2. TADF Synopsis

Clinical Study Report Synopsis: Study H7T-MC-TADF

Title of Study: A Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (PCI) Or as Pretreatment At the Time of Diagnosis in Patients with Non-ST-Elevation Myocardial Infarction (NSTEMI): The ACCOAST Study

Number of Investigators: This multicenter study included 181 principal investigators.

Study Centers: This study was conducted at 171 study centers in 19 countries. The higher number of principal investigators (PIs) is due to changes in PIs at 10 study centers over the course of the study.

Publications Based on the Study:

Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, ten Berg J, Widimsky P, Luo J, Miller DL, Goedicke J. A comparison of prasugrel at the time of percutaneous coronary intervention or as pretreatment at the time of diagnosis in patients with non-ST-segment elevation myocardial infarction: design and rationale for the ACCOAST study. *Am Heart J*. 2011 Apr;161(4):650-656.e1.

Length of Study:	**Phase of Development:** 3
Date of first subject visit: 06 December 2009 Date of last subject visit: 18 February 2013	

Primary Objective

The primary objective was to test the hypothesis that, for subjects with non-ST-segment elevation myocardial infarction (NSTEMI) with elevated troponin who were scheduled for coronary angiography/percutaneous coronary intervention (PCI), a prasugrel loading dose (LD) given at the time of qualifying diagnosis would be superior to a prasugrel LD given at the time of the PCI procedure, as measured by a reduction in the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), stroke, urgent revascularization (UR), or glycoprotein (GP)IIb/IIIa inhibitor bailout through 7 days from randomization.

Secondary Efficacy Objectives

- The key secondary objective was to evaluate net clinical benefit (composite of all-cause death, MI, stroke, or all coronary artery bypass graft [CABG] or non-CABG Thrombolysis in Myocardial Infarction [TIMI] major bleeding) through 7 days from randomization.

- Additional secondary efficacy objectives were to compare the 2 prasugrel LD regimens in terms of the incidence of the following:

  - CV death, MI, or stroke through 30 days from randomization
  - CV death or MI through 30 days from randomization
  - CV death, MI, or UR through 30 days from randomization
  - CV death through 30 days from randomization
  - Definite or probable stent thrombosis according to the Academic Research Consortium (ARC) criteria through 30 days from randomization
  - Net clinical benefit (composite of all-cause death, MI, stroke, or all TIMI major bleeding) through 30 days from randomization

  And in addition:
  - Rise in troponin from baseline (obtained at Visit 1) to pre-PCI (obtained at Visit 3)

Secondary Safety Objectives

- The key safety objective was to evaluate all CABG or non-CABG TIMI major bleeding through 7 days from randomization.

- Safety Objectives were to evaluate the incidence of:
  - All TIMI major, major-life-threatening, and minor bleeding in subjects through 30 days from randomization
  - All CABG surgery-related TIMI major, minor, and composite of TIMI major or minor bleeding through 30 days from randomization
  - Non-CABG surgery-related TIMI major and minor bleeding through 30 days from randomization
  - Non-CABG surgery-related TIMI major, minor, and the composite of TIMI major or minor bleeding at the end of the initial cardiac catheterization procedure (including PCI, if performed)
  - Total chest tube drain volumes in subjects undergoing CABG surgery
  - Transfusion volumes including units of whole blood, packed red blood cells (PRBCs), and platelets in CABG and non-CABG subjects
  - The overall safety and tolerability of prasugrel administration based on clinical findings, laboratory values, and the occurrence of hemorrhagic or nonhemorrhagic treatment-emergent adverse events (TEAEs).

Study Design:

Study TADF was a Phase 3, multicenter, randomized, parallel-group, double-blind study. The study was designed to compare 2 prasugrel LD regimens in subjects with NSTEMI with elevated troponin who were scheduled for coronary angiography/PCI. Subjects were randomized in a parallel, 1:1 manner at the site level. Enrolled subjects were randomly assigned to the Prasugrel Pretreatment [PP] or the Prasugrel Non-Pretreatment (PNP) cohort. Subjects, as well as all site personnel, were blinded to the study drug LD. The PNP group received the approved LD of prasugrel 60 mg given at the time of PCI and the PP group received prasugrel 30 mg prior to coronary angiography, with an additional prasugrel 30 mg given at the time of PCI. Maintenance dosing of prasugrel followed the Summary of Product Characteristics (SPC) recommendations; the first MD was administered within 18 to 24 hours of the second LD.

