

8. Have any of the following:
  - a. Prior history of hemorrhagic stroke
  - b. Intracranial neoplasm, arteriovenous malformation, or aneurysm
  - c. Ischemic stroke  $\leq$  3 months prior to screening
9. Have an International Normalized Ratio (INR) known to be  $> 1.5$  at the time of screening
10. Have a platelet count of  $< 100,000/\text{mm}^3$  at the time of screening
11. Have anemia (hemoglobin [Hgb]  $< 10 \text{ gm/dl}$ ) at the time of screening

**Prior/Concomitant Therapy Exclusion Criteria**

12. Have received one or more doses of a thienopyridine (ticlopidine or clopidogrel)  $\leq 5$  days prior to PCI
13. Have been administered a GPIIb/IIIa inhibitor within the past 7 days or plans to use a GPIIb/IIIa inhibitor during PCI
14. Are receiving or will receive oral anticoagulation or oral antiplatelet therapy (other than aspirin) that cannot be safely discontinued for the duration of the study
15. Are receiving daily treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX2) inhibitors that cannot be discontinued or are anticipated to require  $> 2$  weeks of daily treatment with NSAID or COX2 inhibitors during the study

**General Exclusion Criteria**

16. Are investigative site personnel directly affiliated with the study or are immediate family of investigative site personnel directly affiliated with the study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
17. Are employed by Eli Lilly & Company, Ube Industries Limited, Daiichi Sankyo company Limited, The TIMI Study Group, or the contract research organization (CRO) (that is, employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family of Lilly employees may participate in Lilly-sponsored clinical studies but are not permitted to participate at a Lilly facility. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
18. Have received treatment within the last 30 days with a drug or device that has not received regulatory approval for any indication at the time of study entry or are presently enrolled in another drug or device study
19. Have previously completed or withdrawn from this study or any other study investigating prasugrel
20. Are women who are known to be pregnant, who have given birth within the past 90 days, who are breastfeeding, or of child-bearing potential who test negative for pregnancy at Period 1, but refuse to use a reliable method of birth control (that is, barrier, hormonal, or abstinence) during the study
21. Have a concomitant medical illness (for example, terminal malignancy or severe hepatic dysfunction) that in the opinion of the investigator is associated with reduced survival over the expected treatment period (maximum of 35 days)
22. Have a condition associated with poor treatment compliance, including alcoholism, mental illness, or drug dependence
23. Have a history of intolerance or allergy to aspirin or approved thienopyridines (ticlopidine or clopidogrel)

**9.2.6 Study Plan**

The study had two phases. Phase 1 included study drug loading dose, cardiac catheterization, PCI (if indicated), and daily maintenance dose for  $14 \pm 2$  days in subjects undergoing PCI. In Phase 2, subjects were crossed over to the alternative daily maintenance dose for an additional  $14 \pm 2$  days.

Approximately 180 subjects were to be randomly assigned in parallel fashion to either a dosing regimen of prasugrel plus aspirin or to clopidogrel plus aspirin. Subjects were to receive either prasugrel 60 mg or clopidogrel 600 mg LD in a double-blind, double-dummy fashion. The LD was to be given as a pretreatment approximately 1 hour and no less than 30 minutes prior to the time that cardiac catheterization was expected to begin.

After randomization and prior to study drug, subjects were to undergo sampling for platelet measures and biomarkers. Subjects were to subsequently receive either prasugrel 60 mg or clopidogrel 600 mg LD in a double-blind, double-dummy fashion. The LD was to be given as a pretreatment approximately 1 hour ( $>30$  minutes) prior

to the time that cardiac catheterization was expected to begin. Treated subjects were to undergo platelet function measures at 30 minutes ( $\pm 5$  minutes). Additionally, 2 hours ( $\pm 10$  minutes) after the LD or following completion of diagnostic angiography, treated subjects were also to undergo platelet function measures.

Subjects who did not undergo PCI, were to have platelet function measures at 6 hours ( $\pm 30$  minutes) following the LD and a telephone call for the Day 15 visit to assess clinical endpoints and adverse events.

