SAVI-PCI

Shortened Aggrastat Versus Integrilin in Percutaneous Coronary Intervention

A Randomized, Multicenter, Open-Label Study to Evaluate the Efficacy of Tirofiban Using a High-Dose Bolus Plus a Shortened Infusion Duration Versus Label-Dosing Eptifibatide in Patients Undergoing Percutaneous Coronary Intervention

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Statistical Analysis Plan
Version 2.0

Statistical Analysis Plan

Study Title:

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(SAVI-PCI)

Study Protocol #: 11002

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACT	Activated clotting time
ADP	Adenosine diphosphate
AHA	American Heart Association
AE	Adverse event
aPTT	Activated partial thromboplastin time
CABG	Coronary artery bypass graft
CBC	Complete blood count
CDS	Clinical development solutions
CK	Creatine kinase
CK-MB	Creatine kinase-myocardial band
CNS	Central nervous system
CRA	Clinical research associate
CRF	Case report form
CVA	Cerebrovascular accident
Da	Dalton
DSMB	Drug Safety Monitoring Board
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESPRIT	Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy
ESRD	End stage renal disease
ENT	Ears, nose, throat
FDA	Food and Drug Administration
GCP	Good clinical practice
GI	Gastrointestinal
GPIIb/IIIa	Glycoprotein IIb/IIIa receptor antagonist
GU	Genitourinary
Hct	Hematocrit
Hgb	Hemoglobin

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HIPAA	Health Insurance Portability and Accountability Act
HDB	High-dose bolus (25 µg/kg tirofiban)
h	Hour(s)
Hg	Mercury
ICF	Informed consent form
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
ITT	Intent to treat
I.V.	Intravenous
kg	kilogram
LTA	Light transmission aggregometry
mg	milligram
MI	Myocardial infarction
min	minute
mL	milliliter
mm	millimeter
MITT	Modified intent to treat
NS	Non-significant
NSTEMI	Non-ST elevation myocardial infarction
NSTE	Non-ST elevation
PCI	Percutaneous coronary intervention
PK	Pharmacokinetic
PPACK	D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone
PPM	Periprocedural myonecrosis
PRISM	The Platelet Receptor Inhibition in Ischemic Syndrome Management
PRISM PLUS	The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited By Unstable Signs and Symptoms PT
PTCA	Prothrombin time
PTCA	Percutaneous transluminal coronary angioplasty

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REPLACE-2	Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events
RESTORE	Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis
RPFA	Rapid platelet function assay
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SCRI	Sarah Cannon Research Institute second
sec	Seconds
SOP	Standard operating procedure
TARGET	Do Tirofiban and ReoPro Give Similar Efficacy Trial
TRAP	Thrombin receptor agonist peptide
STEMI	ST elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction
uTVR	Urgent target vessel revascularization
u	Units
ULN	Upper limit of normal
uFH	Unfractionated heparin
uTVR	Urgent target vessel revascularization
vs.	versus
WHF	World Heart Federation
µg	microgram
µL	microliter

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1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a detailed description of the statistical analyses that will be performed according to the study protocol.

The SAP presents a summary of the study protocol and describes the populations that will be analyzed. Relevant subject characteristics and parameters to be evaluated are described along with the specific statistical methods assessing the study endpoints.

2 PROTOCOL SUMMARY

2.1 Background

An estimated 596,000 patients underwent percutaneous coronary intervention (PCI) procedures in the United States in 2009, and the majority of these patients received a coronary stent as part of their treatment. The number of percutaneous revascularization procedures performed has dramatically increased in the last decade, and PCI is the most common procedure performed on hospitalized adult Americans [1].

PCI carries an inherent risk of thrombotic complications. Patients therefore receive periprocedural pharmacotherapies targeted at inhibiting anticoagulation, including platelet aggregation. The same mechanisms that confer the benefits of these agents, however, also increase the risk of bleeding which has been correlated with adverse outcomes [2, 3]. Selecting the appropriate pharmacotherapies requires close attention to the delicate balance between reducing the risk of ischemic events and minimizing bleeding risk.

A broad range of antiplatelet agents are available, including aspirin, thienopyridines, and glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, all of which have shown considerable efficacy and satisfactory safety in the population of patients undergoing PCI. Antiplatelet therapy is relevant during PCI since disruption of the arterial wall results in platelet activation, adhesion and

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aggregation, which leads to thrombus formation. Aspirin reduces the incidence of acute thrombotic complications during PCI and is considered standard therapy. However, aspirin is a relatively weak platelet inhibitor, inhibiting the cyclooxygenase pathway, which is only one of the many pathways to platelet aggregation. More potent antiplatelet agents have been proven superior to aspirin, and when administered together are synergistic [4]. When combined with aspirin, oral thienopyridines such as ticlopidine, clopidogrel, prasugrel and ticagrelor provide additional platelet inhibition, thereby reducing the rate of ischemic events, particularly among patients receiving a coronary stent. Direct and indirect thrombin inhibitors (e.g. bivalirudin and unfractionated heparin), while not providing substantial antiplatelet inhibition, are used in conjunction with, and sometimes in place of, GPIIb/IIIa inhibitors.

Three GPIIb/IIIa inhibitors are approved for use in the United States: abciximab (Eli Lilly & Company, Indianapolis, Indiana), eptifibatide (Merck & Co., Whitehouse Station, New Jersey), and tirofiban HCl (Medicure Pharma Inc., Princeton, New Jersey) [5]. These agents block the GPIIb/IIIa receptor on platelets, blocking what has frequently been termed the final common pathway of aggregation, i.e., fibrinogen-mediated cross-linkage [6]. Their efficacy in preventing PCI-related complications [7-14] and in treatment of non- ST-segment-elevation (NSTE) acute coronary syndrome (ACS) [15-19] has been demonstrated in multiple large-scale trials, with overall risk reductions in adverse thrombotic events in PCI populations of 35% and in NSTE ACS of 44% [5].

Tirofiban, more specifically, is a highly selective non-peptide antagonist of the GPIIb/IIIa receptor whose structure mimics the RGD peptide sequence in fibrinogen. Tirofiban is similar to eptifibatide but is a smaller molecule (495Da vs. 832Da), is more potent (143 nM vs. 810 nM for concentration required to achieve 50% platelet inhibition), with a slightly shorter half-life (2h vs. 2.5h). Compared to abciximab, tirofiban is reversible, is not known to be immunogenic, and, in combination with heparin, has been shown to be effective in reducing ischemic events among patients with acute coronary syndrome. Data from 6 large clinical trials using tirofiban at the currently approved label dose [14, 15, 17, 20-22] demonstrated its efficacy and safety in reducing

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acute ischemic events in a broad range of patients (cumulative N >12,000) with ACS, moderate to high-risk coronary lesion anatomy, or both. Despite evidence for efficacy of the approved dosing in ACS, further investigations established the tirofiban label-dosing to be suboptimal for settings such as PCI and stent setting where rapid (<30 minute) attainment of therapeutic platelet inhibition is required and that a higher dose bolus (HDB) regimen of tirofiban (25 µg/kg followed by a 0.15 µg/kg/min maintenance infusion) is necessary. Data for the HDB tirofiban regimen from 15 clinical studies and 50 peer-reviewed publications since 2003 have clearly demonstrated its efficacy and safety profile [23-46]. The tirofiban high-dose bolus regimen is approved for use in the setting of PCI in Europe and the United States.