Subjects who underwent PCI received open-label study drug of once-daily prasugrel maintenance dosing following the procedure for approximately 30 days. Post-study, the subject's physician could consider prescribing antiplatelet therapies such as clopidogrel, ticlopidine, ticagrelor, or prasugrel (if commercially available in that country).

Treatment of subjects who did not have PCI but had medical management (MM) and/or CABG surgery was left to the investigator's discretion (for example, open-label clopidogrel or ticlopidine) and subjects remained in the study through the 30 Day (±3 days) visit to be assessed in the intent-to-treat (ITT) analysis.

Number of Subjects:

Planned: Study TADF was an event-driven study. Enrollment was to continue until an estimated 400 subjects experienced an adjudicated primary endpoint through 7 days from randomization. It was originally anticipated that a total of 4100 subjects would be randomized in order to reach 400 adjudicated events. Once an estimated 400 adjudicated events occurred, entry into the study was to end.

Randomized: 4033 (1996 PNP, 2037 PP)
Treated (at least 1 dose): 4033 (1996 PNP, 2037 PP)
Completed through Day 30 Visit: 3882 (1924 PNP, 1958 PP)

Diagnosis and Main Criteria for Inclusion: Subjects aged 18 years and above presenting with NSTEMI with elevated troponin (≥1.5 times the upper limit of normal [ULN]) who were scheduled for coronary angiography/PCI ≥2 and <24 hours from planned randomization were included. If necessary due to timing constraints, coronary angiography/PCI could be scheduled the next day with the intention to perform coronary angiography/PCI within 24 hours but definitely no later than 48 hours from randomization. Subjects with a medical history considered a contraindication for therapy with prasugrel (for example, history of stroke or transient ischemic attack [TIA]) or current use of a GPIIb/IIIa inhibitor were excluded. Enrolled subjects were to meet all inclusion criteria and sign the informed consent document.

Test Product, Dosage and Mode of Administration (Prasugrel Pretreatment [PP] Cohort):
Subjects in the PP cohort received a split LD regimen with 30 mg of prasugrel administered immediately after NSTEMI diagnosis and prior to diagnostic coronary angiography and the remainder of the LD (prasugrel 30 mg) given at the time of PCI. Subsequently, subjects received daily maintenance doses of prasugrel study drug until the Day 30 Visit. Subjects who were ≥75 years of age or who had a body weight of <60 kg received a maintenance dose of 5 mg per day, and all others received 10 mg per day. The first maintenance dose was to be administered within 18 to 24 hours of the second LD (given at time of PCI). Subjects not proceeding to PCI could be treated with a thienopyridine (that is, open-label clopidogrel or ticlopidine) according to routine treatment patterns and according to the investigator's discretion.

Reference Therapy, Dose and Mode of Administration (Prasugrel Non-Pretreatment [PNP] Cohort):
Subjects in the PNP cohort received inactive tablets immediately after NSTEMI diagnosis and prior to the diagnostic coronary angiography. A 60-mg prasugrel LD was given immediately after coronary angiography when proceeding to PCI. Subsequently, subjects received daily maintenance doses of prasugrel study drug until the Day 30 Visit. Subjects who were ≥75 years of age or who had a body weight of <60 kg received a maintenance dose of 5 mg per day, and all others received 10 mg per day. The first maintenance dose was to be administered within 18 to 24 hours of the second LD (given at time of PCI). Subjects not proceeding to PCI could be treated with a thienopyridine (that is, open-label clopidogrel or ticlopidine) according to routine treatment patterns and according to the investigator's discretion.

Duration of Treatment:
In subjects undergoing PCI, prasugrel study drug continued through the Day 30 Visit (performed within 27 to 33 days from randomization). In available subjects who underwent PCI, the Day 90 Visit was to occur within 85 to 95 days from randomization; this visit consisted of a telephone subject-status phone call.

Variables:

Efficacy: The primary endpoint was a composite of CV death, MI, stroke, UR, or GPIIb/IIIa inhibitor bailout through 7 days from randomization.