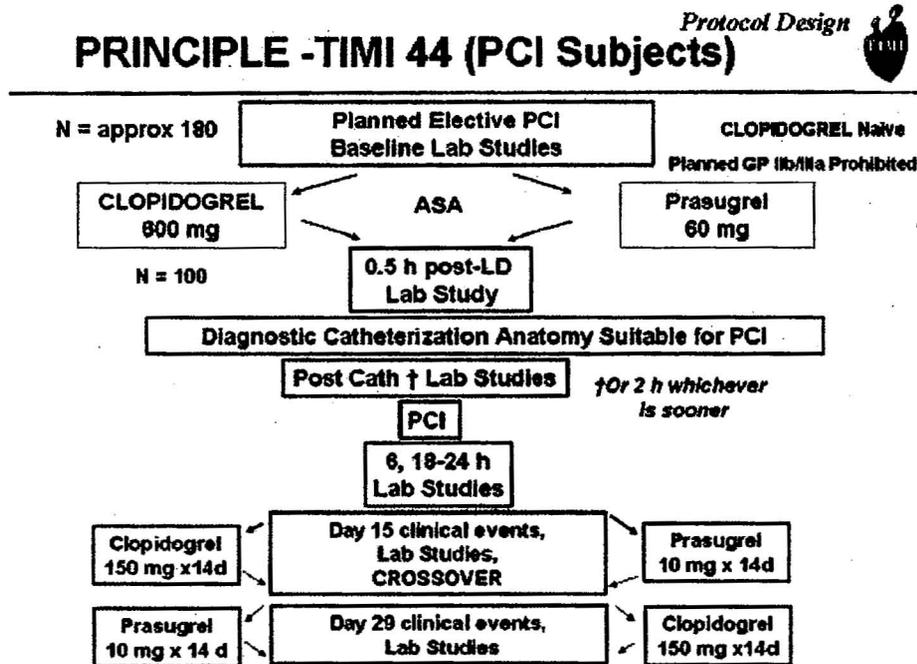
Subjects who were treated and underwent PCI were to have platelet function measures at 6 hours ( $\pm 30$  minutes) and 18-24 hours following the LD. These patients were to receive once daily maintenance dosing of either prasugrel 10 mg or clopidogrel 150 mg per LD assignment and were to follow-up at Day 15 for platelet function measures, inflammatory biomarkers, and clinical endpoint and safety assessments. The first maintenance dose was to be given after the Day 2 platelet measures (18 to 24 hours after loading dose).

At the Day 15 visit, the subject would be "crossed over" to the alternative regimen so that patients previously on clopidogrel would receive prasugrel 10 mg daily and patients previously on prasugrel would receive clopidogrel 150 mg daily for an additional  $14 \pm 2$  days. Subjects would report for a follow-up visit on Day 29.

Procedural anticoagulation with unfractionated heparin, low molecular weight heparin, or bivalirudin was at the discretion of the investigators; however, planned use of glycoprotein (GP) IIb/IIIa receptor inhibitors was prohibited.

The study design is displayed in Figure 28.

Figure 28. Study Design (Protocol H7T-MC-TABL)



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Oral enteric coated aspirin (325 to 500 mg) was recommended to be administered with the LD of study drug in subjects not receiving chronic aspirin therapy. Subsequently, each subject was to receive a daily enteric coated aspirin (75 to 325 mg).