In addition, several studies involving GPIIb/IIIa inhibitor therapies have investigated the clinical effectiveness and safety of using a bolus plus a shortened infusion duration or a bolus- only dosing regimen in the PCI setting. These reduced regimens are seen as attractive to interventional cardiologists since it has potential to reduce bleeding tendencies, lower the cost of therapy, and reduce the need for overnight hospitalization without compromising efficacy.

Bertrand and co-workers [47] showed a high-dose bolus only of abciximab to be not clinically inferior to the standard bolus plus 12 hour infusion of abciximab after uncomplicated PCI in their study patient population. Fung and co-workers [48] showed that a <2 hour infusion of eptifibatide is non-inferior to the standard 18 hour eptifibatide infusion in preventing ischemic outcomes and is superior in reducing major bleeding after successful coronary intervention. Marmur and co-workers [31] showed that a high-dose of tirofiban (25 µg/kg) during PCI is safe and, in a sub-population of ACS patients, compares favorably to the post-PCI MI incidence of REPLACE-2 [49]. These studies suggest a bolus plus a shortened infusion of GPIIb/IIIa inhibitor therapy can be safe and effective in the setting of PCI.

2.2 Rationale

Anti-platelet therapy is established as improving outcomes in the setting of PCI of which GPIIb/IIIa inhibitors are the most potent and efficacious. Both eptifibatide and tirofiban

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experienced serious challenges in establishing an optimal dosing regimen during their clinical development. After refinement of dosing, treatment guidelines now recommend their use to improve outcomes [50, 51]. Over time, and with the continued evolution of therapy, concerns linked to safety and inconvenience of the relatively long infusion have complicated and limited the use of these agents despite their demonstrated efficacy. There is, therefore, a clear medical and scientific interest to re-evaluate and to further optimize the GPIIb/IIIa inhibitor therapy dosing regimen.

This clinical protocol was designed to evaluate the efficacy and safety of a 25 µg/kg bolus dose of tirofiban followed by an infusion 0.15 µg/kg/min for the duration of PCI procedure plus a minimum of one hour and up to a maximum of two hours post-PCI among patients undergoing PCI with a planned placement of a coronary stent and to compare the efficacy and safety of this regimen of tirofiban to label-dosing eptifibatide. In addition, a comparison of tirofiban using a shortened infusion duration versus tirofiban using a longer infusion duration will also be evaluated to isolate any clinical differences using different infusion durations of the same drug. The third comparison of tirofiban versus eptifibatide (using a 12-18 hour infusion duration for both treatment arms) will be evaluated to isolate any clinical differences between the two drugs using the same infusion duration.

2.3 Study Objectives

2.3.1 Primary Objective:

The first primary objective of this study is to assess whether a tirofiban regimen of a high dose bolus plus a shortened infusion duration compared to label-dosing of eptifibatide in patients undergoing PCI is associated with a non-inferior composite rate of death, PPM, uTVR or in-hospital major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

The co-primary objectives of this study are to assess whether:

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(i) a short tirofiban regimen of a high-dose bolus plus a 1-2 hour infusion post procedure compared to a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion, and (ii) a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion compared to label-dosing eptifibatide, are associated with non-inferior composite rates of death, PPM, uTVR, or in-hospital major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

2.3.2 Secondary Objective(s):

The first secondary objective of this study is to assess whether a tirofiban regimen of a high-dose bolus plus a shortened infusion duration is safe compared to label-dosing eptifibatide among patients undergoing PCI, as assessed by the incidence of major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

The co-secondary objectives of this study are to assess whether: (i) a short tirofiban regimen of a high-dose bolus plus a 1-2 hour infusion post procedure is safe compared to a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion, and (ii) a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion is safe compared to label-dosing eptifibatide, among patients undergoing PCI as assessed by the incidence of major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

2.4 Study Design

This is a randomized, multicenter, open-label study comparing tirofiban I.V. bolus injection followed by a maintenance infusion for the duration of the PCI procedure plus a minimum of one hour and up to a maximum of two hours post-PCI versus label-dosing eptifibatide. Patients were randomized to tirofiban or eptifibatide using a 1:1 allocation ratio. At 159 randomized patients, a 1:1:1 randomization was initiated, randomizing patients to short tirofiban, eptifibatide or long tirofiban. Enrolment in the long tirofiban arm has been completed. Patients are mandated to stay a minimum of 18 hours following PCI.

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Physician-directed standard background therapies will include dual oral antiplatelet therapy with aspirin and an approved oral P2Y12 antagonist as well as antithrombotic therapy with unfractionated heparin. Physician-directed P2Y12 antagonist therapy and choice of femoral or radial access site must be pre-specified prior to randomization.

The first 159 patients were randomized to the following two treatment arms on a 1:1 basis:

1. Tirofiban (25 µg/kg bolus followed by a 0.15 µg/kg/min infusion for the duration of the PCI procedure plus a minimum of one hour and up to a maximum of two hours post-PCI).
2. Eptifibatide (180 µg/kg bolus followed by a 2.0 µg/kg/min infusion for 18 hours post-PCI [minimum 12 hours mandated], with a second 180 µg/kg bolus 10 min after the first).

The three treatment arms for enrollment after the 159th patient were:

1. Short Tirofiban (25 µg/kg bolus followed by a 0.15 µg/kg/min infusion for the duration of the PCI procedure plus a minimum of one hour and up to a maximum of two hours post-PCI).
2. Eptifibatide (180 µg/kg bolus followed by a 2.0 µg/kg/min infusion for 18 hours post-PCI [minimum 12 hours mandated], with a second 180 µg/kg bolus 10 min after the first).
3. Long Tirofiban (25 µg/kg bolus followed by a 0.15 µg/kg/min infusion for 18 hours post-PCI) [minimum 12 hours mandated].

The short tirofiban versus eptifibatide comparison involves approximately 500 patients; the short tirofiban versus long tirofiban comparison involves approximately 350 patients; and the long tirofiban versus eptifibatide comparison involves approximately 350 patients. Approximately 550 patients will be enrolled into the study.

The study procedures to take place during the course of the study are summarized in the following Schedule of Evaluations and Procedures (Table 1).