1) Cardiovascular Death (CV Death): Death due to documented cardiovascular cause. Additionally, death not clearly attributable to noncardiovascular causes was considered CV death.

2) Myocardial Infarction (MI): The definition of MI was based on the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Health Federation Task Force for the Redefiniton of Myocardial Infarction criteria (Thygesen et al. 2007) and dependent on the clinical timing of the event in relation to the presenting syndrome and cardiovascular procedures.

Myocardial infarctions included as primary efficacy endpoints had to be distinct from the qualifying MI event. Due to the slow kinetics of troponin and the fast sequence of qualifying MI (troponin-positive subjects) and PCI (expected median delay from randomization of 12 hours), troponin alone was not suitable for detection of peri-procedural MIs, which were expected to be reduced by pretreatment with prasugrel. Thus, both creatine kinase myocardial bands (CK-MB) or total CK and troponin I or T were drawn and the results were documented. CK-MB was preferred, but if sites did not have readily available CK-MB, total CK was acceptable. When total CK was used, a rise in the troponin level must have been seen as well. The diagnosis of an MI was based on the local laboratory ULN.

3) Stroke: Stroke was defined as the rapid onset of a new, persistent neurologic deficit that lasted for more than 24 hours. Stroke was classified as either ischemic or hemorrhagic based on computed tomography (CT) or magnetic resonance imaging (MRI) scan, if available, or uncertain cause if imaging data was not available. In the case of a clinical diagnosis of stroke, CT or MRI scan imaging was strongly recommended. Supplemental information from previous head CT or MRI scans determined if there was a demonstrable lesion compatible with an acute stroke.

4) Urgent Revascularization (UR):

Prior to planned coronary angiography/ (PCI or CABG surgery): driven by symptoms of ischemia which worsened while waiting for the initially scheduled coronary angiography/PCI that, in the investigator's opinion, required catheterization prior to the planned time of the procedure.

Occurring after PCI for the Index Event:
Recurrent signs of ischemia leading to new, emergent revascularization (PCI or CABG surgery) of the vessel(s) dilated at the initial procedure (for example, stent thrombosis).

Recurrent symptoms of ischemia leading to a new emergent revascularization (PCI or CABG surgery) of a vessel not initially dilated. This excluded any staged procedures.

5) Glycoprotein (GP) IIb/IIIa Inhibitor bailout: Symptoms necessitating the unplanned use of a GPIIb/IIIa inhibitor.

While waiting for coronary angiography/PCI, during PCI, or through 24-hour post-PCI time point, GPIIb/IIIa inhibitors given by the investigator for any of the following were considered as bailout: clinical instability, hemodynamic instability, electrocardiogram instability, biological instability, arrhythmic instability, TIMI flow grades of 0-1 or no reflow prior to the start of PCI, development of new visible thrombus on angiography after the start of PCI, dissection with decreased flow, distal embolization, side-branch closure, abrupt closure of the culprit vessel, stent thrombosis, or non-satisfactory revascularization.

Safety: The bleeding classification from the TIMI Study Group was used to define the key safety endpoint. The key safety objective was to evaluate all CABG or non-CABG TIMI major bleeding through 7 days from randomization. TIMI major and minor bleeding, as well as the incidence of all CABG or non-CABG-related TIMI major and minor bleeding were prespecified safety endpoints that were closely monitored during the study.

Any bleeding event requiring medical attention was adjudicated by an independent CEC in a blinded fashion. The following TIMI hemorrhage classification scheme was used:

- **Major:** Defined as either 1) intracranial, or 2) clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥5 g/dL (or, when Hgb was not available, an absolute drop in hematocrit [Hct] of >15%)*.
    - **Life-threatening:** Any TIMI major bleeding that was fatal, led to hypotension that required treatment with intravenous inotropic agents, required surgical intervention for ongoing bleeding, or necessitated the transfusion of 4 or more units of blood (whole blood or packed red blood cells (PRBCs) over a 48-hour period, or any symptomatic intracranial hemorrhage (ICH).
- **Minor:** Any clinically overt sign of hemorrhage (including imaging) that was associated with a fall in Hgb of 3 to <5 g/dL (or, when Hgb was not available, a fall in Hct of 9 to ≤15%)*.
- **Minimal:** Any clinically overt sign of hemorrhage (including imaging) that was associated with a fall in Hgb <3 g/dL (or, when Hgb was not available, a fall in Hct of <9%)*.