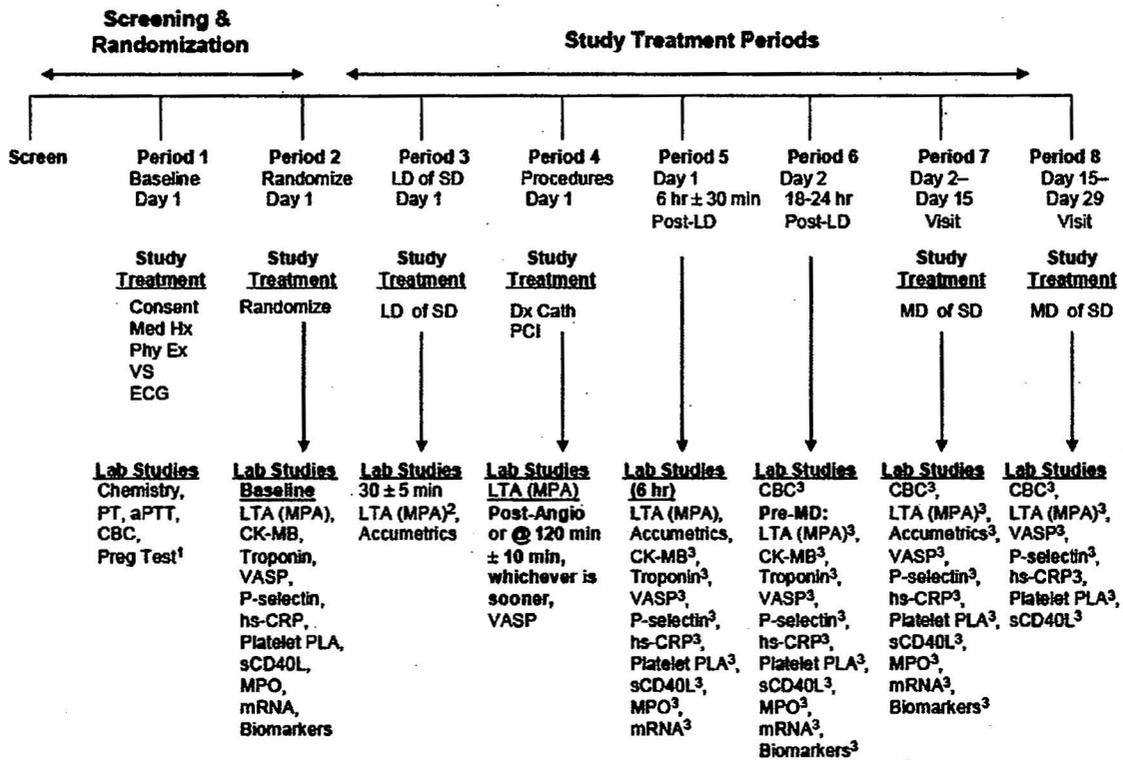
If unfractionated heparin was used during PCI, the recommended target ACT was between 200 to 300 seconds

If the subject required an emergency or urgent CABG or another urgent surgical procedure, study drug was to be temporarily discontinued and restarted when the investigator thought it was safe to do so. If a subject had an elective surgical procedure, including CABG, the study drug was to be discontinued at least 5 days before surgery.

### 9.2.7 Schedule of Evaluations and Procedures

The schedule of evaluations and procedures is displayed in Figure 29.

Figure 29. Schedule of Evaluations and Procedures (Protocol H7T-MC-TABL)



Abbreviations: Angio=angiography; aPTT=activated partial thromboplastin time; cath=catheterization; Dx=diagnostic; ECG=12-lead electrocardiogram; hr=hour; LD=loading dose; hs-CRP=high sensitivity C-reactive protein; IPA=inhibition of platelet activation; LTA=light transmittance aggregometry; MD=maintenance dose; Med Hx=medical history; min=minute; MPA=mean platelet aggregation; MPO=myeloperoxidase; mRNA=mononuclear cell mRNA; PCI=percutaneous coronary intervention; Phy Ex=physical exam; PLA=Platelet-Leukocyte aggregates; Preg Test=pregnancy test; PT=protime; SD=study drug; VASP=vasodilator-stimulated phosphoprotein; VS=vital signs.

<sup>1</sup>Pregnancy test for female subjects of child-bearing potential. <sup>2</sup>If the cardiac catheterization is unexpectedly delayed, IPA is also measured at 120 minutes (± 10 minutes). <sup>3</sup>Subjects who received PCI.