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Table 1. Schedule of Evaluations and Procedures

EVALUATION/ PROCEDURE	Timing						
	Within 7 days of randomization	Within 24 h of randomization	Just Prior to PCI	Just After PCI	9±3 h following PCI	21 ±3 h following PCI	42±6 h following PCI
Informed Consent	X						
Inclusion/Exclusion Review	X						
Physical Exam	X						
Brief Medical History	X						
Serum/Urine pregnancy if of child bearing potential	X						
Serum Creatinine		X					
PT-INR	X[3]						
Hemoglobin/Hematocrit/ Platelet Count		X	X[5]		X[5]	X[5]	X[1]
Vital Signs	X[4]				X[6]		
Activated Clotting Time			X	X[7]			
Troponin I/T (Local Lab)			X[5]		X[5]	X[5]	X[1]
Randomization			X				
Unfractionated Heparin			X				
Bolus (study drug)			X				
Infusion Initiated (study drug)			X				
Concomitant Medications	X	X	X		X	X	X[2]
Adverse Events			X		X	X	X[2]

1 42±6 h sample is required if patient stays in the hospital longer than 36 h following PCI.
2 42±6 h assessment is required if patient stays in the hospital longer than 36 h following PCI.
3 PT-INR for patients receiving oral anticoagulation (warfarin derivatives) within 7 days prior to randomization (assessment must be done subsequent to last dose); if the last value prior to PCI (within 24 hours prior to randomization) is >1.3 times the control, patient
is not eligible for enrollment (within 24 hours)
4 Vital signs within 7 days prior to randomization include height and weight, body temperature, heart rate and systolic and diastolic blood pressure.

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5 Sampling is **mandated**.

6 Vital signs at 9±3 hours following PCI include heart rate and systolic and diastolic blood pressure only.

7 ACT measurement at start of study drug.

2.5 Study Duration

Subject enrolment in the Long Tirofiban arm has been completed. Enrolment continues in the Short Tirofiban and Eptifibatide arms as outlined in Section 2.4 above.

2.6 Sample Size

The primary outcome variable for this trial is the composite of death, PPM, uTVR or REPLACE-2 major bleeding.

Sample size calculations ensure that the one-sided non-inferiority hypothesis of the first primary outcome can be tested with a type-I error rate of 2.5% and 99% power. An event rate of 32.5% was assumed for the active control and test group, which was then later adjusted to be 51% based on pooled analysis after 159 randomized patients. A sample size re-estimation was conducted after 159 randomized patients.

For the two co-primary tests, a sample size of approximately 350 was obtained by setting the non-inferiority margin at 19.1%, power at 94.5% and a 1-sided alpha at 0.025 assuming an event rate of 51%.

For the secondary endpoints involving ≥ 10 times troponin and comparing short tirofiban to eptifibatide, a sample size of approximately 500 was obtained by setting the noninferiority margin at 12.4%, power at 85% and a 1-sided alpha at 0.025 assuming an event rate of 32% (based on ≥10 times troponin elevation data from the 159 randomized patients).

SAS version 9.2 (SAS Institute, Cary, NC) was used for the sample-size calculations.

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2.7 Subject Selection

Patients who meet all of the inclusion criteria and none of the exclusion criteria at the time of randomization will be eligible for the study.

2.7.1 Inclusion Criteria

a. Age ≥ 18 years of age
b. Scheduled to undergo PCI with an FDA approved or cleared device (stent or procedures such as balloon angioplasty, rotoblation, AngioSculpt, laser atherectomy, etc.) in one or more native coronary target lesions
c. Written informed consent.

2.7.2 Exclusion Criteria

a. Primary PCI for STEMI as index procedure
b. Prior STEMI within 48 hours before randomization
c. Prior PCI within 30 days before randomization
d. Planned staged PCI within the subsequent 48 hours after index PCI
e. Planned PCI of vein graft lesions only
f. Use of abciximab within 7 days before randomization
g. Use of tirofiban or eptifibatide within 12 hours before randomization
h. Use of low-molecular weight heparin within 12 hours before randomization
i. Use of bivalirudin within 12 hours before randomization
j. Use of warfarin within 7 days before randomization unless INR ≤ 1.3
k. Use of dabigatran or rivaroxaban within 3 days prior to randomization
l. Use of thrombolytic agents administered within 24 hours before randomization
m. Pregnant
n. Active pericarditis
o. Presumed or documented history of vasculitis
p. Uncontrolled hypertension (blood pressure > 180/110 mm Hg)
q. Dependency on renal dialysis

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r. Active internal bleeding or bleeding diathesis, surgery, trauma or gastrointestinal / genitourinary tract bleeding within 6 weeks prior to randomization
s. Prior intracranial hemorrhage, hemorrhagic stroke, cerebrovascular accident (CVA) within 2 years or CVA with significant residual neurological deficit, intracranial neoplasm, arteriovenous malformation, aneurysm, or structural abnormality
t. Thrombocytopenia (platelet count <100 x 10^3µL) or history of thrombocytopenia following heparin, tirofiban or eptifibatide
u. Planned participation in any other clinical trial of an investigational drug or device, or a clinical trial of an approved drug or device for a non-approved use, up to 48 hours following PCI
v. Participation in another clinical trial 30 days prior to participation in the current study
w. Any other condition that in the opinion of the investigator may compromise the safety or compliance of the patient or would preclude patient successfully completing the trial
x. Known inability to comply with the protocol for the duration of the study.

2.8 Randomization

Once all baseline examinations and tests are completed, the site will once again carefully review the inclusion and exclusion criteria described in the protocol to ensure that the patient is eligible to enter the study.

Naming of oral P2Y12 antagonist agent (clopidogrel, prasugrel, or ticagrelor) to be used post-randomization must be pre-specified prior to randomization.

Selection of either the femoral or radial access site must be pre-specified prior to randomization.
Randomization may occur only if all of the following criteria are satisfied:

a. Consented patient is confirmed to be eligible for the study, AND
b. name of intended oral P2Y12 antagonist agent used post-randomization is prespecified, AND
c. access site for PCI is pre-specified, AND

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d. decision to proceed to PCI is finalized, AND
e. timing between randomization and initiation of the PCI procedure is less than 2 hours.

Once the above criteria are satisfied, the patient may be randomized. The timing for randomization in this study is critical. The reason for timing the study drug administration so close to time of PCI is to minimize inappropriate patient enrollment. Situations where this might occur include the procedure where PCI is aborted or otherwise not performed or when a decision is made not to administer study medication for whatever reason.

At randomization, the patient will be assigned a study number that will allow identification of the patient throughout the study, and the appropriate staff will prepare the corresponding study drug. Patients will be randomized via a centralized randomization system to receive either tirofiban or eptifibatide.

The randomization will stratify patients according to femoral or radial access.

2.9 Study Endpoints

The following sections describe the study endpoints used to address the study objectives.

2.9.1 Efficacy Measures

2.9.1.1 Primary Endpoint

The primary objective will be assessed with the composite of death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

- First primary test: A short tirofiban regimen of a high-dose bolus plus a shortened infusion duration is non-inferior to label-dosing eptifibatide among patients undergoing PCI with respect to death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.
- Co-primary tests:

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- (i) a short tirofiban regimen of a high-dose bolus plus a 1-2 hour infusion post procedure is non-inferior to a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion with respect to death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first, and
- (ii) a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion is non-inferior to label-dosing eptifibatide with respect to death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first. No adjustments for multiple testing will be made.

