, the evaluation of the incidence of TIMI major bleeding reported in subjects who undergo CABG.

Pharmacodynamic objectives:

Platelet aggregation will be measured by the Accumetrics VerifyNow™ P2Y12 assay. Key platelet function objectives are:

- To demonstrate a lower risk of the composite endpoint of CV death or MI in subjects with lower platelet reactivity while on study drug for both groups combined.
- To compare the prasugrel and clopidogrel groups with respect to degree of platelet aggregation.
- To compare the prasugrel and clopidogrel groups with respect to intrasubject and intersubject variability

in platelet aggregation during maintenance dosing.
- To assess the incidence of bleeding events by degree of platelet aggregation.

Genetic study objectives:
- To test that genetic variation in CYP2C19 resulting in reduced metabolic function demonstrates a gene-dose effect by predicted metabolic phenotype (extensive metabolizer [EM], intermediate metabolizer [IM], and poor metabolizer [PM]) and is associated with decreased platelet response to clopidogrel.
- To potentially test variation in the other genes involved in prasugrel and clopidogrel metabolism with prior evidence for association with PD response to clopidogrel (for example, CYP2C9 and CYP2B6).
- To potentially test variation in the other genes involved in prasugrel and clopidogrel metabolism (for example, CYP1A2, CYP3A4, and CYP3A5), if present at sufficient frequency, for association with PD response.
- To potentially examine for a trend toward increased cardiovascular clinical event rate in those patients taking clopidogrel with reduced metabolic function in CYP2C19.
- To potentially examine for a trend toward increased cardiovascular clinical event rate in those patients with reduced metabolic function in the other genes involved in the metabolism of thienopyridines (for example, CYP2C9, CYP2B6, CYP3A4, CYP3A5, and CYP1A2).
- To potentially evaluate the effect of other genes involved in the metabolism, transport, or activity of the drugs (for example, $P2Y_{12}$) on clinical response or cardiovascular disease susceptibility.

Study Design
This was a Phase 2, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study. The study population included consecutive, eligible subjects with coronary artery disease (CAD) and clinical indication for PCI. Subjects were enrolled after successful PCI with implantation of at least 1 DES, and a VerifyNow™ P2Y12 PRU measurement >208 measured 2 to 7 hours after a non-study-related clopidogrel MD the morning after PCI, at Day 1, administered as standard of care at the study sites. Subjects with non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI) as the index event, or within 14 days prior to randomization, were not eligible.

Study TACW was terminated early due to a lower than anticipated rate of the primary endpoint (a composite of CV death or MI).

Number of Subjects:
Planned: 2150 (1075 per study arm)
Randomized: 423 subjects, 212 prasugrel, 211 clopidogrel
Treated (at least 1 dose): 420 subjects, 210 prasugrel, 210 clopidogrel
Completed: 273 subjects, 136 prasugrel, 137 clopidogrel

Diagnosis and Main Criteria for Inclusion: Eligible subjects included males or females aged 18 to 80 years with CAD who had undergone successful, elective PCI with implantation of at least one DES. Eligible subjects had been treated with a standard-of-care clopidogrel 600-mg LD (along with aspirin) between 24 hours before and at the time of PCI. Only subjects with a high on-clopidogrel platelet reactivity ($P2Y_{12}$ reaction units [PRU] >208 as assessed by the VerifyNow™ device) to initial treatment of clopidogrel (600-mg LD and a single 75-mg MD) were eligible.

Subjects with non-ST segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI) within 14 days prior to randomization were excluded. Other exclusion criteria were: body weight < 60 kg; glycoprotein (GP) IIb/IIIa inhibitors eptifibatide or tirofiban within 24 hours before or during PCI or abciximab within 10 days before or during PCI; daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or COX2 inhibitors that could not be discontinued or were anticipated to require >2 weeks of daily treatment during the study.

Study Drug Dose, and Mode of Administration: One-time prasugrel 60-mg oral loading dose (LD) and 10-mg once daily oral maintenance dose (MD) up to 6 months

Comparator Dose, and Mode of Administration: One-time placebo LD and clopidogrel 75-mg oral daily MD up to 6 months

Duration of Treatment: Up to 6 months

Variables:

Efficacy:

Cardiovascular Death (CV Death): Death due to documented CV cause and death not clearly attributable to noncardiovascular causes.