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Table 52. Study Schedule Protocol PRINCIPLE - TIMI 44

	Screen	Obtain Signed Consent	Randomization	Medical History	Phy Exam and VS	12-lead ECG	Study Drug	Chemistry, PT, aPTT	CBC	LTA (MPA)	Accumetrics (AA, P2Y12)	CK-MB / Troponin	Platelet/Inflammatory Markers <sup>c</sup>	VASP	mRNA	Biomarkers <sup>e</sup>
Screening to Consent	X															
Period 1 (Consent to Randomization)		X		X	X	X		X <sup>g</sup>	X							
Period 2 (Randomization to SD Administration)			X							X		X	X	X	X	X
Period 3 (LD to dx Cath)							X			X <sup>c,d</sup>	X <sup>c</sup>					
Period 4 (Cath to PCI)										X				X		
Period 5 (6 hr ± 30 minutes post-LD)										X <sup>e</sup>	X <sup>e</sup>	X <sup>e,f</sup>	X <sup>e,f</sup>	X <sup>e,f</sup>	X <sup>e,f</sup>	
Period 6 – Day 2 (18-24 hr post-LD)								X <sup>f</sup>	X <sup>f</sup>		X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>
Period 7/Day 15 (1 <sup>st</sup> MD to Day 15) <sup>h</sup>							X <sup>h,i</sup>	X <sup>h,j</sup>	X <sup>h,k</sup>	X <sup>h,k</sup>	X <sup>h</sup>		X <sup>h,l</sup>	X <sup>h,l</sup>	X <sup>h,l</sup>	X <sup>h</sup>
Period 8/Day 15 to Day 29							X <sup>i</sup>	X <sup>i,j</sup>	X <sup>i,k</sup>	X <sup>i,k</sup>			X <sup>i,l</sup>	X <sup>i,l</sup>		X <sup>i</sup>

Abbreviations: AA = Aspirin Assay; aPTT = activated partial thromboplastin; CBC = complete blood count; Cath = cardiac catheterization; CK-MB = creatine kinase-MB isoform; dx = diagnostic; ECG = electrocardiogram; hsCRP = high sensitivity C-Reactive Protein; IPA = inhibition of platelet aggregation; LD = loading dose; LTA = light transmittance aggregometry; MPA = maximum platelet aggregation; MD = maintenance dose; MPO = myeloperoxidase; mRNA = mononuclear cell mRNA; PCI = percutaneous coronary intervention; Phy = physical; PLA = platelet leukocyte aggregates; PT = prothrombin; sCD40L = soluble CD40 Ligand; SD = study drug; VASP = vasodilator-stimulated phosphoprotein; VS = vital signs.

<sup>a</sup> This also includes a pregnancy test for female subjects of child-bearing potential (see Appendix 16.1.1).

<sup>b</sup> P-selectin, hs-CRP, PLA, sCD40L, MPO (MPO will not be drawn on Day 29).

<sup>c</sup> Labs to be drawn at 30 minutes (± 5 minutes).

<sup>d</sup> If the cardiac catheterization is unexpectedly delayed, IPA is also measured at 120 minutes (± 10 minutes).

<sup>e</sup> Labs to be drawn at 6 hours (± 30 minutes). If 6 hours (± 30 minutes) occurs during PCI, samples may be obtained immediately following PCI.

<sup>f</sup> For those subjects who received PCI.

<sup>g</sup> Labs to be drawn once on Day 15 and once on Day 29.

<sup>h</sup> Daily MD of study drug. At Day 15, subjects will be crossed over to the alternate therapy.

<sup>i</sup> To be drawn once on Day 15.

<sup>j</sup> For a subject who was treated and did not receive PCI, a telephone call will be performed for Day 15.

<sup>k</sup> Serum and plasma samples will be stored. These samples may be used to measure markers relevant to the study of subjects with coronary artery disease. The samples will be destroyed within 20 years after last patient visit for the study. The samples will be stored in the United States by the TIMI Study Group at Brigham and Women's Hospital in Boston, Massachusetts.

Note: Shading denotes core labs.