2.9.1.2 Secondary Endpoints

Secondary endpoints will be:

– First secondary test: A short tirofiban regimen of a high-dose bolus plus a shortened infusion duration is non-inferior to label-dosing eptifibatide among patients undergoing PCI with respect to the following list:
  - death, PPM or uTVR within 48 hours following PCI or hospital discharge, whichever comes first
  - PPM within 48 hours following PCI or hospital discharge, whichever comes first
  - uTVR within 48 hours following PCI or hospital discharge, whichever comes first
  - death within 48 hours following PCI or hospital discharge, whichever comes first
  - death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first, where PPM is defined as at least one troponin elevation of ≥ 10 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory within 48 hours following PCI or hospital discharge, whichever comes first (a non-inferiority margin of 12.4% will be used for the short tirofiban versus eptifibatide comparison)
  - at least one troponin elevation of ≥ 10 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first (a

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noninferiority margin of 12.4% will be used for the short tirofiban versus eptifibatide comparison)

- at least one troponin elevation of ≥ 20 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first
- at least one troponin elevation of ≥ 50 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first.

– Co-secondary tests:
  - (i) a short tirofiban regimen of a high-dose bolus plus a 1-2 hour infusion duration post procedure is non-inferior to a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion, and
  - (ii) a long tirofiban regimen of a high-dose bolus plus a 12-18 hour infusion is non-inferior to label-dosing eptifibatide with respect to the same secondary tests in the list above.

2.9.1.3 Definition of Composite Endpoint

– Death due to any cause will be assessed through to 48 hours following PCI or hospital discharge, whichever comes first.
– Periprocedural myonecrosis will have occurred if there is at least one troponin (troponin I or troponin T) value of ≥ 3 times the upper limit of normal and at least 20% or greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first.
  - To be included in the primary composite endpoint analysis and in the secondary PPM endpoint analysis, a patient must have the pre-PCI troponin Local Laboratory measurement and at least one troponin Local Laboratory measurement within 48 hours following PCI or hospital discharge, whichever comes first.

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- Patients without a pre-PCI troponin Local Laboratory measurement will not be included in the PPM endpoint analysis but will still be included in the intention to treat analysis and be analyzed for death and uTVR.
- Patients without any troponin Local Laboratory measurements within 48 hours following PCI or hospital discharge, whichever comes first will not be included in the PPM endpoint analysis but will still be included in the intention to treat analysis and be analyzed for death, uTVR and major bleeding.

– Urgent Target Vessel Revascularization (uTVR) is either a PCI following the index PCI, or any CABG procedure performed after the index PCI on a non-selective basis in the target vessel because of recurrent myocardial ischemia. A revascularization procedure in the target vessel is considered urgent if it is due to one or more episodes of chest pain, presumed to be ischemic in origin and lasting at least 5 minutes, and results in either urgent repeat PCI or urgent coronary artery bypass surgery involving the target vessel. In the absence of pain, new ischemic ST-segment or T-wave changes, acute pulmonary edema, ventricular arrhythmias presumed to be ischemic in origin will constitute sufficient evidence of ischemia. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guidewire removal. For uTVR to count towards the primary composite endpoint, uTVR will have to be initiated during the course of the study (i.e., 48 hours following PCI or hospital discharge, whichever comes first).

– Major bleeding is defined using the criteria from the REPLACE-2 trial. Major bleeding is defined as follows:

a. transfusion of ≥ 2 units whole blood or packed red blood cells, or
b. intracranial hemorrhage, or
c. retroperitoneal hemorrhage, or
d. decrease in Hgb more than 4 g/dL (or 12% of Hct) with no bleeding site identified despite attempts to determine, or
e. spontaneous or non-spontaneous blood loss associated with a Hgb drop > 3 g/dL (or 10% of Hct) with an overt site of hemorrhage.

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The REPLACE-2 Major bleeding definition takes into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dl or 3%, respectively, for each unit of blood transfused.

Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between two blood measurements is calculated as follows:

- Δ Hemoglobin = [baseline Hgb - post-transfusion Hgb] + [number of transfused units];
- Δ Hematocrit = [baseline Hct - post-transfusion Hct] + [number of transfused units x 3].

2.9.2 Safety

Safety will be assessed with:

- Nature, severity, and study drug relationship of all bleeding events, specifically,
  - Bleeding events according to REPLACE-2 Major bleeding definition
  - Bleeding events according to TIMI Major bleeding definition
  - Bleeding events according to REPLACE-2 Minor bleeding definition
  - Bleeding events according to TIMI Minor bleeding definition
  - Bleeding events according to REPLACE-2 Plus Major bleeding definition
  - Bleeding events according to TIMI Plus Major bleeding definition
  - Sum of REPLACE-2 Major and Minor bleeding
  - Sum of REPLACE-2 Plus Major and Minor bleeding
  - Sum of TIMI Major and Minor bleeding
  - Sum of TIMI Plus Major and Minor bleeding
- Non-bleeding adverse events
- Change in lab parameters, specifically,
  - Thrombocytopenia (< 100,000 cells/µL)
  - Severe Thrombocytopenia (< 50,000 cells/µL)
  - Profound Thrombocytopenia (< 20,000 cells/µL)
- Length of hospital stay.

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3 STATISTICAL METHODS

3.1 Statistical Handling Policy

3.1.1 Analysis Conventions

This section details general guidelines to be used for the statistical analyses. Deviations from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general conventions. The following policies will be applied to all data presentations and analyses:

- Two-tailed tests will be performed for analyses that use statistical testing with a significance level of $\alpha = 0.05$. One-tailed tests will be performed for analyses with a significance level of $\alpha = 0.025$, if applicable.
- Summary descriptive statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, maximum, and 95% confidence interval for continuous variables.
- All mean and median values will be formatted to one decimal place. Standard deviation values will be formatted to two decimal places.
- All percentages will be rounded to one decimal place. Where appropriate, the number and percentage of responses will be presented in the form XX (XX.X %), where the percentage is in the parentheses.
- For any analysis output, estimates and their corresponding standard deviations and/or standard errors will be reported up to the 3rd or 4th decimal place, per the default output of SAS.
- All p-values will be rounded to 4 decimal places (SAS format p-value). All p-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'. Any p-value ≤ 0.05 will be considered statistically significant.
- All listings will be sorted for presentation in order of treatment group, site number, subject number, and date of procedure or event, when applicable.

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- When necessary for analysis purposes, partial dates will be imputed (i.e., turned into complete dates) using the most conservative approach.
- Where appropriate, all analyses and summary tables will have the population sample size for each treatment group in the column heading.
- Tables will include titles with the corresponding analysis population and footnotes describing the analyses involved, and listings of covariates included in the analyses, where relevant.
- Version 20.0 (or higher) of MedDRA will be used for adverse event and pre-treatment conditions coding.
- Version 2015 (or later) of the World Health Organization (WHO) Drug Classifications will be used for the coding of medications.
- Version 9.4 (or later) of SAS® will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

3.2 Analysis Population

The Modified Intent-to-treat (mITT) Population is defined as all randomized patients who underwent PCI and received study drug.

The Per Protocol (PP) Population will consist of all randomized patients who completed the full course of the study without major protocol violations.

The Safety Population is defined as all randomized subjects who received any study treatment.
All efficacy analyses will be performed on the modified intent-to-treat population (mITT) and on the per-protocol population (PP). Safety analyses will be performed on the safety population.

3.3 Subject Disposition and Discontinuations

Patient disposition will be summarized for the total enrolled population and by treatment group. The following data will be presented:

- The number of patients who were screened, enrolled and randomized

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- The number and proportion of patients in each analysis population
- The number and percentage of patients who completed the study
- The number and percentage of patients who discontinued prematurely from the study and the associated reasons.