- **Significant:** The combination of major plus minor hemorrhage.
- **Instrumented:** Any hemorrhage that occurred as a result of an invasive procedure.
- **Spontaneous:** Any hemorrhage that was not the direct result of an invasive procedure (such as gingival bleeding, epistaxis, gastrointestinal bleeding)

*To account for transfusion, Hgb and Hct measurements were adjusted for any PRBCs or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood was assumed to result in an increase of 1 g/dl in Hgb or of 3% in Hct. Thus, to calculate the true change in Hgb or Hct if there was an intervening transfusion between two blood measurements, the following calculations were performed:

Δ Hemoglobin = [baseline Hgb – post transfusion Hgb] + [number of transfused units]

Δ Hematocrit = [baseline Hct – post transfusion Hct] + [number of transfused units x 3]

Platelet Function Substudy: The primary analysis was to evaluate the drug effect of prasugrel on platelet aggregation (PA) for subjects taking a prasugrel LD of 60 mg following coronary angiography (that is, the PNP treatment group). Platelet aggregation (PA) was measured by the VerifyNow® P2Y12 assay, using data encryption to maintain study blinding. The effect of study drugs on platelet aggregation was assessed by the VerifyNow P2Y12 assay from 2 measures:

1. $P2Y_{12}$ Reaction Units ("PRU") was an estimate of $P2Y_{12}$ receptor-mediated PA (rate and extent) in response to adenosine diphosphate (ADP) in the ADP/ prostaglandin E1 (PGE1) channel.
2. The device-reported percent inhibition was the percent difference between the "PRU" and "BASE" values on any given occasion. All substudy analyses were performed using PRU and percent inhibition as the outcome variables, separately.

Poor Responder Analyses: A PRU $\geq$235 or percent inhibition $\leq$15% was considered a poor response to prasugrel.

Statistical Methods: Enrollment was to continue until 400 subjects reached one of the events described in the composite primary endpoint (CV death, MI, stroke, UR, or GPIIb/IIIa bailout through 7 days from randomization). The study was to provide 80% power with a 2-sided log-rank test at an overall significance level (alpha) of 0.05 to establish superiority with regards to the primary endpoint. In order to have 80% power to detect a 24% relative risk reduction (RRR) on pretreatment of prasugrel, it was anticipated that 4100 subjects would need to be randomized (2050 in each cohort) to yield 400 subjects reaching the primary endpoint through 7 days from randomization.

An independent Clinical Endpoints Committee (CEC) adjudicated all death, MI, stroke, UR or GPIIb/IIIa bailout, stent thrombosis, and all TIMI major, major-life-threatening and minor bleeding in a blinded fashion. Primary analyses were conducted on CEC-adjudicated endpoints.

Safety monitoring was conducted under the auspices of an independent, external data monitoring committee (DMC) assigned to this study. A formal interim efficacy analysis was conducted when 200 subjects met the primary composite efficacy endpoint (CV death, MI, stroke, UR, or GPIIb/IIIa bailout) through 7 days from randomization.

The primary endpoint analysis and all other key efficacy and safety analyses were conducted using the two-sided log-rank test from a time-to-first event analysis, unless otherwise specified. Time-to-event was defined as the time from randomization to the onset of the endpoint.

Summary:

Early Study Enrollment Termination by External DMC:

On November 16, 2012 a decision based on the recommendation of the ACCOAST external DMC was made to immediately stop enrollment in the study. Enrollment was stopped because the pretreatment arm of the study was associated with an increased risk of early TIMI major bleeding, including life threatening, with no observed reduction in cardiovascular events. At the time of the early enrollment termination and through the end of the study, there was no mortality imbalance between the 2 treatments.

DEMOGRAPHICS AND INDEX EVENT CHARACTERISTICS

Demographics
Of 4033 randomized subjects, 98.5% completed the study through 7 days from randomization and 96.3% completed the Day 30 study visit.