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## 9.2.8 Endpoints

### 9.2.8.1 Primary Efficacy Measures

1. Inhibition of platelet aggregation (IPA) to 20  $\mu$ M adenosine diphosphate (ADP) by light transmission aggregometry (LTA) at 6 hours ( $\pm$  30 minutes) after loading dose of study drug. IPA is defined as  $(1 - [\text{maximal platelet aggregation at time } x \text{ after drug treatment}] / [\text{maximal platelet aggregation before drug treatment}]) \times 100$ .
2. IPA to 20  $\mu$ M ADP measured after  $14 \pm 2$  days of prasugrel 10 mg daily maintenance dose (MD) and the IPA after  $14 \pm 2$  days of clopidogrel 150 mg daily MD (this includes subjects receiving clopidogrel and prasugrel in either order during the crossover phase)

### 9.2.8.2 Additional Efficacy Measures

#### Phase 1

##### 1. Platelet Function Measures

- IPA to 20  $\mu$ M ADP at 30 min, 2 hours, 18 to 24 hours following loading dose of study drug
- IPA to 5  $\mu$ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- Maximum platelet aggregation (MPA) to 20  $\mu$ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- MPA to 5  $\mu$ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- Final extent of platelet aggregation (at 6 minutes after ADP addition) to 5 or 20  $\mu$ M ADP at 30 min, 2 hours, 6 hours, 18 to 24 hours following loading dose of study drug
- Thienopyridine hyporesponsiveness defined as IPA to 20  $\mu$ M ADP < 20% at 2 hours, 6 hours, and 18 to 24 hours following loading dose of study drug
- Vasodilator-stimulated phosphoprotein (VASP) phosphorylation ratio at 2 hours, 6 hours, 18 to 24 hours and  $14 \pm 2$  days following loading dose of study drug
- sCD40L at 6 and 18 to 24 hours after loading dose of study drug and after  $14 \pm 2$  days of maintenance therapy with study drug
- Peak sCD40 ligand (L) during follow-up (out to  $14 \pm 2$  days)
- Platelet P-selectin at 6 and 18 to 24 hours after loading dose of study drug and after  $14 \pm 2$  days of maintenance therapy with study drug
- Peak platelet P-selectin during follow-up (out to  $14 \pm 2$  days)
- Platelet-leukocyte aggregates (PLA) at 6 and 18 to 24 hours after loading dose of study drug and after  $14 \pm 2$  days of maintenance therapy with study drug
- Peak PLA during follow-up (out to  $14 \pm 2$  days)

##### 2. Inflammation Measures

- hs-CRP, myeloperoxidase (MPO) at 6 and 18 to 24 hours after loading dose of study drug and after  $14 \pm 2$  days of maintenance therapy with study drug
- Peak hs-CRP, MPO during follow-up (out to  $14 \pm 2$  days)

##### 3. Myonecrosis Measures

- Creatine kinase-myocardial bands (CK-MB), troponin at 6 and 18 to 24 hours
- CK-MB > 1 x upper limit of normal (ULN) during the first 24 hours after PCI
- CK-MB > 2 x ULN during the first 24 hours after PCI
- CK-MB > 3 x ULN during the first 24 hours after PCI
- CK-MB > 5 x ULN during the first 24 hours after PCI
- CK-MB > 10 x ULN during the first 24 hours after PCI

- Troponin > ULN during the first 24 hours after PCI
  - Troponin > decision limit for myocardial infarction (MI) during the first 24 hours after PCI
  - Peak CK-MB, troponin during follow-up
4. The major clinical efficacy measure is MACE, a composite of cardiovascular (CV) death, myocardial infarction (MI), stroke, during  $14 \pm 2$  days of maintenance therapy in subjects who were treated and received PCI.
  5. Other clinical endpoints during  $14 \pm 2$  days of maintenance therapy in subjects who were treated and received PCI:
    - Subacute stent thrombosis
    - Urgent target vessel revascularization (UTVR)
    - Individual components of MACE

## **Phase 2**

### **1. Platelet Function Measures**

- IPA to 5  $\mu$ M ADP at the end of the second phase (pooled subject data from both crossover periods)
- Final extent of platelet aggregation to 5 or 20  $\mu$ M ADP at the end of the second phase
- Thienopyridine hyporesponsiveness defined as IPA to 20  $\mu$ M ADP < 20% at the end of the second phase
- VASP phosphorylation ratio at the end of the second phase
- sCD40L level at the end of the second phase
- Platelet P-selectin level at the end of the second phase
- PLA level at the end of the second phase
- hs-CRP at the end of the second phase

