2. TABY Synopsis

Clinical Study Report Synopsis: Study H7T-MC-TABY

Title of Study: A Comparison of Prasugrel and Clopidogrel in Acute Coronary Syndrome (ACS) Subjects with Unstable Angina/Non-ST-Elevation Myocardial Infarction (UA/NSTEMI) Who are Medically Managed – The TRILOGY ACS Study

Number of Investigators: This multicenter study included 970 principal investigators.

Study Centers: This study was conducted at 970 study centers in 52 countries; 4 sites in India were discontinued from participation due to findings of non-compliance with Good Clinical Practice (GCP) requirements

Publications Based on the Study:

Chin CT, Roe MT, Fox KAA, Prabhakaran D, Marshall DA, Petitjean H, Lokhnygina Y, Brown E, Armstrong PW, White HD, Ohman EM. Study design and rationale of a comparison of prasugrel and clopidogrel in medically managed patients with unstable angina/non–ST-segment elevation myocardial infarction: The TaRgeted platelet Inhibition to cLarify the optimal strateGy to medicallY manage Acute Coronary Syndromes (TRILOGY ACS) trial. Am Heart J. 2010;160:16-22.e1.

Gurbel PA, Erlinge D, Ohman EM, Jakubowski JA, Goodman SG, Huber K, Chan MY, Cornel JH, White HD, Fox KAA, Prabhakaran D, Armstrong PW, Tantry US, Roe MT. First Large-Scale Platelet Function Evaluation in an Acute Coronary Syndromes Trial - The TRILOGY ACS Platelet Function Sub-study. American Heart Association - 85th Scientific Session 2012. Accepted Abstract.

Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng CD, Merkely B, Gasparovic V, Corbalan R, Cinteză M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM; the TRILOGY ACS Investigators. Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization. N Engl J Med. 2012 Aug 25. [Epub ahead of print].

Length of Study:	**Phase of Development:** 3
Date of first patient enrolled (assigned to therapy): 27 June 2008 Date of last patient completed: 30 March 2012	

Objectives:

Primary Objective

The primary objective of this study was to test the hypothesis that prasugrel and aspirin is superior to clopidogrel and aspirin in the treatment of medically managed subjects enrolled within 10 days of the unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) index event. Superiority was assessed by the reduction in risk of the composite endpoint of first occurrence of cardiovascular (CV) death, myocardial infarction (MI), or stroke throughout the study. The primary analysis was conducted in a hierarchical manner, with evaluation of the primary endpoint performed first in medically managed UA/NSTEMI subjects <75 years. Conditional on successfully establishing superiority in the primary analysis, the same composite endpoint was to be evaluated in the entire population.

Secondary Objectives

The secondary efficacy objectives were to compare the prasugrel and clopidogrel groups with respect to:

- The risk of the composite endpoint of first occurrence of CV death or MI
- The risk of the composite endpoint of first occurrence of all-cause death or MI
- The risk of the composite endpoint of first occurrence of all-cause death, MI, or stroke
- The first occurrence of stent thrombosis.

Secondary Objectives (continued)

- Components of the primary and secondary composite endpoints that were analyzed individually included:
  - All MI
  - All stroke
  - CV death
  - All-cause death
  - Rehospitalization for recurrent UA
  - Any coronary revascularization (PCI or CABG).
  - Definite or probable stent thrombosis, (either stents placed during study or previously in place prior to entering study).

Safety Objectives

In subjects receiving prasugrel or clopidogrel, the safety objectives were to evaluate the incidence of:

- Non-coronary artery bypass graft (non-CABG)-related life-threatening bleeding (a subset of the Thrombolysis in Myocardial Infarction [TIMI] major bleeding).
- Non-CABG-related TIMI major bleeding.
- Non-CABG-related TIMI major or minor bleeding.
- Non-CABG-related TIMI major, minor, or minimal bleeding.
- Non-CABG-related Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening bleeding.
- Non-CABG-related GUSTO severe or life-threatening bleeding or moderate bleeding.
- Non-CABG-related GUSTO severe or life-threatening, moderate, or mild bleeding.
- International Society of Thrombosis and Hemostasis (ISTH) major bleeding fits any of the following criteria:
  - Fatal bleeding, and/or
  - Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
  - Bleeding causing a fall in hemoglobin level at least 2g/dL or leading to transfusion of 2 or more units of whole blood or red cells.
- Fatal bleeding or intracranial hemorrhage (ICH).
- CABG-related bleeding.