- There was a small imbalance in treatment groups with 41 more subjects randomly assigned to PP compared with PNP (2037 versus 1996, respectively); this imbalance was possibly due to randomization occurring at the site level.
- Three subjects were lost to follow-up (vital status unknown at 30 days).
- The 2 treatment groups (PP and PNP) appeared well balanced for baseline demographics, medical history, characteristics of the index event, and estimates of treatment compliance. There were numerical, but not statistically significant, between-treatment differences in the overall population and in the 4 subcohorts.
- 40.6% of the ITT population had single vessel disease, 8.0% had left main disease.

Timing of LD
- The median time from symptom onset to first LD was 14.8 hours for both treatment groups in the overall ITT population.
- The median time from the first LD to catheterization/PCI was 4.3 hours for both treatment groups in the overall ITT population and the PCI Only subcohort.
- Of 314 patients who underwent CABG Only, 126 (40.13%) had CABG <4 days, 112 (35.67%) from 4 to 7 days, and 76 (24.20%) had CABG >7 days from the first LD.

EFFICACY RESULTS

Primary Efficacy Endpoint
- The incidence of the primary composite endpoint through 7 days from first LD (randomization) was not significantly different for the PP versus PNP in the ITT population (9.97% versus 9.77%; HR [95% CI]: 1.024 [0.841, 1.246], p=0.812).
- As observed in the KM curves, events came very early, essentially within the first 24 hours from first LD.
- Of the 398 primary composite efficacy endpoint events through 7 days, 363 were in the PCI cohort, 20 in the CABG cohort and 15 in the medical management cohort.

<u>Individual Components of the Primary Efficacy Endpoint</u>
- No difference in CV death at 7 or 30 days between PP versus PNP treatment groups
- The most common components of the primary efficacy were MI and GPIIb/IIIa inhibitor bailout
    - Majority of MIs were post-PCI biomarker related (Type 4a) and occurred within 24 hours of PCI.
    - Majority of GPIIb/IIIa inhibitor bailout administered for angiographically defined thrombus after cardiac catheterization and prior to PCI or at the time of PCI.

Net Clinical Benefit (all cause death, MI, stroke, and all TIMI major bleeding)
- Through 7 days from first LD in the overall population, no net clinical benefit for PP versus the PNP group (8.64% versus 7.57%; HR [95% CI]: 1.146 [0.922, 1.424], p=0.218).

Secondary Efficacy Endpoints
- There were no significant differences (that is, no benefit of pretreatment) in rates of the following secondary efficacy composite endpoints or for individual components through 7 or through 30 days from first LD for any population including overall, PCI Only, PCI Plus CABG, or MM:

  - CV death/MI/stroke
  - CV death/MI/UR
  - CV death/MI
  - Definite or probable stent thrombosis
    - Stent thrombosis was rare with a total of 7 definite or probable stent thrombosis within the first 30 days.
- There was no difference in total mortality at 7 or 30 days.

PLATELET FUNCTION SUBSTUDY

- Following LD1, data showed significantly greater platelet inhibition pre-loading dose 2 (LD2) and 30 minutes post LD2 for the PP versus PNP treatment arm for both PRU and device-reported percent inhibition.
- By 2 hours post-LD2, the PRU values and percent inhibition for the PNP arm LD of 60 mg (LD2) were similar to the PP arm

SAFETY RESULTS

Safety Overview

TIMI Bleeding Events through 7 Days

The majority of TIMI bleeding events in all treated subjects and in subcohorts occurred early, essentially within the first 48 to 72 hours.