### **9.2.9 Safety Measures**

#### **9.2.9.1 Primary Safety Measure**

Non-CABG-related TIMI significant bleeding defined as the occurrence of TIMI major or minor bleeding in the treated population at the Day 15 visit

#### **9.2.9.2 Other Prespecified Safety Measures**

1. Non-CABG-related TIMI Major bleeding
2. Non-CABG-related TIMI life-threatening bleeding
3. Non-CABG-related TIMI Minor bleeding

#### **9.2.10 Definitions**

- **Non-CABG-related TIMI major bleeding:** any intracranial hemorrhage (ICH) OR any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in hemoglobin (Hgb) of  $\geq 5$  gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as one unit packed red blood cells = 1 gm/dL Hgb = 3% hematocrit [Hct])
- **Non-CABG-related TIMI life-threatening bleeding:** any non-CABG-related TIMI major bleeding that is fatal, leads to hypotension that requires treatment with intravenous inotropic agents, OR requires surgical

intervention for ongoing bleeding, OR necessitates the transfusion of 4 or more units of blood (whole blood or packed red blood cells [RBC]) over a 48-hour period, OR any symptomatic ICH

- **Non-CABG-related TIMI minor bleeding:** any clinically overt bleeding (including bleeding evident on imaging studies) associated with a fall in Hgb of  $\geq 3$  gm/dL but  $< 5$  gm/dL from baseline (accounting for the effect of transfusions on change in Hgb, defined as one unit packed red blood cells = 1 gm/dL Hgb = 3%).

Table 53. TIMI Hemorrhage Criteria (TAAL)

	TIMI Hemorrhage Criteria <sup>a</sup>		
	ICH	Clinically Overt (including imaging)	Hgb Drop <sup>b,c</sup> (g/dL)
<b>Major Bleeding</b>	x	x	$\geq 5$
<b>Minor Bleeding</b>	-	x	3 to $< 5$
<b>Minimal Bleeding</b>	-	x	$< 3$

Abbreviations: Hgb = hemoglobin; ICH = intracranial hemorrhage; TIMI = The TIMI Study Group.

<sup>a</sup> Accounting for the effect of transfusions on change in Hgb as described in footnote b.

<sup>b</sup> One unit packed red blood cells = 1 g Hgb = 3% hematocrit (Hct).

<sup>c</sup> Hgb drop must be associated with clinically overt bleeding.

(Reproduced from Sponsor, Table 2, page 893)

- **Cardiovascular Death (CV Death):** death due to documented cardiovascular cause. Additionally, death not clearly attributable to noncardiovascular causes will be considered CV death.
- **Nonfatal Myocardial Infarction (MI):** the definition of MI is adapted from the standard ACC definition. The biomarker levels required for the diagnosis of MI are dependent on relationship to cardiac procedures. If the suspected event is within 48 hours of PCI, the CK-MB value must be  $> 3x$  the ULN, on a single measurement; no symptoms are required.

If the suspected event is within 48 hours of CABG, the CK-MB value (on a single measure) must be  $> 10x$  the upper limit of normal; no symptoms are required.

If the suspected event is not within 48 hours of PCI or CABG, the diagnostic criteria are met if the subject has CK-MB or cardiac troponin  $> ULN$  and the presence of either chest pain  $> 20$  minutes in duration or ST-segment deviation  $> 1$  mm on the ECG. If cardiac biomarkers are elevated at the time of suspected onset of an MI, there must be demonstration that biomarkers were falling prior to the suspected event and that the peak post-event CK-MB is  $> 50\%$  higher than the previous trough value.

In any clinical circumstance, the appearance of new Q-waves on the electrocardiogram (ECG) distinct from the baseline electrocardiogram (ECG) distinct from the baseline ECG or pathologic evidence (such as autopsy) showing a new myocardial infarction felt to have occurred after loading dose of study drug would be considered appropriate evidence for MI, as would ST-segment elevation ( $> 1$  mm in 2 contiguous leads) lasting for at more than 20 minutes and accompanied by ischemic chest pain or hemodynamic decompensation.

