Supplementary Online Content


eAppendix.

Executive Committee, Data Safety and Monitoring Board, and Investigators
Protocol Definitions for Efficacy and Safety Assessments
Study exclusion criteria

eTable 1. P2Y\textsubscript{12} (PRU) Results for Stage 1 Patients

eTable 2. Prior Thienopyridine and Infusion Duration in the Safety Population

eTable 3. Frequency of Valid P2Y\textsubscript{12} (PRU) Measurement in Intention-to-Treat Population

eTable 4. ACUITY Minor Bleeding Events in the Safety Population

eTable 5. Incidence of Post Surgery Ischemic End Points (Through 30 Days)

eTable 6. Incidence of Postbaseline Clinically Significant Results for Serum Chemistry Parameters (to 7 Days or Discharge)

eTable 7. Incidence of Postbaseline Clinically Significant Results for Hematology Parameters (to 7 Days or Discharge)

This supplementary material has been provided by the authors to give readers additional information about their work.
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Protocol Definitions for Efficacy and Safety Assessments

**Efficacy: Protocol section 7.2.7**

*Assessment of efficacy*

VerifyNow™ P2Y₁₂ Assay will be performed at baseline, daily during the infusion period, just prior to surgery, immediately post-surgery, and 24 h (± 1 h) post-surgery. These blinded assessments will be analyzed and used to determine the level of platelet inhibition achieved at these various study time points. Only those assessments made while the patient is receiving randomized therapy will be included in the assessment of the primary endpoint.

Percent inhibition, as reported by the VerifyNow™ P2Y₁₂ Assay device, will be used in the determination of the appropriate dose to move forward with in Stage II. PRU will be used for assessment of efficacy for Stage II.

*Assessment of Myocardial Infarction (MI)*

Pre-operative myocardial infarction (from time of randomization) will be identified by the treating physician based on the presence of at least two of the following criteria:

- Characteristic ischemic chest pain occurring at rest or with minimal exercise, lasting longer than 20 minutes or requiring sublingual nitroglycerin or narcotic analgesia for the relief of the pain,
- Elevation of CK to at least twice the upper limit of normal for the given laboratory, and/or CK-MB and/or troponin T or I (at least the upper limit of normal values for the laboratory), in the absence of other explanation,
- Development of ≥ 40 msec Q waves in at least two adjacent ECG leads, or development of a new dominant R wave in V1 (R ≥ 1 mm > S in V1).

Post-operative myocardial infarction will be identified by the treating physician as is standard of care at the site based on the presence of at least:

- New Q waves on two contiguous leads on ECG, and/or
- CPK-MB >5x ULN

In any situations where it is unable to be determined by the site if a myocardial infarction has occurred the event will be adjudicated by the DSMB.

*Assessment of Stroke*

Stroke will be defined by the treating physician based upon clinical examination and radiographic imaging at the study site. If stroke occurs after hospital discharge source documents will be obtained, reviewed and confirmed by the investigator. Events will be reviewed by the research site investigators.
Assessment of urgent revascularization

Urgent revascularization will be defined as the urgent or emergent need for a Percutaneous Coronary Intervention (PCI) with or without stent placement or coronary artery bypass graft (CABG) surgery due to investigator-identified refractory cardiac ischemia.

Safety: Protocol sections 8 and 9

Assessment of safety

The primary safety endpoint for this trial is excessive CABG-related bleeding. Excessive CABG-related bleeding is defined as the occurrence of one or more of the following 3 components during the CABG procedure or post-operative hospitalization:

- Surgical re-exploration,
- 24 hour CT output > 1.5 liters
- Incidence of PRBC transfusion > 4 units.

Bleeding during the pre-operative period will be assessed using TIMI, GUSTO and ACUITY bleeding criteria from the time of randomization up to time of the operation.

In addition, all blood product transfusions, adverse events, and serious adverse events will be collected from randomization through hospital discharge.

CABG related bleeding:

CABG-related bleeding defined as the occurrence of one or more of the following 5 components during the CABG procedure will be measured through hospital discharge:

- Fatal bleeding
- Perioperative intracranial bleeding within 48 hours
- Reoperation following closure of sternotomy for the purpose of controlling bleeding
- Transfusion of $\geq 5$ units of whole blood or packed red blood cells within a 48 hour period. Cell saver products will not be counted. Platelet transfusions should be recorded and reported, but not included in the definition of major bleeding, until further information is obtained about the relationship to outcomes.
- Chest tube output $\geq 2$ L within a 24 hour period

Pre-operative bleeding

Pre-operative bleeding will be assessed as noted above but also using TIMI, GUSTO and ACUITY criteria.
TIMI criteria:
Hemorrhage will be classified as major or minor as detailed below:

**Major:** Any intracranial bleeding, or any bleeding associated with clinically overt signs associated with a drop in hemoglobin of >5 g/dL (or, when hemoglobin is not available, an absolute drop in hematocrit >15%)*

**Minor:** Any clinically overt sign of bleeding (including observation by imaging techniques) that is associated with a fall in hemoglobin of ≥3 g/dL and ≤5 g/dL (or, when hemoglobin is not available, an absolute drop in hematocrit of ≥9% and ≤15%)*

Bleeding events will also be classified as instrumented or spontaneous as defined below:

- **Instrumented:** Any hemorrhage that occurs as a result of an invasive procedure
- **Spontaneous:** Any hemorrhage which is not the direct result of an invasive procedure (e.g. gingival bleeding, epistaxis, gastrointestinal bleeding).