AND

- To evaluate the overall safety and tolerability (based on vital signs, laboratory values, non-benign neoplasms, the occurrence of treatment-emergent adverse events (TEAEs) including adverse events meeting the regulatory definition of a serious adverse event, and those events leading to permanent discontinuation of study drug) in subjects receiving prasugrel or clopidogrel.

Substudy Objectives

Three substudies were performed in Study TABY including the Platelet Function Substudy (PFS), the Pharmacogenetic Substudy (TABY PGx) and the Health Outcomes Substudy. Both age cohorts (subjects <75 years and ≥75 years) were eligible for participation in these substudies. Approximately one third of Study TABY subjects participated in the PFS substudy where platelet function was assessed by VerifyNow® P2Y12 and VerifyNow Aspirin assays throughout the study including before and after switching from clopidogrel to prasugrel. The PFS was comprised of a pharmacodynamic (PD) and a biomarker component and results are included in a separate PFS report. The TABY PGx Substudy and Health Outcomes Substudy results are also provided in separate reports.

Study Design: Study H7T-MC-TABY (TABY, also referred to as TRILOGY ACS) was a Phase 3, multicenter, randomized, parallel-group, double-blind, double-dummy, active-controlled study in subjects who experienced recent (within 10 days) unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) acute coronary syndromes (ACS) and who were to be medically managed.

Number of Patients:

Planned: Approximately 10,300 subjects would include approximately 7800 subjects <75 years of age and a maximum enrollment of 2500 subjects ≥75 years of age.

Randomized: Subjects <75 years: 7243 subjects (3620 prasugrel, 3623 clopidogrel); Subjects ≥75 years: 2083 subjects (1043 prasugrel, 1040 clopidogrel); All subjects: 9326 subjects (4663 prasugrel; 4663 clopidogrel)

Treated (received ≥1 dose of study drug): Subjects <75 years: 7180 subjects (3590 prasugrel, 3590 clopidogrel); Subjects ≥75 years: 2060 subjects (1033 prasugrel, 1027 clopidogrel); All subjects: 9240 subjects (4623 prasugrel; 4617 clopidogrel)

Completed: Subjects <75 years: 6838 subjects (3421 prasugrel, 3417 clopidogrel); Subjects ≥75 years: 1915 subjects (957 prasugrel, 958 clopidogrel); All subjects: 8753 subjects (4378 prasugrel; 4375 clopidogrel)

Diagnosis and Main Criteria for Inclusion:

- Male or female, 18 years of age or older who had a UA/NSTEMI index event within 10 days (240 hours) prior to randomization.
- Had a decision for medical management (that is, neither PCI nor CABG is planned for management of the index event). This decision was made with reasonable certainty and was based on angiography and/or the subject's known clinical information (may have included, but did not need to be limited to known coronary anatomy, age, or co-morbidity).
  - For subjects whose medical management decision and randomization occurred no later than 72 hours following onset of the index event, prior clopidogrel treatment was not a consideration for eligibility.
  - For subjects with a medical management decision that were randomized beyond 72 hours of onset of the index event, open-label clopidogrel (prior to randomization) must have been received according to standard of care practice guidelines no later than 72 hours following the onset of the index event.
  - Had at least 1 of the following 4 high-risk features at the time of the UA/NSTEMI event:
    - Age ≥60 years old.
    - Prior MI evidenced by pre-existing Q waves, or demonstration of infarction on imaging studies, or prior documentation of elevated cardiac markers.
    - Diabetes Mellitus - defined by concomitant treatment with an oral hypoglycemic agent and/or insulin.
    - Coronary revascularization performed at least 30 days before the onset of the index ACS event (PCI or CABG).

Prasugrel, Dose, and Mode of Administration: Prasugrel, supplied as film-coated 5-mg or 10-mg tablets, was administered orally either as a once-daily 5-mg or 10-mg maintenance dose (MD); or a 30-mg loading dose (LD) followed by a once-daily 5-mg or 10-mg MD). The 5-mg prasugrel MD was administered to subjects who were ≥75 years of age or who had a body weight <60 kg at the time of randomization. All subjects were treated with adjunctive aspirin (open-label and commercially available), not to exceed 162 mg, for the duration of the study.