3.4 Treatment Exposure and Dosing

Treatment exposure will be calculated in terms of number of hours exposed to treatment using SAS function 'INTCK' in the following formula, and presented by the descriptive statistics including mean, median, SD, minimum, maximum and 95% CI of the mean:

Exposure (hours) = INTCK ("Hour", Start of Dosing, End of Dosing)

In addition, the cumulative dosing medication used will be calculated for each patient by computing the sum of study drug of tirofiban or eptifibatide administered pre and post-PCI.

3.5 Subject Demographics and Baseline Characteristics

Descriptive statistics will be presented for all patient demographic and characteristics data including age, gender, ethnicity and race. Age will be calculated as follows: Age = Largest Integer ≤ [(Visit 1 Date – Date of Birth + 1)/365.25; or as per the SAS function Age=YRDIF (date of birth, baseline date, 'ACTUAL').

3.6 Medical History

Medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the number and percentage of subjects with medical history will be reported by System Organ Class (SOC) and Preferred Term (PT).

3.7 Vital Signs/Physical Examination

The vital signs at each visit will be assessed by treatment group using descriptive statistics.

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3.8 Clinical Laboratory Assessments

The hematology and urine analysis tests will be described with the number and percentage of subjects reporting normal and abnormal (NCS and CS) results. In addition the actual results for all hematology tests will be summarized by treatment group using descriptive statistics.

3.9 Concomitant Medications

All concomitant medications recorded on the CRF will be coded and summarized according to the generic drug names using the WHO Drug Classifications. Summary will give the number and percentage of patients in the safety population who took medications that were coded to each generic drug name, as well as the number and percentage of patients that took any medication at all.

3.10 Analysis of the Study Endpoints

3.10.1 Analysis of the Primary Endpoint

To evaluate the effectiveness of tirofiban versus eptifibatide, we look at the proportion of patients with at least one of the following endpoint measurements: death, PPM, uTVR or REPLACE-2 Major bleeding within 48 hours following PCI or hospital discharge, whichever comes first. For each pairwise comparison:

- The short tirofiban group is non-inferior to the eptifibatide group;
- The short tirofiban group is non-inferior to the long tirofiban group;
- The long tirofiban group is non-inferior to the eptifibatide group;

The following hypothesis will be tested:

H_0: C – T $\leq$ -0.191

H_1: C – T > -0.191

To test this hypothesis, the difference (C – T) and its associated one-sided 97.5% confidence interval will be calculated. If the lower bound of the interval is greater than -0.191, the non-inferiority will be claimed. In order to compute the risk (proportion) difference for data with binary

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response ("Yes" vs. "No"), a bivariate logistic regression will be performed for each pairwise comparison with the following specifications:

- The dependent variable will be "composite endpoint" and the independent factor will be "treatment group";
- The risk (proportion) difference between two methods as well as its confidence interval will be estimated;
- The non-inferiority margin is 19.1%

3.10.2 Analysis of the Secondary Endpoints

The analysis of the secondary endpoints will be conducted in the same way as for the primary endpoint.

3.10.3 Analysis of Safety Endpoints

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the following information will be summarized:

- Overall AEs will also be described according to seriousness, severity, action taken with study drug, relationship to study drug and outcome of AE.
- The total number of AEs, the total number and proportion of patients experiencing at least one AE during the treatment period will be summarized by system organ class (SOC) and preferred term (PT). To count the number of patients who experience each AE, patients experiencing the same AE multiple times will only be counted once for the corresponding PT. AEs will be tabulated presenting the SOCs alphabetically.
- AEs will also be summarized as described above for serious adverse events (SAEs).

Furthermore, the analysis of these safety endpoints will compare the incidence in the short tirofiban treatment group to the incidence in the eptifibatide group, the incidence in the short tirofiban treatment group to the incidence in the long tirofiban treatment group and the incidence in the long tirofiban treatment group to the incidence in the eptifibatide group, by using the Fisher's mid-p test (Berry and Armitage, 1995) and Student t-test for binary and quantitative safety outcomes,

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respectively. Serious adverse events will also be tabulated overall and by severity for each treatment group.

3.10.4 Potential Covariates and/or Subgroups

As an exploratory analysis, appropriate univariate statistics will be used to identify potential confounders for inclusion in multivariable regression models for assessment of the primary endpoint. The following covariates will be considered:

- Patient with acute coronary syndromes (defined as any previous diagnosis of unstable angina, NSTEMI or STEMI)
- STEMI > 48 hours
- Stable angina
- Baseline troponin (positive vs. negative)
- Planned PCI access (femoral vs. radial)
- Number of stents implanted
- Number of vessels treated (multivessel vs. single vessel)
- Total infusion time
- Patients receiving P2Y12 antagonist therapy between 24 and 6 hours prior to randomization
- Patients receiving P2Y12 antagonist therapy between 6 and 1 hours prior to randomization
- Patients receiving P2Y12 antagonist therapy between 1 hour prior to randomization and 15 minutes after completion of the PCI procedure
- Type 2 diabetes mellitus
- Age < 65 years, ≥ 65-74 years and ≥ 75 years
- Sex
- Clopidogrel
- Prasugrel
- Ticagrelor
- Indication for PCI (Urgent vs. Elective)

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3.11 Multiplicity

The clinical decision rule is that tirofiban can only claim to have demonstrated an effect if it shows a clinical benefit based on the primary endpoint (death, PPM, uTVR or REPLACE-2 Major bleeding) within 48 hours following PCI or hospital discharge, whichever comes first), irrespective of the outcome of the secondary endpoints. No adjustments for multiple testing will be made.

3.12 Interim Analysis

No interim analyses will be conducted.

3.13 Accounting for Missing, Unused, and Spurious Data

Imputation methods will not be used for missing data.

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5 HISTORICAL CHANGE

Version Number	Section(s) Changed	Reason(s) for change
1	N/A	New document
2	3.1.1 Analysis Conventions	Addition of further specifications with respect to the analysis conventions for rounding, decimal places, listing and table formatting, date imputation , and statistical software to be used.

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6 MOCK TABLES & FIGURES

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Table 1. Patient Disposition

Disposition	Treatment Group			Total
	Short Tirofiban	Eptifibatide	Long Tirofiban	
Eligible, n				
Randomized, n				
Modified Intent-to-Treat Population (mITT) [1], n (%) [*]				
Per-Protocol Population (PP) [2], n (%) [*]				
Safety Population I [3], n (%)				
Completed the study, n (%) [*]				
Yes				
No				
If no, reason for non-completion of the study, n (%) [†]				
Non-compliance with study protocol				
Adverse event				
Death				
Withdrawal of consent				
Treating physician decision to withdraw subject				
Other reason				

[1] Defined as all randomized patients who underwent PCI and received study drug.

[2] Defined as all randomized patients who completed the full course of the study without major protocol violations.

[3] Defined as all randomized patients who received any study treatment.

[*] Percentages based on the total number of mITT patients in each treatment group.

[†] Percentages based on the total number of mITT patients who had a premature study discontinuation.