Myocardial Infarction (MI): The definition of MI was adapted from the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction criteria and was dependent on the clinical timing of the event in relation to presenting syndrome and CV procedures.

Stent thrombosis: Stent thrombosis was assessed according to the Academic Research Consortium (ARC) criteria. The ARC consensus is that both timing of events and levels of evidence can be stratified to imply different pathophysiological mechanisms and to define varying degrees of certainty (that is, definite, probable, or possible stent thrombosis).

UTVR: PCI or CABG for recurrent ischemia that, in the investigator's opinion, could not be delayed for more than 24 hours and was defined by the investigator as a nonelective procedure. Revascularization, either with CABG or PCI, included the vessel(s) dilated at the initial procedure.

Stroke

Rehospitalization for cardiac ischemic events: Rehospitalization for symptoms of myocardial ischemia at rest with at least one of the following:

- new ST-segment deviation ≥1 mm or
- performance of a coronary revascularization procedure (PCI or CABG) during the same hospital stay. Revascularization may include the vessel(s) dilated at the initial procedure and/or additional vessels. Planned rehospitalization for performance of staged PCI identified at the time of index hospitalization is not included under the definition of rehospitalization for cardiac ischemic events.

All-cause death: Defined as death due to cardiac or noncardiac cause.

Safety: Non-CABG-related bleeding was classified by the TIMI hemorrhage classification scheme as defined below:

Minimal: Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in hemoglobin (Hgb) <3 g/dL (or, when Hgb is not available, a fall in hematocrit (Hct) of <9%) that requires medical attention.
Minor: Any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to ≤5 g/dL (or, when Hgb is not available, a fall in Hct of 9 to ≤15%) that requires medical attention.
Major: 1.) if it is intracranial, or 2.) clinically significant overt signs of hemorrhage associated with a drop in Hgb of >5 g/dL (or, when Hgb is not available, an absolute drop in Hct of >15%) that requires medical attention.
Significant: The combination of major plus minor hemorrhage.
Instrumented: Any hemorrhage that occurs as a result of an invasive procedure.
Spontaneous: Any hemorrhage that is not the direct result of an invasive procedure (for example, gingival bleeding, epistaxis, gastrointestinal bleeding).

Pharmacodynamic: Platelet aggregation variables included PRU and instrument reported percent inhibition as reported by the VerifyNow™ P2Y12 assay.

Evaluation Methods:
Due to the fact that the study was terminated prematurely with only one primary endpoint event , a high-level summary of any efficacy endpoints was performed, but further detailed analyses (for example, subgroup analyses, etc.) could not be performed.

Efficacy: Primary efficacy events comprised CEC adjudicated endpoints. Specific definitions of efficacy and safety endpoints were included in the protocol and in the CEC Charter. In the composite endpoint analyses, reaching any component of the composite endpoint was considered as reaching the composite endpoint. In analyzing noncomposite endpoints, reaching only the specific endpoint was considered (whether or not it was the first endpoint to occur).

Efficacy endpoint analyses were carried out using the intent-to-treat (ITT) set. Efficacy endpoints that occurred after discontinuation of the study drug were included in the efficacy analyses unless otherwise specified. Time-to-event was defined as the time from randomization to the onset of the endpoint. Time-to-first-event for a composite endpoint was defined as the time from randomization to the occurrence of the first event of the composite endpoint. Comparison of the treatment groups relative to primary and secondary efficacy endpoints were carried out using time-to-first event analyses via a 2-sided log-rank test.

Due to the premature termination of the study and low event rate, these tests were only performed if a total (across treatment groups) of more than 5 events occurred. When ≤5 total events occurred, a simple summary was provided (that is, count and percentage). For various outcomes, confidence intervals for hazard ratios (under the assumption of proportional hazards) and/or relative risks were provided. All confidence intervals were 2-sided with a 95% confidence level, and all hypothesis tests were 2-sided carried out at a significance level of 0.05.

Safety: Safety endpoint analyses were carried out using the treated dataset. The focus of the safety analyses was any safety event (including bleeding events and other treatment-emergent adverse events) that occurred in a treated subject while "at risk." Subjects were classified as "treated" if they received at least one dose of study drug. A subject was considered "at risk" during the period from the administration of the first dose of study drug through 7 days after permanent study drug discontinuation or the subject's discontinuation visit, whichever was earlier. If an adverse event was classified by the investigator as "study drug related," it was considered part of the "at risk" set, regardless of the timing. Safety events that occurred after 7 days of permanent discontinuation of study drug and that were not considered related to study drug were not included in the analyses but were reported separately.