Clopidogrel, Dose, and Mode of Administration: Clopidogrel, supplied as film-coated 75 -mg tablets (Plavix® [clopidogrel bisulfate], Sanofi-Synthelabo), was administered orally either as a 300-mg LD followed by 75-mg MD or continuation of the once-daily 75-mg MD for subjects on commercial clopidogrel at randomization. All subjects were treated with adjunctive aspirin (open-label and commercially available), not to exceed 162 mg, for the duration of the study.

Duration of Treatment: Subjects remained on study drug for a maximum of 30 months or until completion of the study, whichever time was earlier.

Variables:

Efficacy:

The primary efficacy endpoint was the time to the first occurrence of the composite of CV death, MI, or stroke.

Secondary efficacy endpoints were the time to the first occurrence of:

- The composite endpoint of CV death and MI.
- The composite endpoint of CV death, MI, stroke, or rehospitalization for recurrent UA.
- The composite endpoint of all-cause death, MI, or stroke.
- Stent thrombosis.

In addition, the components of the primary and secondary composite endpoints were analyzed individually in a similar fashion to the primary and secondary composite endpoint (time to first occurrence): CV death, all-cause death, MI, stroke, rehospitalization or for recurrent UA, and any coronary revascularization. All secondary endpoint events were adjudicated by the CEC and additional detail regarding endpoint determination can be found in the CEC charter.

Safety: Safety endpoints included the following bleeding events classified according to the TIMI criteria (Bovill et al. 1991) and GUSTO definitions (GUSTO Investigators 1993):

- **Non-CABG-related TIMI major bleeding** is any ICH OR any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in hemoglobin (Hgb) of ≥5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed red blood cells [RBCs] = 1 gm/dL Hgb = 3% hematocrit [Hct]).
- **Non-CABG-related TIMI life-threatening bleeding** is any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension that requires treatment with intravenous vasopressor agents, OR requires surgical intervention for ongoing bleeding, OR necessitates the transfusion of 4 or more units of blood (whole blood or packed RBCs) over a 48-hour period, OR any symptomatic ICH.
- **Non-CABG-related TIMI minor bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of ≥3 gm/dL, but <5 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL Hgb = 3% Hct).
- **Non-CABG-related TIMI minimal bleeding** is any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of <3 gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as 1 unit packed RBCs = 1 gm/dL Hgb = 3% Hct).
- **Non-CABG-related GUSTO severe or life-threatening bleeding** is any ICH OR any bleeding event resulting in substantial hemodynamic compromise requiring treatment.
- **Non-CABG-related GUSTO moderate bleeding** is any bleeding event resulting in the need for transfusion that is not considered a GUSTO severe or life-threatening bleed.
- **Non-CABG-related GUSTO mild bleeding** is any other bleeding event that does not require transfusion or cause hemodynamic compromise.
- **All GUSTO severe or life-threatening bleeding events** meet criteria for severe or life-threatening but include both non-CABG-related and CABG-related bleeding events.
- **The "modified" GUSTO bleeding** -threatening bleed was "required surgical treatment" on the case report form (CRF), the CEC adjudicated these bleeding events (blinded review prior to data base lock) to determine which of the 3 GUSTO criteria were met (severe/life threatening, moderate or mild). The reason for CEC adjudication of these possible GUSTO severe/life threatening bleeding events was that many events that met the criterion of "requiring surgical treatment" actually required only minor procedures such as cauterization for spontaneous epistaxis.

Safety measures collected also included TEAEs, concomitant therapies, laboratory data, vital signs, and ECGs.

Variables (continued):

Pharmacodynamic: Two separate study reports provide results of pharmacodynamic (PD) analyses:

- The **Platelet Function Substudy** examined platelet function as assessed by VerifyNow® P2Y12 and VerifyNow Aspirin assays
- The **Pharmacogenetic Substudy** examined the influence of genetic variants on, metabolism of, and adverse events related to treatment (prasugrel and/or clopidogrel).

Health Outcomes: The **Health Outcomes Substudy** examined major health care resource use, medical costs, and incremental cost-effectiveness assessed as a function of treatment assignment and platelet function in certain countries participating in the main Study TABY. Health-related quality-of-life outcomes were also assessed.