* To account for transfusion, hemoglobin (Hgb) and hematocrit (Hct) measurements will be adjusted for any packed red blood cells or whole blood given between baseline and post-transfusion measurements. A transfusion of one unit of blood will be 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 has been an intervening transfusion between two blood measurements, the following calculations will be performed:
  
  \[ \Delta \text{Hgb} = [\text{baseline Hgb} – \text{post transfusion Hgb}] + [\text{number of transfused units}] \]
  
  \[ \Delta \text{Hct} = [\text{baseline Hct} – \text{post transfusion Hct}] + [\text{number of transfused units x 3}] \]

GUSTO criteria:
Hemorrhage will be classified according to severity as mild, moderate or severe/life-threatening. Bleeding will be classified as mild (no transfusion or hemodynamic compromise), moderate (transfusion is required), or severe/life-threatening (intracranial hemorrhage or if hemodynamic compromise results).

ACUITY criteria:
Clinically significant bleeding will be defined as any 1 of the following: intracranial, retroperitoneal, intraocular, access site hemorrhage requiring radiological or surgical intervention, ≥5 centimeter (cm) diameter hematoma at puncture site, reduction in hemoglobin concentration of > 4 grams (g)/deciliter (dL) without an overt source of bleeding, reduction in hemoglobin concentration of > 3g/dL with an overt source of bleeding, re-operation for bleeding, use of any blood product transfusion. Minor bleeding will be defined as all other bleeding and will also be assessed.

Systematic analysis of in-hospital hemoglobin laboratory reports may be performed for all patients to detect unreported bleeding. All episodes of hemorrhage will be codified as to their relationship with CABG surgery. As these patients all require CABG surgery, autotransfusion (e.g. use of a cell saver) will not be considered an adverse bleeding event nor will the amount be assessed as a transfusion.

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**Adverse event**

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the drug was given or the subject was randomized in a clinical study are not to be considered AEs.

The severity of an AE and the relationship to study drug will be assessed by the investigator (see Appendix 3). The investigator should ensure that any patient experiencing an AE receives appropriate medical support until the event resolves.

**Serious adverse event**

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (It does not include an event that, had it occurred in a more severe form, might have caused death),
- results in persistent or significant disability/incapacity,
- requires in-subject hospitalization or prolongs hospitalization,
- is a congenital anomaly/birth defect, or
- is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe.
**Study Exclusion Criteria**

1. Need for urgent CABG

2. Confirmed or suspected pregnancy (in woman of child-bearing potential) or lactating females

3. Cerebrovascular accident within the previous year

4. Intracranial neoplasm or history of intracranial surgery

5. History of bleeding diathesis

6. Thrombocytopenia (platelet count of less than 100,000/µL)

7. Known International Normalized Ratio (INR) greater than 1.5

8. Requirement for dialysis treatment (hemodialysis or peritoneal)

9. Estimated glomerular filtration rate (GFR) <30 ml/min

10. Administration of abciximab within 24 hours of randomization or administration of eptifibatide or tirofiban within 12 hours of randomization

11. Plans to continue oral anticoagulant, thienopyridine or glycoprotein (GP) IIb/IIIa antagonist therapy in the pre-operative period

12. Known or suspected coagulopathy

13. Refusal to receive blood transfusion

14. Receipt of fibrinolytic therapy within 12 hours prior randomization

15. Allergy, and hypersensitivity, or contraindication to cangrelor, mannitol, sorbitol, or microcrystalline cellulose

16. High likelihood of being unavailable for follow-up

17. Participation in other clinical research studies involving evaluation of other investigational drugs or devices within 30 days of randomization

18. Any disease or condition which, in the judgment of the investigator, would place the patient at undue risk by being enrolled in the trial.
**eTable 1.** P2Y₁₂ (PRU) Results for Stage 1 Patients

<table>
<thead>
<tr>
<th></th>
<th>Cangrelor, 0.5 μg/kg/min (N= 5)</th>
<th>Cangrelor, 0.75 μg/kg/min (N= 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients maintain all PRU &lt; 240, n (%) and 95% CI</td>
<td>4/5 (80.0%, 28.4-99.5%)</td>
<td>6/6 (100%, 54.1-100.0%)</td>
</tr>
</tbody>
</table>