TIMI Major Bleeding Events through 7 Days

- For the population of all treated subjects, a significantly higher rate of all TIMI major bleeding was observed for PP versus PNP (2.55% versus 1.35%; HR [95% CI]: 1.900 [1.193, 3.024], p=0.006).
- A similar pattern of TIMI major bleeding through 7 days from the first LD was observed in the subcohorts with a higher event rate for PP versus PNP:
  - **PCI Only subcohort**: 1.36% versus 0.51%; HR (95% CI): 2.692 (1.132, 6.403), p=0.020
  - **CABG Only subcohort**: 20.66% versus 13.68%; HR [95% CI]: 1.591 [0.849, 2.980], p=0.143
  - **MM subcohort**: 5 PP versus 0 PNP
- The pattern of non-CABG bleeding event rates in all treated subjects and in the PCI Only subcohort were similar to results for all TIMI major bleeding, with a numerically higher event rate observed for PP versus PNP.
- The pattern of CABG bleeding event rates in all treated subjects and in the CABG Only subcohort were similar to results for all TIMI major bleeding, with a numerically higher event rate observed for PP versus PNP.
  - Within 5 days after the first LD, PP subjects had numerically higher chest tube output compared to PNP subjects from the first LD to CABG; then beyond 5 days, chest tube output was similar between PP and PNP subjects.
- The majority of TIMI major bleeding events were post-procedural (that is, PCI- or CABG-related events), occurred at the surgical incision or vascular access site and required transfusion or surgery.

TIMI Fatal Bleeding Events through 7 Days

- There were 3 TIMI fatal bleeding events, all in the PP group

- 1 in MM subcohort, subject received 1 LD only, died of alveolar hemorrhage at 5.8 days after first LD
- 2 in PCI subcohort (1 ICH at 9.7 days from first LD and 1 CV other at 18.2 days from first LD)

TIMI Life-Threatening Bleeding Events through 7 Days

- In the population of all treated subjects through 7 days from the first LD, a significantly higher rate of all TIMI life-threatening bleeding was observed for PP versus PNP (n=30 [1.47%] versus n=11 [0.55%]; HR [95% CI]: 2.684 [1.345, 5.355], p=0.004).
- A similar pattern of TIMI life-threatening bleeding through 7 days was observed in the subcohorts, with a higher event rate observed for PP versus PNP:
  - **PCI Only subcohort**: 12 (0.86%) versus 2 (0.15%); HR (95% CI): 5.932 (1.328, 26.497), p=0.008
    - The majority were vascular access site, pericardial, and retroperitoneal.
    - 2 PCI Only subjects in the PP group with TIMI life-threatening bleeding died:
      - ✓ 1 death from cardiogenic shock at 9.68 days from first LD
      - ✓ 1 death from a non-hemorrhagic stroke at 32.36 days from first LD
    - 7 PP subjects required a surgical procedure versus 0 in the PNP group
  - **CABG Only subcohort:** 13 (10.74%) versus 7 (5.98%); HR (95% CI) 1.866 (0.744, 4.677), p=0.176
  - **MM subcohort:** 3 PP, 0 PNP
  - The pattern of non-CABG bleeding life-threatening event rates in all treated subjects and in the PCI Only subcohort were similar to results for all TIMI life-threatening bleeding, with a numerically higher event rate observed for PP versus PNP.
  - The pattern of CABG life-threatening bleeding event rates in all treated subjects and in the CABG Only subcohort were similar to results for all TIMI life-threatening bleeding, with a numerically higher event rate observed for PP versus PNP.
- The majority of TIMI life-threatening bleeding events were post-procedural (that is, PCI- or CABG-related events), occurred at the surgical incision or vascular access site and required transfusions or surgery.
- For subjects who underwent PCI, notable interventions for TIMI life-threatening bleeding events included the need for surgical repair at the vascular access site. Transfusions were also required for TIMI life-threatening bleeding events for subjects who underwent PCI or CABG.

TIMI Major or Minor Bleeding Events through 7 Days

- Through 7 days from the first LD, a significantly higher rate of all TIMI major or minor bleeding was observed in the PP versus PNP (4.66% versus 2.20%; HR [95% CI]: 2.147 [1.502, 3.069], p<0.001).
- A similar pattern of TIMI major or minor bleeding through 7 days from the first LD was observed in the subcohorts with a higher event rate for PP versus PNP:
  - **PCI Only subcohort:** 3.37% versus 1.16%; HR (95% CI): 2.939 [1.666, 5.182], p<0.001
  - **CABG Only subcohort**: 28.10% versus 19.66%; HR (95% CI): 1.521 (0.896, 2.582), p=0.118
  - **MM subcohort:** 2.13% versus 0.20%; 10.692 (1.381, 82.815), p=0.005
- The addition of TIMI minor bleeding events to TIMI major increased the number, but did not affect the types of events.