Statistical Methods

An independent Clinical Endpoint Committee (CEC) adjudicated, in a blinded fashion, all efficacy and safety endpoints that were reported by the investigator according to the procedures and the criteria described in the CEC Charter. Reported potential neoplasm events were adjudicated by an independent group of external experts that remained blinded to treatment allocation, known as the Clinical Endpoint Committee (CEC) for Cancer Adjudication or the CEC-CA (which was separate from the CEC for adjudication of other events in this trial).

In the composite endpoint analyses, reaching any component of the composite endpoint was considered as reaching the composite endpoint. In analyzing non-composite endpoints, reaching only the specific endpoint was considered (whether or not it was the first event to occur).

Two key datasets were of interest: the intent-to-treat (ITT) set consisting of all randomized subjects and the treated set consisting of subjects receiving at least 1 dose of study drug (including the loading dose). Efficacy endpoint analyses were carried out using the ITT set. Efficacy endpoints that occurred after discontinuation of the study drug were included in the efficacy analysis unless otherwise specified.

Safety endpoint analyses were carried out using the treated set. The focus of the safety analyses was any safety event (including bleeding events, treatment-emergent adverse event, or abnormal laboratory value) that occurred in a treated subject while "at risk." A subject was classified as "treated" if they received at least one dose of study drug, either a loading dose or maintenance dose. A subject was considered "at risk" during the period from the administration of the first dose of study drug up 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 occurring after 7 days of permanent discontinuation of study drug and was not considered related to study drug, it was not included in the analyses but was reported separately.

All analyses were carried out for the subjects <75 years of age, subjects ≥75 years of age, and all subjects.

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 was carried out using time-to-first event analysis via a stratified two-sided log-rank test. Stratification variables were based on 3 categories of baseline commercial clopidogrel status including Strata 1 (clopidogrel-naive or not at steady state on commercial clopidogrel), Strata 2 (received a commercial clopidogrel LD of at least 300 mg within 72 hours of onset of index event followed by daily MD) and Strata 3 (received commercial clopidogrel treatment prior to index event, deemed to be at steady state at time of onset of index event, and maintained MD up until time of randomization). This stratification was performed so that any possible bias related to switching subjects with prior commercial clopidogrel exposure to prasugrel may be evaluated. The stratification variable of age (<75, ≥75 years)

was also used when analyzing all subjects together. The p-value from the log-rank test was considered the primary p-value for determining significance in time-to-event analyses. In addition to the reported p-value from the stratified log-rank test, Kaplan-Meier curves are shown, and hazard ratios are given along with a 95% confidence intervals. To encompass repeated events, an Andersen-Gill intensity model was used. This type of model used all available primary efficacy events. For example, if a subject had 2 MIs and then died, all 3 events were included. Within this repeated events model, a "landmark" analysis was performed. This analysis looked at the treatment effect before and after a timepoint and estimated the HR for both time periods. Available information on the vital status of subjects lost to follow-up or who withdrew consent was included in the analyses of the all-cause death endpoint.

The potential influence of baseline risk factors was assessed in an exploratory manner using the Cox proportional hazards model. Investigator or site effect on the treatment difference was not assessed.

For various outcomes, confidence intervals (CIs) for hazard ratios (HRs; under the assumption of proportional hazards) and/or relative risks were provided. All CIs were 2-sided with a 95% confidence level, and all hypothesis tests were 2-sided carried out at a significance level of 0.05. Study TABY was a large trial with adequate power to find statistically significant differences which may not have clinical relevance. Interaction p-values between subgroups and treatment were considered statistically significant at the 0.10 level.

Pharmacodynamic: Refer to separate reports for Platelet Function Substudy and Pharmacogenetic Substudy.
Health Outcomes: : Refer to separate report for Health Outcomes Substudy.

SUMMARY AND CONCLUSIONS:

BASELINE DEMOGRAPHICS AND CHARACTERISTICS

- Study TABY was a large, well-designed, Phase 3 study which enrolled 9326 subjects (7243 subjects <75 years, 2083 subjects ≥75 years) at 966 sites in 52 countries:
  - Baseline characteristics were well balanced between treatment groups for all 3 cohorts (<75 years, ≥75 years, and all subjects).
  - A total of 573 subjects (6.1%) did not complete the study and vital status was not collected for 18 subjects at study end.