**eTable 2.** Prior Thienopyridine and Infusion Duration in the Safety Population

<table>
<thead>
<tr>
<th></th>
<th>Median (25th, 75th)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cangrelor (n= 106)</td>
</tr>
<tr>
<td>Time from Last Thienopyridine Use to Study Drug Start (hrs)</td>
<td>29.1 (11, 38)</td>
</tr>
<tr>
<td>Duration of Infusion (hrs)</td>
<td>67.0 (59, 91)</td>
</tr>
<tr>
<td>Time From Infusion End to Procedure Start</td>
<td>3.2 (2, 5)</td>
</tr>
</tbody>
</table>

**eTable 3.** Frequency of Valid P2Y₁₂ (PRU) Measurement in the Intention-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>Median (25th, 75th)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cangrelor (n= 84)</td>
</tr>
<tr>
<td>Valid PRU Values per Subject</td>
<td>3.0 (2, 4)</td>
</tr>
<tr>
<td>Preprocedure</td>
<td>n/N (%)</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>13/106 (12.3%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>2/106 (1.9%)</td>
</tr>
<tr>
<td>Hematoma &lt;5 cm at puncture site</td>
<td>2/106 (1.9%)</td>
</tr>
<tr>
<td>Oozing at puncture site</td>
<td>3/106 (2.8%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0/106 (0.0%)</td>
</tr>
<tr>
<td>Platelet count &lt;100,000</td>
<td>0/106 (0.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>4/106 (3.8%)</td>
</tr>
</tbody>
</table>
### eTable 5. Ischemic and Adverse Events, Safety Population

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>n/N (%)</th>
<th>Cangrelor (n=106)</th>
<th>Placebo (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence of Pre-Procedure Ischemic End Points (Randomization to Surgery)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/MI/IDR/Stroke</td>
<td>3 / 106 (2.8)</td>
<td>4 / 101 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 / 106 (0.9)</td>
<td>3 / 101 (3.0)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>2 / 106 (1.9)</td>
<td>0 / 101 (0.0)</td>
<td></td>
</tr>
<tr>
<td>IDR</td>
<td>1 / 106 (0.9)</td>
<td>0 / 101 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0 / 106 (0.0)</td>
<td>1 / 101 (1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Incidence of Post Surgery Ischemic End Points (through 30 days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death/MI/IDR/Stroke</td>
<td>4 / 102 (3.9)</td>
<td>4 / 96 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 / 102 (1.0)</td>
<td>2 / 96 (2.1)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>2 / 102 (2.0)</td>
<td>1 / 96 (1.0)</td>
<td></td>
</tr>
<tr>
<td>IDR</td>
<td>2 / 102 (2.0)</td>
<td>0 / 96 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1 / 102 (1.0)</td>
<td>1 / 96 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>
eTable 6. Incidence of Post-baseline Clinically Significant Results for Serum Chemistry Parameters (to 7 Days or Discharge)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Criteria</th>
<th>Cangrelor (N= 106)</th>
<th>Placebo (N= 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/SGPT (U/L)</td>
<td>=&gt; 3 * ULN</td>
<td>2 / 88 ( 2.3)</td>
<td>3 / 80 ( 3.8)</td>
</tr>
<tr>
<td>AST/SGOT (U/L)</td>
<td>=&gt; 3 * ULN</td>
<td>1 / 84 ( 1.2)</td>
<td>0 / 81 ( 0.0)</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>=&gt; 2</td>
<td>3 / 97 ( 3.1)</td>
<td>3 / 90 ( 3.3)</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>=&gt; 1.5 * ULN</td>
<td>0 / 81 ( 0.0)</td>
<td>0 / 79 ( 0.0)</td>
</tr>
</tbody>
</table>

The percentages are calculated relative to the number of patients with non-PCS baseline values and at least one post-baseline assessment. ULN = Upper Normal Limit

eTable 7. Incidence of Post-baseline Clinically Significant Results for Hematology Parameters (to 7 Days or Discharge)

<table>
<thead>
<tr>
<th>Parameter (units)</th>
<th>Criteria</th>
<th>Cangrelor (N= 106)</th>
<th>Placebo (N= 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>&lt; 0.9 * LLN</td>
<td>72 / 82 (87.8)</td>
<td>69 / 84 (82.1)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>&lt; 0.9 * LLN</td>
<td>70 / 84 (83.3)</td>
<td>76 / 88 (86.4)</td>
</tr>
<tr>
<td>Platelets (k/uL)</td>
<td>&lt;= 75 OR =&gt; 700</td>
<td>9 / 101 ( 8.9)</td>
<td>5 / 99 ( 5.1)</td>
</tr>
<tr>
<td>WBC (k/uL)</td>
<td>&lt;= 2.8 OR =&gt; 16</td>
<td>23 / 101 (22.8)</td>
<td>28 / 99 (28.3)</td>
</tr>
</tbody>
</table>

The percentages are calculated relative to the number of patients with non-PCS baseline values and at least one post-baseline assessment. LLN = Lower Normal Limit