Pharmacokinetic/Pharmacodynamic: Study sites utilized 2 Accumetrics VerifyNow™ instruments. The instrument used for screening provided unencrypted PRU readings to assess eligibility for enrollment. The second instrument provided encrypted platelet function data that were collected at days 90 and 180 or at early study drug discontinuation. If a subject experienced an efficacy endpoint event or a bleeding event, an attempt was made to obtain an additional blood sample for platelet function measures. Inhibition of platelet aggregation was measured by the Accumetrics VerifyNow™ P2Y12 assay that gives 3 values:

- P2Y12 Reaction Units ("PRU"), which is an estimate of P2Y12 receptor mediated platelet aggregation (rate and extent) in response to ADP in the ADP/PGE1 channel;
- "BASE" is an independent measurement based on the rate and extent of platelet aggregation in the Thrombin Receptor Activating Peptide (TRAP) channel.
- Device reported percent inhibition is the percent difference between the "PRU" and "BASE" values on any given occasion. The "BASE" value serves as an estimate of the subject's baseline platelet function independent of P2Y12 receptor inhibition. Percent inhibition, as reported by the Accumetrics VerifyNow™ P2Y12 device, is calculated from PRU and BASE values as follows: Inhibition = (Base-PRU)x100/Base.

Pharmacokinetic/Pharmacodynamic Comparisons between Treatment Groups:
Platelet aggregation (PA), as measured by VerifyNow™ P2Y12 PRU and calculated percent inhibition, was compared between treatment groups using separate ANOVA at each visit (Day 90, Day 180) with treatment and baseline platelet aggregation (the PRU values used to determine study eligibility) in the model.

Bleeding and Platelet Aggregation Analyses:
This analysis was not performed, as a total of only 5 TIMI major or minor bleeding events occurred in the at risk treated population during the course of the study.

Summary:

Patient Disposition and Baseline Characteristics:

Of 3525 patients screened, 423 patients were randomly assigned to treatment, 420 received at least 1 dose of study drug, 273 completed the study, and 147 did not complete the study. The majority of screen failures were due to PRU ≤208. For randomized patients, the most common reason for early discontinuation was the early termination of the study due to a lower than anticipated rate of the primary endpoint (a composite of CV death or MI). Among all randomized subjects, the majority of subjects were white (98.8%) and male (72.6%). The mean age was 66.1 years and the mean weight was 88.5 kg. Subject characteristics were balanced across the treatment groups. For the index event, the majority (94.3%) of subjects underwent PCI within 6 hours and provided a VerifyNow™ sample between 2 to 4 hours (92.4%) of receiving the clopidogrel 600-mg LD.

During the study, study drug treatment compliance was similar for the 2 treatment groups (91.8% for the prasugrel group and 93.6% for the clopidogrel group) and there were no statistically significant differences.

Primary and Secondary Efficacy Outcome Measures:

Only 1 primary efficacy event occurred during the study (1 MI in the clopidogrel group and no CV deaths); therefore, no statistical analysis was performed for the primary composite endpoint. Incidence of individual secondary efficacy endpoints was as follows: 0 stent thrombosis, 3 UTVRs (2 prasugrel, 1 clopidogrel), 1 ischemic stroke (clopidogrel), 1 all-cause death (clopidogrel), and 6 rehospitalizations for cardiac ischemic events (2 prasugrel, 4 clopidogrel). There were no statistically significant differences between treatment groups for any individual or composite endpoints for which statistical analyses were performed.

Pharmacodynamic Results:

At the time of randomization (baseline), platelet aggregation measures were similar for subjects randomly assigned to receive prasugrel and clopidogrel, respectively (mean [SD] PRU: 263.7 [84.7] and 261.9 [61.4]; mean [SD] percent inhibition 16.3% [11.6] and 15.7% [12.2]). Platelet aggregation analyses (PRU and percent inhibition) at Day 90 and at Day 180 showed statistically significantly lower platelet aggregation for the prasugrel group versus the clopidogrel group (least square [LS] mean PRU [SE] for Day 90: 93.1 [4.8] for prasugrel and 237.1 [4.8] for clopidogrel; Day 180: 95.9 [6.1] for prasugrel and 236.3 [5.9] for clopidogrel; percent inhibition [SE] for Day 90: 76.9 [4.3] for prasugrel and 27.8 [3.9] for clopidogrel; Day 180: 71.6 [1.6] for prasugrel and 26.3 [1.5] for clopidogrel).