- The Study TABY subject population represented a high risk ACS population who presented with UA/NSTEMI to be managed medically without revascularization:
  - In subjects <75 years: 38.9% had a history of diabetes (12.2% insulin-dependent), 44.1% had a prior MI, 36.7% had a history of coronary revascularization (PCI or CABG), and 64.9% were ≥60 years of age. Results were similar for those ≥75 years (except for percentage ≥60 years [100%]).
  - Among all randomized subjects, 41.3% had a coronary angiography performed prior to randomization for the index event (n=3851). Of those, 93.8% had coronary artery disease as defined per protocol (coronary artery stenosis >30%), with 83.9% having significant CAD (coronary artery stenosis ≥50%) and 66.4% having coronary anatomy that was indicated by the investigator as not suitable for revascularization.
  - During follow-up, 571 of the 7243 subjects <75 years (7.9%) and 130 of the 2083 subjects ≥75 years (6.24) underwent revascularization (PCI or CABG).

- Duration of treatment was sufficient to establish that Study TABY assessed the long-term treatment of medically managed subjects with UA/NSTEMI;
  - More than half (56.4%) of all treated subjects continued on study drug for more than 1 year and 20.6% continued on study drug for ≥24 months.

- Median duration of study drug treatment was 443 days with no significant difference between treatment groups.

EFFICACY

- Results of the primary efficacy analysis (first occurrence of CV death, MI, or stroke) did not demonstrate superiority of prasugrel and aspirin compared with clopidogrel and aspirin in the treatment of medically managed UA/NSTEMI subjects in any cohort:
  - Subjects <75 years: 10.1% versus 11.0%, HR [95% CI]: 0.915 [0.793, 1.055], p=0.210). Kaplan-Meier curves overlapped for the first year after randomization and then diverged with fewer prasugrel-treated subjects experiencing a component of the primary efficacy endpoint.
  - Subjects ≥75 years: 24.6% versus 24.1%; (HR [95% CI]: 1.029 [0.865, 1.225], p=0.731). Kaplan-Meier curves were similar or overlapping throughout the study.
  - All randomized subjects (13.3% versus 13.9%; HR [95% CI]: 0.960 [0.860, 1.072], p=0.451). Kaplan-Meier curves were similar to those for subjects <75 years, although the divergence was not as pronounced.

- Andersen Gill analyses of recurrent events detected a significant treatment effect for prasugrel-treated subjects versus clopidogrel for the entire study duration for subjects <75 years:
  - In subjects < 75 years, a significant treatment effect was observed for prasugrel compared with clopidogrel across the entire study period (HR [95% CI]: 0.863 [0.762, 0.978], p=0.021).
    - In subjects <75 years, a differential treatment effect was observed prior to 1 year versus after 1 year (interaction p-value = 0.007); the HR prior to 1 year was not significant (HR [95% CI]:0.961 [0.830, 1.112] p=0.593) compared with a significant treatment effect after 1 year (HR [95% CI]: 0.653 [0515, 0.830]; p<0.001).
  - In subjects ≥75 years, there were no significant treatment effects observed by recurrent event analysis. In the cohort of all randomized subjects, results were similar to those for subjects <75 years.
- In the analysis of time from first nonfatal to second primary endpoint for all randomized subjects, a significantly lower proportion of prasugrel-treated subjects experienced a second primary endpoint event compared with clopidogrel-treated subjects (34.6% versus 39.7%; HR [95% CI]: 0.791 [0.630, 0.993], p=0.042).

- Significant treatment-by-subgroup interactions (that is, interaction p<0.1) for the primary endpoint were noted for the following in subjects <75 years:
  - Those who had versus those who did not have diagnostic coronary angiography for the index ACS event (interaction p=0.080):
    - Prasugrel-treated subjects who underwent diagnostic coronary angiography had a significantly lower rate of the primary endpoint compared with clopidogrel-treated subjects (8.0% versus 10.2%; HR [95% CI]: 0.782 [0.617, 0.990], p=0.043), whereas there was no difference between treatment groups for those not undergoing diagnostic coronary angiography.
  - Subjects on a PPI versus those who were not on a PPI at randomization (interaction p=0.023):
    - In subjects on a PPI at randomization (23% of subjects <75 years), prasugrel-treated subjects had a significantly lower rate of the primary endpoint compared with clopidogrel (10.8% versus 15.0%; HR [95% CI]: 0.699 [0.533, 0.918], p=0.009), whereas, there was no difference between treatment groups for those not on a PPI.
  - In the analysis by tobacco use (interaction p=0.008):
    - Prasugrel-treated subjects currently using tobacco had significantly lower rates of the primary endpoint compared with clopidogrel, whereas there was no difference between treatment groups for those who were not current cigarette smokers.