- **Stroke:** the rapid onset of new-persistent neurologic deficit lasting more than 24 hours. In the case of clinical diagnosis of stroke, computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging is strongly recommended. Stroke will be classified as either ischemic or hemorrhagic based on imaging data, if available or uncertain cause if imaging data is not available.

- **Urgent Target Vessel Revascularization (UTVR):** PCI or CABG for recurrent ischemia that, in the investigator's opinion, cannot be delayed for more than 24 hours and is defined by the investigator as a non-elective procedure. Revascularization, either with PCI or CABG, must include the vessel(s) dilated at the initial procedure.
- **Subacute Stent Thrombosis (SAT):** documented stent occlusion within 30 days following the completion of the index procedure felt to be thrombotic in nature by the treating physician. Thrombosis occurring during the index procedure will not be considered SAT.
- **Major Adverse Cardiac Event (MACE):** the occurrence of any of the following: CV death, MI, stroke, or UTVR.

#### 9.2.11 Statistical Considerations

The primary endpoint was the between treatment comparison of mean inhibition of platelet aggregation (IPA) to 20  $\mu$ M ADP 6 hours ( $\pm$  30 minutes) after the LD of study drug. The IPA at 6 hours was the relative decrease in maximum platelet aggregation (MPA) from the baseline to MPA at 6 hours after the loading dose multiplied by 100. The primary comparison was the IPA with prasugrel 60 mg LD with clopidogrel 600 mg relative to the primary endpoint at a two-sided significance level of 0.05. The primary analysis was analysis of covariance (ANCOVA), with factors for treatment group and study site (pooled, where necessary) and a covariate for MPA at baseline, in the "on treatment population" who did not receive GP IIb/IIIa inhibitors (receiving as bailout).

The sponsor was also interested in evaluating the "on treatment population" undergoing PCI who did not receive GP IIb/IIIa inhibitors.

There were no adjustments for multiple comparisons.

In Protocol Amendment (a) dated May 11, 2006, the "on treatment population" was defined as

"all randomized subjects who [had] received study therapy according to the protocol. For measures within the first 24 hours of therapy, this [would] include all subjects who received the full loading dose of study drug. For the follow-up visits (Day 15 visit and Day 29 visit), this [would] include subjects who [had] missed no more than 2 doses within the 14 days prior to the follow-up date and who [had] taken at least one dose of medication within 24 hours of the follow-up visit."

In the Statistical Analysis Plan (SAP) dated July 25, 2007, the definitions of the study populations to be analyzed were defined as follows:

- **On-treatment population:** consisted of all subjects that received the loading dose of the study medication. This was defined as subjects where the start time of study medication had been provided, or it had otherwise been confirmed that the subject took the study medication.
- **Acute phase population:** consisted of subjects in the "on-treatment population" who did not receive a glycoprotein (GP) IIb/IIIa antagonist. This population would be used for all analyses of IPA within 24 hours after the LD

Analysis of IPA measurements within 24 hours after the LD would be repeated amongst all subjects in the "acute phase population" that underwent a PCI after receiving the loading dose of study medication.

- The "chronic phase population" would consist of subjects in the "on-treatment population" that received a PCI irrespective of whether they received a GP IIb/IIIa inhibitor. This population was to be used for all analyses of IPA more than 24 hours after the LD.

In the Clinical Study Report dated October 1, 2007, the "on-treatment population" is defined as

“All subjects that received the loading dose of the study medication. This is defined as subjects where the start time of study medication was provided, or it was otherwise confirmed that the subject took the study medication.”