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Table 2a. Treatment Exposure and Dosing by Treatment Group – mITT Population without renal insufficiency[1]

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Number of hours exposed to treatment drug			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Cumulative treatment drug received (µg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			

[1] Creatinine clearance >60 mL/min

Note: This table will also be repeated for Per-Protocol Population.

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Table 2b. Treatment Exposure and Dosing by Treatment Group – mITT Population with renal insufficiency[1]

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Number of hours exposed to treatment drug			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Cumulative treatment drug received (µg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			

[1] Creatinine clearance ≤60 mL/min

Note: This table will also be repeated for Per-Protocol Population.

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Table 3. Patient Demographics and Baseline Characteristics by Treatment Group – mITT Population

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Age (years)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Gender, n (%)			
Female			
Male			
Ethnicity, n (%)			
Latino			
Non-Latino			
Race, n (%)			
White			
Black or African American			
Asian			
Native Hawaiian or other Pacific Islander			
American Indian or Alaska Native			
Other			

Note: This table will also be repeated for Per-Protocol Population.

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Table 4. Concomitant Medications by Treatment Group– mITT Population

	Treatment Group		
Medication	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Aspirin, n (%)			
Yes			
No			
Oral P2Y12 antagonist -Clopidogrel, n (%)			
Yes			
No			
Oral P2Y12 antagonist - Prasugrel n (%)			
Yes			
No			
Oral P2Y12 antagonist- Ticagrelor, n (%)			
Yes			
No			
I.V. Heparin, n (%)			
Yes			
No			
Oral, sublingual, topical, or I.V. nitrates, n (%)			
Yes			
No			
Calcium channel blockers n (%)			
Yes			
No			

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	Treatment Group		
Medication	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Lipid-lowering therapy n (%)			
Yes			
No			
Ace-inhibitors n (%)			
Yes			
No			
Beta-blocker n (%)			
Yes			
No			
Nonsteroidal anti-inflammatory agents n (%)			
Yes			
No			
Other cardioactive medications n (%)			
Yes			
No			
Angiotensin Receptor Blockers n (%)			
Yes			
No			
Diuretics n (%)			
Yes			
No			
Insulin n (%)			

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	Treatment Group		
Medication	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Yes			
No			

Note: This table will also be repeated for Per-Protocol Population.

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Table 5. Concomitant Antiplatelet/Anticoagulant Dose by Treatment Group – mITT Population

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Aspirin (mg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Oral P2Y12 antagonist loading dose- Clopidogrel (mg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Oral P2Y12 antagonist maintenance dose- Clopidogrel (mg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Oral P2Y12 antagonist loading dose- Prasugrel (mg)			
Available n			
Mean ± SD			

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	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
95% CI for Mean			
Median (IQR)			
Min - Max			
Oral P2Y12 antagonist maintenance dose- Prasugrel (mg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Oral P2Y12 antagonist loading dose- Ticagrelor (mg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Oral P2Y12 antagonist maintenance dose- Ticagrelor (mg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
IV Heparin (IU)			

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	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			

Note: This table will also be repeated for Per-Protocol Population.

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Table 6. Medical History by Treatment Group – mITT Population

System Organ Class (SOC) Preferred Term (PT)	Short Tirofiban (N=)		Eptifibatide (N=)		Long Tirofiban (N=)	
	Event	Subject (%)	Event	Subject (%)	Event	Subject (%)
TOTAL (ALL SOC/PT)						
SOC 1						
PT 1.1						
PT 1.2						
SOC 2						
PT 2.1						
PT 2.2						

Note: Medical history were coded by MedDRA version x. A patient may have reported more than one medical history. Percentages based on the total number of mITT patients in treatment group.

NA= Not Applicable

Note: This table will also be repeated for Per-Protocol Population.

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Table 7(a). Vital Signs Prior to Randomization by Treatment Group – mITT Population

	Treatment Group		
Vital Signs	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Height (cm)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Weight (kg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Body temperature (°C)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Heart rate (beats/minute)			
Available n			
Mean ± SD			

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	Treatment Group		
Vital Signs	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
95% CI for Mean			
Median (IQR)			
Min - Max			
Systolic blood pressure (mmHg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Diastolic blood pressure (mmHg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			

Note: This table will also be repeated for Per-Protocol Population.

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Table 7(b). Vital Signs at 9±3 Hours following PCI by Treatment Group – mITT Population

	Treatment Group		
Vital Signs	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Heart rate (beats/minute)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Systolic blood pressure (mmHg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Diastolic blood pressure (mmHg)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			

Note: This table will also be repeated for Per-Protocol Population.

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Table 8. Physical Examination Prior to Randomization by Treatment Group – mITT Population

	Treatment Group		
Body System	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Cardiovascular, n (%)			
Normal			
Abnormal			
Dermatological, n (%)			
Normal			
Abnormal			
Endocrine, n (%)			
Normal			
Abnormal			
Gastrointestinal, n (%)			
Normal			
Abnormal			
Genitourinary, n (%)			
Normal			
Abnormal			
H/E/N/T, n (%)			
Normal			
Abnormal			
Hematological, n (%)			
Normal			
Abnormal			

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	Treatment Group		
Body System	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Hepatobiliary, n (%)			
Normal			
Abnormal			
Immunological, n (%)			
Normal			
Abnormal			
Lymphatic, n (%)			
Normal			
Abnormal			
Musculoskeletal, n (%)			
Normal			
Abnormal			
Nervous, n (%)			
Normal			
Abnormal			
Renal, n (%)			
Normal			
Abnormal			
Reproductive, n (%)			
Normal			
Abnormal			
Respiratory, n (%)			

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	Treatment Group		
Body System	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Normal			
Abnormal			
Other, n (%)			
Normal			
Abnormal			

Note: This table will also be repeated for Per-Protocol Population.

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Table 9. Serum Creatinine Results Prior to Randomization by Treatment Group – mITT Population

	Treatment Group		
Tests	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Serum creatinine (mg/dL)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Creatine clearance (ml/min)[1]			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Serum creatinine, n (%)			
Clinically significant			
Non-clinically significant			

[1] Cockcroft and Gault formula

Note: This table will also be repeated for Per-Protocol Population.