- Secondary efficacy endpoints included 4 composite endpoints (CV death or MI; all-cause death or MI; all-cause death, MI or stroke; and CV death, MI, stroke or rehospitalization due to recurrent MI) and 7 individual efficacy events (all MI, all stroke, CV death, all cause death, rehospitalization for recurrent UA, any coronary revascularization (PCI or CABG), and definite or probable stent thrombosis).
  - No statistically significant differences were seen between treatment groups for the 4 composite secondary efficacy endpoints or the 7 individual secondary endpoints in any cohort (<75 years, ≥75 years, or all subjects).

SAFETY

- The primary safety analyses were non-CABG-related TIMI bleeding events which were independently adjudicated by the CEC in a blinded fashion. Rates of the most clinically important endpoints of non-CABG-related TIMI fatal bleeding, TIMI life-threatening bleeding, and TIMI major bleeding (which includes life-threatening events) were low and similar between treatments in subjects <75 years and in subjects ≥75 years.
- Adjudicated rates of non-CABG-related TIMI bleeding categories for subjects <75 years and ≥75 years were as follows:
  - Non-CABG-related TIMI fatal bleeding in prasugrel- versus clopidogrel-treated subjects, respectively:
    - Subjects <75 years: (4 [0.1%] versus 4 [0.1%]; HR [95% CI]: 1.013 [0.253, 4.049]; p=0.986)
    - Subjects ≥75 years: (3 [0.3%] versus 5 [0.5%]; HR [95% CI]: 0.615 [0.147, 2.576]; p=0.545)
      - The majority were intracranial or GI and most were spontaneous or trauma-related, with no significant between-treatment differences observed for these bleeding event-related characteristics in either age cohort.

  - Non-CABG-related TIMI life-threatening bleeding in prasugrel- versus clopidogrel-treated subjects, respectively:
    - Subjects <75 years: (16 [0.5%] versus 17 [0.5%]; HR [95% CI]: 0.947 [0.479, 1.875]; p=0.878)
    - Subjects ≥75 years: (9 [0.9%] versus 10 [1.0%]; HR [95% CI]: 0.936 [0.380, 2.305]; p=0.904)
      - The majority were intracranial or GI and most were spontaneous or trauma-related, with no significant between-treatment differences observed for these bleeding event-related characteristics in either age cohort.

  - Non-CABG-related TIMI major bleeding in prasugrel- versus clopidogrel-treated subjects, respectively:
    - Subjects <75 years: (39 [1.1%] versus 30 [0.8%]; HR [95% CI]: 1.309 [0.813, 2.107]; p=0.265)
    - Subjects ≥75 years: (19 [1.8%] versus 18 [1.8%]; HR [95% CI]: 1.089 [0.572, 2.076]; p=0.786)
      - The majority were GI or intracranial and most were spontaneous or trauma-related, with no significant between-treatment differences observed for these bleeding event-related characteristics in either age cohort.

  - Non-CABG-related TIMI major or minor bleeding in prasugrel- versus clopidogrel-treated subjects, respectively:
    - Subjects <75 years: (70 [2.0%] versus 46 [1.3%]; HR [95% CI]: 1.538 [1.060, 2.232]; p=0.022)
    - Subjects ≥75 years: (27 [2.6%] versus 31 [3.0%]; HR [95% CI]: 0.896 [0.535, 1.502]; p=0.654)
      - The majority were GI or intracranial and most were spontaneous or trauma-related. In subjects <75 years, a significantly higher rate of GI-related TIMI major or minor bleeding events was observed in the prasugrel versus the clopidogrel group; no other significant between-treatment differences were observed for these bleeding event-related characteristics in either age cohort.

- Non-CABG-related TIMI major, minor or minimal bleeding in prasugrel- versus clopidogrel-treated subjects, respectively:
  - Subjects <75 years: (16.9% versus 10.3%; HR [95% CI]: 1.711 [1.503, 1.947]; p<0.001)
  - Subjects ≥75 years: (16.8% versus 12.7%; HR [95% CI]: 1.385 [1.103, 1.739]; p=0.005)
    - Prasugrel-treated subjects in both age cohorts had significantly higher rates of the following common bleeding-related event characteristics compared with clopidogrel-treated subjects: locations including cutaneous bleeding (bruising, contusion and ecchymosis), epistaxis and GI-related; types including spontaneous and trauma-related.