TIMI Bleeding Events through 30 Days

- Beyond 7 days through 30 days after the first LD, patterns of results for TIMI bleeding events through 30 days from the first LD were similar to results observed through 7 days from the first LD, with a higher event rate observed for PP versus PNP.
- The main difference observed for 7 versus 30 day TIMI bleeding events was in TIMI major or minor bleeding through 30 days in which there was an increase in GI bleeding events with a need for endoscopies.

Subgroup Analyses of TIMI Bleeding Events through 7 Days

Prespecified analyses were conducted to determine the influence of baseline and post-baseline characteristics and risk factors on the incidence of the key bleeding endpoints. Subgroup analyses included demographic and baseline

characteristics (including gender, age and weight), medical history, concomitant medications, and index event characteristics.

Additional subgroup analyses included type of initial procedure (such as PCI or CABG), baseline creatinine clearance, sheath location, maximum stenosis and country and were performed for TIMI bleeding event endpoints.

Subgroup Analyses of Non-CABG-related TIMI Major or Minor Bleeding Events through 7 days: PCI Only Subcohort

- There were no statistically significant treatment-by-subgroup interaction for gender (p=0.349), age (p=0.403) or weight (0.500). However, significantly higher rates of non-CABG-related TIMI major or minor bleeding events for PP versus PNP were observed for females, males, subjects <75 years, and subjects ≥75 years.
- Although treatment-by-subgroup interactions were not significant, a significantly higher rate of non-CABG-related TIMI major or minor bleeding was also observed for PP subjects versus PNP in subgroups of subjects who received higher doses of aspirin, antithrombin monotherapy, UFH, GPIIb/IIIa bailout, a femoral sheath, and in both subgroups for use of closure device (yes/no).
- A significant treatment-by-subgroup interaction was observed based on region (Eastern Europe versus the rest of the world; interaction p = 0.090).
    - In the "rest of the world", the PP group had a significantly higher rate of TIMI major or minor versus PNP (4.01% versus 0.94%; HR (95% CI): 4.339 [2.008, 9.372], p<0.001).

Subgroup Analyses of CABG-Related TIMI Major or Minor Bleeding Events through 7 Days: CABG Only Subcohort

- There were no significant treatment-by-subgroup interactions based on gender (p=0.463), age (p=0.250) or weight (p=0.447). However, subjects <75 years of age in the PP group had statistically significantly higher event rates than the PNP group.
- Although there was not a significant treatment-by-subgroup interaction based on antithrombin use (p=0.224), PP subjects in the multiple therapies subgroup had a significantly higher rate of TIMI major bleeding compared with the PNP group.
- There was a significant treatment-by-use of closure device interaction (p=0.005). While a clinical explanation is not immediately obvious, this significant interaction may be related to regional differences in radial versus femoral arterial access.
    - For subjects who did not receive a closure device, the PP treatment group had a significantly higher rate of CABG-related TIMI major or minor bleeding compared with the PNP treatment groups (29.41% versus 10.26%; HR [95% CI]: 3.290 [1.483, 7.297]; p=0.002).
    - For those who received a closure device, there was not a significant difference between PP and PNP treatment groups.
- There was not a significant treatment-by-sheath location interaction (p=0.387), however within the radial subgroup, PP subjects had a significantly higher rate of CABG-related TIMI major bleeding compared with the PNP treatment group.

TREATMENT-EMERGENT ADVERSE EVENTS THROUGH 30 DAYS (WHILE AT RISK) IN ALL TREATED SUBJECTS

Fatal SAEs

- The rate of fatal SAEs, both hemorrhagic and non-hemorrhagic were similar for the PP and PNP treatment groups through 30 days from the first LD in the population of all treated subjects (0.64% versus 0.80%, p=0.539).
    - Through 7 days from the first LD, there were 2 fatal hemorrhagic SAEs:
        - 1 pulmonary alveolar haemorrhage in the PP group of the MM subcohort (cause of death was CEC-adjudicated "noncardiac hemorrhage – not intracranial")

- 1 cardiac tamponade in the PNP group of the PCI Only (cause of death was CEC-adjudicated MI at 18.21 days from the first LD).