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Table 10. Hematology Lab Results at Each Visit by Treatment Group – mITT Population

	Treatment Group		
Tests	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Hemoglobin (g/dL)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Hemoglobin, n (%)			
Clinically significant			
Non-clinically significant			
Hematocrit (%)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Hematocrit, n (%)			
Clinically significant			
Non-clinically significant			
Platelet count, 10^9/L			
Available n			
Mean ± SD			

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	Treatment Group		
Tests	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
95% CI for Mean			
Median (IQR)			
Min - Max			
Platelets, n (%)			
Clinically significant			
Non-clinically significant			

Note: This table will also be repeated for the Per-Protocol Population and for each of the following timepoints:

- ***Prior to Randomization***
- ***Prior to PCI***
- ***9±3 h following PCI***
- ***21±3 h following PCI***
- ***42±6 h following PCI***

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Table 11. Troponin Results at Each Visit by Treatment Group – mITT Population

	Treatment Group		
Tests	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Troponin (µg/L)			
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Troponin, n (%)			
Clinically significant			
Non-clinically significant			

Note: This table will be repeated for the Per-Protocol Population and for each of the following timepoints:

- ***Prior to PCI***
- ***9±3 h following PCI***
- ***21±3 h following PCI***
- ***42±6 h following PCI***

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Table 12. Descriptive Statistics of Bleeding Sites and Treatment of Bleed by Treatment Group – mITT Population

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Bleeding Site, n (%)			
Intracranial			
Retroperitoneal			
Sheath puncture site			
Other puncture site			
ENT bleed			
GI bleed			
GU bleed			
Cardio/pulmonary bleed			
Other			
Treatment of Bleed, n (%)			
Transfusion			
Pressure Dressing			
No treatment			
If transfusion, type of transfusion, n (%)			
Heparinized pump blood replacement			
Whole blood			
PRBCs			
FFP			
Platelets			
Cryoprecipitate			

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	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Cell-saver			
Albumin			
Other			

Note: This table will also be repeated for Per-Protocol Population

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Table 13. Descriptive Statistics of Potential Covariates Not Summarized Elsewhere by Treatment Group – mITT Population

Parameter	Treatment Group		
	Short Tirofiban (N=)	Eptifibatide (N=)	Long Tirofiban (N=)
Age category, years, n (%)			
< 65			
≥ 65- 74			
≥ 75			
Patient with acute coronary syndromes [1], n (%)			
Yes			
No			
STEMI > 48 hours, n (%)			
Yes			
No			
Stable angina, n (%)			
Yes			
No			
Troponin baseline, n (%)			
Negative			
Positive			
Planned PCI access, n (%)			
Femoral			
Radial			
Number of stents implanted			

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Parameter	Treatment Group		
	Short Tirofiban (N=)	Eptifibatide (N=)	Long Tirofiban (N=)
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			
Vessel involvement, n (%)[2]			
Single Vessel			
Mulitvessel			
Patients receiving P2Y12 antagonist therapy between 24 and 6 hours prior to randomization, n (%)			
Yes			
No			
Patients receiving P2Y12 antagonist therapy between 6 and 1 hours prior to randomization, n (%)			
Yes			
No			
Patients receiving P2Y12 antagonist therapy between 1 hour prior to randomization and 15 minutes after completion of the PCI procedure, n (%)			
Yes			
No			
Type 2 diabetes mellitus, n (%)			
Yes			
No			
Indication for PCI, n (%)			

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Parameter	Treatment Group		
	Short Tirofiban (N=)	Eptifibatide (N=)	Long Tirofiban (N=)
Elective			
Urgent			

[1] Defined as any previous diagnosis of unstable angina, NSTEMI or STEMI

[2]Ascertained by 'Number if stents implanted' indicated on the Procedure Report Form; ≥1 implanted stent = multivessel

Note: This table will also be repeated for Per-Protocol Population.

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Table 14. Descriptive Statistics of Primary Outcome by Treatment Group – mITT Population

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Eptifibatide (N=)**	**Long Tirofiban (N=)**
Primary outcome, n (%)			
Yes			
No			
Death, n (%)			
Yes			
No			
Periprocedural myonecrosis (PPM), n (%)			
Yes			
No			
Urgent target vessel revascularization (uTVR), n (%)			
Yes			
No			
REPLACE-2 major bleeding, n (%)			
Yes			
No			

Note: The primary outcome is the composite of death, PPM, uTVR or REPLACE-2 major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

Note: This table will also be repeated for Per-Protocol Population.

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Table 15. Bivariate Logistic Regression Model for Primary Outcome – mITT Population

Parameter	Level	Estimate	Standard Error (SE)	Odds Ratio (OR)	95% CI for OR	Risk (Proportion Difference)	Standard Error (SE) of Risk Difference	95% CI for Risk Difference	p-value *
Primary composite outcome	Short Tirofiban vs. Eptifibatide								
Primary composite outcome	Short Tirofiban vs. Long Tirofiban								
Primary composite outcome	Long Tirofiban vs. Eptifibatide								

* p-value is the overall p-value from the logistic regression model.

Note: The primary outcome is the composite of death, PPM, uTVR or REPLACE-2 major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

Note: This table will also be repeated for Per-Protocol Population.

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Table 15 (a) Multivariate Logistic Regression Models for Primary Outcome – mITT Population

Parameter	Level	Estimate	Standard Error (SE)	Odds Ratio (OR)	95% CI for OR	Risk (Proportion Difference)	Standard Error (SE) of Risk Difference	95% CI for Risk Difference	p-value *
Primary composite outcome	Short Tirofiban vs. Eptifibatide								
Primary composite outcome	Short Tirofiban vs. Long Tirofiban								
Primary composite outcome	Long Tirofiban vs. Eptifibatide								

* p-value is the overall p-value from the logistic regression model.

Note: The following potential covariates, as well as all significant 2-way interaction terms, will be assessed using appropriate univariate statistics for consideration in the multivariate regression models:

- ***Patient with acute coronary syndrome***
- ***STEMI > 48 hours***
- ***Stable angina***
- ***Baseline troponin (positive vs. negative)***
- ***Planned PCI access (femoral vs. radial)***
- ***Number of stents implanted***
- ***Number of vessels treated (multivessel vs. single vessel)***
- ***Total infusion time***
- ***Patients receiving P2Y12 antagonist therapy between 24 and 6 hours prior to randomization***
- ***Patients receiving P2Y12 antagonist therapy between 6 and 1 hours prior to randomization***
- ***Patients receiving P2Y12 antagonist therapy between 1 hour prior to randomization and 15 minutes after completion of the PCI procedure***
- ***Type 2 diabetes mellitus***
- ***Age < 65 years, ≥ 65- 74 years and ≥ 75 years***

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- ***Sex***
- ***Clopidogrel***
- ***Prasugrel***
- ***Ticagrelor***
- ***Indication for PCI (Urgent vs. Elective)***

Note: This table will also be repeated for Per-Protocol Population.

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Table 16. Descriptive Statistics of Secondary Outcomes by Treatment Group – mITT Population

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Secondary outcome 1, n (%)			
Yes			
No			
Secondary outcome 2, n (%)			
Yes			
No			
Secondary outcome 3, n (%)			
Yes			
No			
Secondary outcome 4, n (%)			
Yes			
No			
Secondary outcome 5, n (%)			
Yes			
No			
Secondary outcome 6, n (%)			
Yes			
No			
Secondary outcome 7, n (%)			
Yes			
No			

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Parameter	Treatment Group		
	Short Tirofiban (N=)	Short Tirofiban (N=)	Short Tirofiban (N=)
Secondary outcome 8, n (%)			
Yes			
No			

Note: The definitions of secondary outcomes are:

- ***Secondary outcome 1: death, PPM or uTVR within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 2: PPM within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 3: uTVR within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 4: death within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 5: death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first, where PPM is defined as at least one troponin elevation of ≥ 10 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory within 48 hours following PCI or hospital discharge, whichever comes first (a non-inferiority margin of 12.4% will be used for the short tirofiban versus eptifibatide comparison)***
- ***Secondary outcome 6: at least one troponin elevation of ≥ 10 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first (a noninferiority margin of 12.4% will be used for the short tirofiban versus eptifibatide comparison)***
- ***Secondary outcome 7: at least one troponin elevation of ≥ 20 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 8: at least one troponin elevation of ≥ 50 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first***

Note: This table will also be repeated for Per-Protocol Population.