- Prasugrel-treated subjects had significantly higher rates of required interventions associated with TIMI bleeding events compared with clopidogrel-treated subjects as follows:
  - In subjects <75 years: transfusions associated with TIMI life-threatening or major bleeding events; transfusions and hospitalizations associated with TIMI major or minor bleeding events; medical treatment, hospitalizations, transfusions, and surgery associated with TIMI major, minor or minimal bleeding events.
  - In subjects ≥75 years: a numerically higher number of hospitalizations and a statistically significantly higher rate of required medical treatment associated with TIMI major, minor, or minimal bleeding events.

- In the cohort of all treated subjects, the following results were observed for analyses of TEAEs in Study TABY:
  - Deaths: The rate of CV and non-CV-related deaths were similar between treatment groups.
  - SAEs: Prasugrel-treated subjects had a higher rate of hemorrhagic SAEs compared with clopidogrel-treated subjects (3.4% versus 2.5%, p=0.017). There were no significant differences in the rates of all or non-hemorrhagic SAEs.
  - TEAEs while at risk: Prasugrel-treated subjects had a higher rate of hemorrhagic TEAEs compared with clopidogrel-treated subjects (19.9% versus 12.7%, p<0.001). There were no significant differences in rates of all or non-hemorrhagic TEAEs.
  - TEAEs leading to study drug discontinuation: Prasugrel-treated subjects had a higher rate of hemorrhagic TEAEs leading to study drug discontinuation compared with clopidogrel-treated subjects (3.6% versus 2.1%, p<0.001). There were no significant differences in the rates of all or non-hemorrhagic TEAEs leading to study drug discontinuation.
- No new safety concerns were identified in Study TABY.

- Neoplasm data were prospectively collected and cases were adjudicated by an independent committee of oncologists blinded to treatment. The following results were observed in the primary neoplasm analysis population:
  - No difference was seen in the total number of new non-benign neoplasms (prasugrel, 82/4554 [1.80%] versus clopidogrel, 78/4551 [1.71%]; HR=1.045; p=0.786).
  - Tumor location was balanced between treatment groups in all locations except colorectal where there were numerically more colorectal cancers in the prasugrel group (14 versus 6). Investigation of GI bleeding or anemia led to the discovery of the majority of these cases (75% [15/20]).
  - Discovery of colorectal neoplasms during investigation of GI bleeding or anemia largely explains the numerical imbalance between treatment groups in the frequency of colorectal cancer; however, the sponsor cannot completely exclude the possibility that colorectal cancer could be associated with prasugrel treatment.

Conclusions

Results of the primary endpoint analysis in Study TABY, a long-term study of UA/NSTEMI subjects to be medically managed without revascularization, did not demonstrate the superiority of prasugrel compared with clopidogrel on a background of aspirin. Although the optimal treatment duration and intensity of P2Y12 inhibition post-ACS for this population remains uncertain (Roe et al. 2012), observations over the course of this study indicated that after 1 year, prasugrel-treated subjects had a reduced rate of primary endpoint events compared with clopidogrel, and that recurrent CV events were reduced with long-term prasugrel treatment compared with clopidogrel. These findings may indicate that longer term treatment with dual antiplatelet therapy may be required to demonstrate efficacy in a medically managed ACS population.

In the TRITON study (Study TAAL), more fatal or life-threatening bleeding events were seen with prasugrel (Murphy et al. 2008). This was not observed in Study TABY, as the rate of fatal and life-threatening bleeding (including intracranial bleeding) was not significantly different for prasugrel versus clopidogrel when the prasugrel MD of 10 mg was reduced to 5 mg for populations identified in TRITON as being at high risk for bleeding, including very elderly subjects ≥75 years and those with low body weight <60 kg. Nonetheless, signs of intensified platelet inhibition with prasugrel were observed given the increased frequency of moderate or minor non-CABG-related bleeding events with prasugrel versus clopidogrel. Finally, the prospective, systematic surveillance and rigorous adjudication of new, non-benign neoplasms in Study TABY demonstrated no increase in the risk of neoplasm development with sustained exposure to prasugrel for up to 30 months (Roe et al. 2012).