Safety Results:

One death was reported during this study; a 70-year-old white male in the clopidogrel group died of sepsis, not considered related to study drug. A total of 78 (18.6%) at-risk subjects had treatment-emergent SAEs (40 prasugrel-treated subjects and 38 clopidogrel-treated subjects). A similar number of at-risk subjects from each treatment group experienced ≥1 hemorrhagic [3 prasugrel-treated subjects (1.4%) and 5 clopidogrel-treated subjects (2.4%)] and ≥1 non-hemorrhagic treatment-emergent SAE [38 prasugrel-treated subjects (18.1%) and 35 clopidogrel-treated subjects (16.7%)]. There were no statistically significant differences between treatment groups.

A total of 17 subjects permanently discontinued study drug prematurely due to an adverse event (6 prasugrel-treated and 11 clopidogrel-treated subjects). One AE leading to discontinuation in the prasugrel group was considered study-drug related, and 3 study-drug-related AEs led to premature study drug discontinuations in the clopidogrel group; differences between treatment groups were not statistically significant.

Overall, statistically significantly more prasugrel-treated subjects compared with clopidogrel-treated subjects experienced ≥1 TEAE (60.5% versus 49.1%, respectively; p=0.019), as well as ≥1 hemorrhagic TEAE (16.7% versus 9.1%, respectively; p=0.020) including epistaxis (9.5% versus 3.8%, respectively; p=0.019). Prasugrel-treated subjects also experienced statistically significantly more non-hemorrhagic TEAEs (≥1 non-hemorrhagic TEAE: 54.8% versus 43.3%, respectively; p=0.019).

Discussion:

The intent of Study TACW was to demonstrate that 6 months of maintenance therapy with prasugrel would be superior to clopidogrel in preventing the primary composite endpoint of MI and CV death in patients who underwent successful elective PCI and had a high on-clopidogrel platelet reactivity (VerifyNow™ PRU >208 in response to a non-study-related standard of care treatment with clopidogrel 600-mg LD and a single 75-mg MD). It was anticipated that a total of 2150 randomized subjects would be required in this event-driven study, which was to continue until at least 100 subjects experienced an adjudicated event of the primary composite endpoint within the 6 month follow-up. Due to a lower-than-expected event rate, with only 1 adjudicated primary endpoint event occurring out of 423 randomized patients, the study was terminated early.

Conclusions:

- For the primary endpoint comparing treatment arms in terms of the relative risk of the composite endpoint of CEC-adjudicated CV death or MI, only 1 MI event occurred in the clopidogrel arm and there were no CV deaths. A statistical analysis was not performed due to the occurrence of only 1 event and due to the early termination of the study.
- As seen with primary endpoint events, incidence of individual secondary efficacy endpoints were low. Occurrence of secondary efficacy events was as follows: 0 stent thrombosis, 3 UTVRs (2 prasugrel, 1 clopidogrel), 1 ischemic stroke (clopidogrel), 1 all-cause death (clopidogrel), and 6 rehospitalizations for cardiac ischemic events (2 prasugrel, 4 clopidogrel). There were no statistically significant differences between treatment groups for any individual or composite endpoints for which statistical analyses were performed.
- Incidence of non-CABG-related TIMI bleeding events during the "at-risk" period was as follows: 4 major bleeding (3 prasugrel, 1 clopidogrel), 1 life-threatening bleeding (clopidogrel), 5 major or minor bleeding (3 prasugrel, 2 clopidogrel). There were no statistically significant differences between treatment groups for any composite bleeding endpoints.
- Of 5 subjects who underwent CABG during the study (2 prasugrel, 3 clopidogrel), no subjects experienced CABG-related TIMI major or minor bleeding events.
- The overall incidence of adverse events and SAEs was similar for subjects taking either prasugrel or clopidogrel.
- Prasugrel demonstrated statistically significantly greater platelet inhibition compared with clopidogrel as measured by PRU and percent inhibition at Day 90 and Day 180.
- The pharmacodynamic objective to assess incidence of bleeding events by degree of platelet inhibition by treatment group was not performed due to insufficient data.