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Table 17. Bivariate Logistic Regression Model for Secondary Outcomes – mITT Population

Parameter	Level	Estimate	Standard Error (SE)	Odds Ratio (OR)	95% CI for OR	Risk (Proportion Difference)	Standard Error (SE) of Risk Difference	95% CI for Risk Difference	p-value *
Secondary outcome	Short Tirofiban vs. Eptifibatide								
Secondary outcome	Short Tirofiban vs. Long Tirofiban								
Secondary outcome	Long Tirofiban vs. Eptifibatide								

* p-value is the overall p-value from the logistic regression model.

Note: The definitions of secondary outcomes are:

- ***Secondary outcome 1: death, PPM or uTVR within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 2: PPM within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 3: uTVR within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 4: death within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 5: death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first, where PPM is defined as at least one troponin elevation of ≥ 10 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory within 48 hours following PCI or hospital discharge, whichever comes first (a non-inferiority margin of 12.4% will be used for the short tirofiban versus eptifibatide comparison)***
- ***Secondary outcome 6: at least one troponin elevation of ≥ 10 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first (a noninferiority margin of 12.4% will be used for the short tirofiban versus eptifibatide comparison)***
- ***Secondary outcome 7: at least one troponin elevation of ≥ 20 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first***
- ***Secondary outcome 8: at least one troponin elevation of ≥ 50 times the upper limit of normal and at least 20% of greater than the baseline troponin value, per the troponin Local Laboratory, within 48 hours following PCI or hospital discharge, whichever comes first***

Note: This table will also be repeated for Per-Protocol Population.

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Table 18. Summary of Incidence of Adverse Events by Treatment Group – Safety Population

	Short Tirofiban (N=)			Eptifibatide (N=)			Long Tirofiban (N=)		
Parameter	**N of Events**	**N of Subjects**	**% of Subjects**	**N of Events**	**N of Subjects**	**% of Patients**	**N of Events**	**N of Subjects**	**% of Subjects**
Is it a Serious Adverse Event?									
Yes									
No									
If yes, serious indicator									
Death									
Life-threatening									
Required/prolonged hospitalization									
Significant/permanent disability									
Medically significant									
Is this event ongoing?									
Yes									
No									
Severity of adverse event									
Mild									
Moderate									
Severe									
Relationship to study drug									
Probably related									
Possibly related									
Unlikely related									

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Parameter	Short Tirofiban (N=)			Eptifibatide (N=)			Long Tirofiban (N=)		
	N of Events	N of Subjects	% of Subjects	N of Events	N of Subjects	% of Patients	N of Events	N of Subjects	% of Subjects
Action taken to the study drug									
None									
Discontinued									
Outcome									
Recovered									
Recovered with sequelae									
Unresolved									
Death									
Unknown									

The percentage is based on the number of serious adverse events.

Note: A patient may have reported more than one adverse event. Percentages based on the total number of safety population patients in each treatment group.

Note: This table will also be repeated for Serious Adverse Events.

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Table 19. Incidence of Adverse Events by System Organ Class (SOC) and Preferred Term (PT) by Treatment Group – Safety Population

	Short Tirofiban (N=)		Eptifibatide (N=)		Long Tirofiban (N=)	
System Organ Class (SOC) **Preferred Term (PT)**	**Event**	**Subject (%)**	**Event**	**Subject (%)**	**Event**	**Subject (%)**
TOTAL (ALL SOC/PT)						
SOC 1						
PT 1.1						
PT 1.2						
SOC 2						
PT 2.1						
PT 2.2						

Note: Adverse Events will be coded by MedDRA version x. A patient may have reported more than one adverse event. Percentages based on the total number of safety population patients in each treatment group.

Note: This table will also be repeated for Serious Adverse Events.

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Table 20. Descriptive Statistics of Safety Outcomes by Treatment Group – Safety Population

	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
REPLACE-2 major bleeding, n (%)			
Yes			
No			
TIMI major bleeding, n (%)			
Yes			
No			
REPLACE-2 minor bleeding, n (%)			
Yes			
No			
TIMI minor bleeding, n (%)			
Yes			
No			
REPLACE-2 plus major bleeding, n (%)			
Yes			
No			
TIMI plus major bleeding, n (%)			
Yes			
No			
Sum of REPLACE-2 major and minor bleeding, n (%)			
Yes			
No			

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	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Sum of REPLACE-2 plus major and minor bleeding, n (%)			
Yes			
No			
Sum of TIMI major and minor bleeding, n (%)			
Yes			
No			
Sum of TIMI plus major and minor bleeding, n (%)			
Yes			
No			
Non-bleeding adverse event, n (%)			
Yes			
No			
Thrombocytopenia (< 100,000 cells/µL), n (%)			
Yes			
No			
Severe thrombocytopenia (< 50,000 cells/µL), n (%)			
Yes			
No			
Profound thrombocytopenia (< 20,000 cells/µL), n (%)			
Yes			
No			
Length of hospital stay (hours)			

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	Treatment Group		
Parameter	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**	**Short Tirofiban (N=)**
Available n			
Mean ± SD			
95% CI for Mean			
Median (IQR)			
Min - Max			

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Table 21. Fisher's Exact Test for Binary Safety Outcomes – Safety Population

Statistic	Level	DF	Value	p-value
Fisher' exact test	Short Tirofiban vs. Eptifibatide			
Fisher' exact test	Short Tirofiban vs. Long Tirofiban			
Fisher' exact test	Long Tirofiban vs. Eptifibatide			

Note: p-value is based on the Fisher's mid-p test.

Note: The Binary Safety Outcomes are the following:

- ***Bleeding events according to REPLACE-2 Major bleeding definition***
- ***Bleeding events according to TIMI Major bleeding definition***
- ***Bleeding events according to REPLACE-2 Minor bleeding definition***
- ***Bleeding events according to TIMI Minor bleeding definition***
- ***Bleeding events according to REPLACE-2 Plus Major bleeding definition***
- ***Bleeding events according to TIMI Plus Major bleeding definition***
- ***Sum of REPLACE-2 Major and Minor bleeding***
- ***Sum of REPLACE-2 Plus Major and Minor bleeding***
- ***Sum of TIMI Major and Minor bleeding***
- ***Sum of TIMI Plus Major and Minor bleeding***
- ***Non-bleeding adverse events***
- ***Thrombocytopenia (< 100,000 cells/µL)***
- ***Severe Thrombocytopenia (< 50,000 cells/µL)***
- ***Profound Thrombocytopenia (< 20,000 cells/µL)***

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Table 22. Student t-Test for Quantitative Safety Outcome – Safety Population

Statistic	Level	DF	t Value	p-value
t-test	Short Tirofiban vs. Eptifibatide			
t-test	Short Tirofiban vs. Long Tirofiban			
t-test	Long Tirofiban vs. Eptifibatide			

Note: p-value is based on the Student t-test.

Note: The Quantitative Safety Outcome is the length of hospital stay.

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