The sponsor estimated that 96 subjects undergoing PCI and not receiving a GP IIb/IIIa inhibitor assigned equally between prasugrel and clopidogrel would provide 90% power to demonstrate higher IPA for prasugrel. Sample size calculations were based on the following assumptions:

1. prasugrel 60 mg yields 15% (absolute) higher mean IPA compared to clopidogrel 600 mg at 6 hours
2. intersubject standard deviation (within a laboratory) of 25% exists for clopidogrel and 15% for prasugrel

The sponsor estimated that about 180 subjects would need to be randomized so that 100 subjects would undergo PCI and there would be at least 96 evaluable subjects with baseline and 6 hour sampling for light transmittance aggregometry (LTA).

No interim analysis was planned for the study.

## 9.2.12 Results

### 9.2.12.1 Sites, Investigators, and Study Dates

The study was conducted from August 24, 2006 to June 20, 2007. There were 15 principal investigators at a total of 14 study centers in 4 countries.

### 9.2.12.2 Good Practice, Monitoring, and Protocol Deviations

The study was conducted in accordance with Good Clinical Practices and the Declaration of Helsinki.

There were a total of 19 (9.5%) subjects with protocol violations including 8 (7.8%) in the prasugrel/clopidogrel group and 11 (11.1%) in the clopidogrel/prasugrel group. Two subjects in each treatment group were in serious violation and required withdrawal of their data from the analysis. The protocol violations are summarized in Table 54.

**Table 54. Protocol Violations (TABL)**

	Prasugrel/Clopidogrel N=102	Clopidogrel/Prasugrel N=99	Total N=201
Any Protocol Violations	8 (7.8%)	11 (11.1%)	19 (9.5%)
Retrospectively found to violate any of the entry criteria	2	6	8
Failed to provide written informed consent	0	0	0
Received any prohibited medications	5	5	10
Did not attend all of the study visits	1	1	2
Did not receive the correct study drug	1	0	1
Poorly compliant with the study drug	1	3	4

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	Prasugrel/Clopidogrel N=102	Clopidogrel/Prasugrel N=99	Total N=201
Any Significant Protocol Violations	2 (2.0%)	2 (2.0%)	4 (2.0%)
<p><b>MD = maintenance dose; N = number of subjects</b>  <b>Note: Poor compliance defined as percentage compliance &lt; 80% or &gt; 120%</b>  <b>Notes: No protocol violations were identified that necessitated excluding a subject from the entire study. The following subjects violated the protocol in a manner that could have compromised individual assessments; these subjects were excluded from the analysis of all efficacy measurements at the relevant time point(s):</b></p> <ul style="list-style-type: none"> <li>• Subject TABL-102-0008 received open-label clopidogrel for 3 days between the Day 2 and Day 15 visits (Day 15 data was excluded)</li> <li>• Subject TABL-301-0055 received open-label clopidogrel and phenprocoumon (for a serious adverse event of atrial fibrillation 5 days post LD) on an ongoing basis after Day 2 (Day 15 and Day 29 data was excluded)</li> <li>• Subject TABL-301-0059 received open-label clopidogrel for 5 days between the Day 2 and Day 15 visits (Day 15 data was excluded)</li> <li>• Subject TABL-302-0003 received the incorrect MD for 8 days between the Day 2 and Day 15 visits (Day 15 data was excluded)</li> <li>• Source: Table TABL.14.5</li> </ul> <p><b>(Reproduced from Sponsor, Table TABL.10.3, Protocol Violations, page 83 of 1590)</b></p>			

9.2.12.3 Disposition of Subjects

A total of 205 subjects were registered in the study via the interactive voice response system (IVRS) and 201 subjects were enrolled, including 102 subjects randomized to prasugrel and 99 subjects randomized to clopidogrel. Of the 102 subjects in the prasugrel treatment group, 54 subjects (52.9%) completed the trial, compared to 55 subjects (55.6%) out of the 99 subjects in the clopidogrel treatment group.

Four subjects withdrew from the study prior to taking study drug LD. One subject withdrew consent due to elevated cardiac enzymes, which was an exclusion criterion. Another subject was referred for stress echocardiography between enrollment and cardiac angiography and required coronary artery bypass grafting with mitral valve replacement. The last two subjects withdrew because one decided not to participate in the study after a discussion with his physician and the other withdrew consent after several unsuccessful attempts at phlebotomy.

Subject disposition is displayed in Figure 30.