- Beyond 7 days from the first LD and through 30 days, there was 1 additional fatal hemorrhagic SAE of ICH in the PP group of the PCI subcohort (cause of death was CEC-adjudicated ICH).

Other Adverse Events

- Significantly higher event rates for PP versus PNP were observed for the following categories of adverse events through 30 days from the first LD:
  - Hemorrhagic SAEs (2.95% versus 1.35%, p<0.001)
    - "Post procedural haemorrhage" is the preferred term for the only hemorrhagic SAE while at risk that occurred at a significantly higher rate for PP versus PNP (0.29% versus 0.0%, p=0.015)
  - Hemorrhagic TEAEs (13.84% versus 10.02%, p<0.001)
    - Haematoma" is the preferred term for the hemorrhagic TEAE while at risk that occurred at a significantly higher rate for PP versus PNP (5.01% versus 3.01%, p=0.001).
  - Adverse events related to study drug (10.85% versus 8.77%, p=0.026)
  - Hemorrhagic adverse events related to study drug (8.59% versus 6.21%, p=0.004)
- No statistically significant differences were observed for PP versus PNP subjects for the following categories of adverse events through 30 days from the first LD:
  - Fatal SAEs (0.64% versus 0.80%, p=0.539)
    - Hemorrhagic (0.10% versus 0.05%)
    - Non-hemorrhagic (0.54% versus 0.75%, p=0.401)
  - SAEs (10.11% versus 8.37%, p=0.056)
    - Non-hemorrhagic (7.95% versus 7.26%, p=0.410)
  - TEAEs leading to study drug discontinuation (1.52% versus 1.25%, p=0.465)
    - Non-hemorrhagic (1.03% versus 0.90%, p=0.675)
  - TEAEs (46.34% versus 45.84%, p=0.750)
    - Non-hemorrhagic (41.92% versus 42.79%, p=0.580).

CONCLUSIONS:

The primary objective of Study TADF was to test the hypothesis that, for subjects with NSTEMI with elevated troponin who were scheduled for coronary angiography/PCI, a prasugrel LD given at the time of qualifying diagnosis would be superior to a prasugrel LD given at the time of the PCI procedure, as measured by a reduction in the composite endpoint of CV death, MI, stroke, UR or GPIIb/IIIa inhibitor bailout through 7 days from randomization. The study was designed to address the fundamental question about the potential benefit from pretreatment as prasugrel was predicted to provide high and rapid inhibition of platelet aggregation (IPA) with either treatment arm. The primary objective was not met; there was not a reduction in ischemic events associated with pretreatment and there was an increased risk of early TIMI major bleeding, including TIMI life threatening bleeding that did not lead to a mortality imbalance between the 2 arms.

Study TADF results, which demonstrated the high and rapid onset of action associated with the prasugrel in addition to the median time from LD to coronary angiography/PCI of only 4.3 hours, provide important evidence addressing the fundamental question about the risk/benefit of pretreatment with a $P2Y_{12}$ inhibitor. In the 69% of study subjects who had PCI, the increased IPA for PP versus PNP subjects at the time of sheath insertion and performance of PCI exposed PP subjects to a higher bleeding risk without a reduction in peri-procedural MI or other ischemic events. Of interest, 31% of study subjects did not need pretreatment as they were medically managed or proceeded to CABG.

Two notable limitations were related to the subject population and the time from the first LD to diagnostic coronary angiography. ACCOAST did not include unstable NSTEMI subjects who were not able to wait a minimum of 2 hours for a diagnostic coronary angiogram and the pretreatment window (that is, the time from the first LD to coronary angiography) was much shorter than originally anticipated (actual median of 4.30 hours versus anticipated time of 12 hours).

In conclusion, Study TADF has demonstrated that prasugrel given at the time of NSTEMI diagnosis, prior to diagnostic coronary angiography, does not provide an additional efficacy benefit and increases the risk of major bleeding. With today's more rapid access to the catheterization laboratory and a rapid onset of action with the

potent $P2Y_{12}$ receptor antagonist prasugrel, there is no need for routine pretreatment in all NSTEMI patients. Study results further support the strategy of administering the prasugrel LD after coronary anatomy is defined at the time of PCI, as studied in TRITON-TIMI 38, in order to optimize the benefit/risk of patients with NSTEMI.