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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Date: February 1, 2018

Study Protocol
Version 3.0

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Medical Monitor
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STUDY TITLE

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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
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	Prothrombin time
PTCA	Percutaneous transluminal coronary angioplasty
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
sec	second
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

PROTOCOL SYNOPSIS

PROTOCOL ACRONYM (WORKING TITLE): SAVI-PCI (Shortened Aggrastat Versus Integrilin in Percutaneous Coronary Intervention)

FULL PROTOCOL TITLE: 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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CLINICAL PHASE: II

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 eptifibatide in patients undergoing percutaneous coronary intervention (PCI) is associated with a non-inferior composite rate of death, periprocedural myonecrosis (PPM), urgent target vessel revascularization (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: (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.

SECONDARY OBJECTIVE: 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.

PRIMARY HYPOTHESIS: The first primary hypothesis is a 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.

The co-primary hypotheses include: (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, among patients undergoing PCI with respect to death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

STUDY DESIGN AND DURATION: 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 initially 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.

Physician-directed standard background therapies will include dual oral antiplatelet therapy with aspirin and an approved oral $P2Y_{12}$ antagonist as well as antithrombotic therapy with unfractionated heparin. Physician-directed $P2Y_{12}$ 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].

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

SAMPLE SIZE: Approximately 550 patients will be enrolled in the trial. The rate of the primary composite endpoint is assumed to be 51% in both the eptifibatide and tirofiban treatment groups. The absolute margin for the difference between the eptifibatide and the short tirofiban group is set at 19.1%. A sample size of approximately 500 for the comparison between the short tirofiban and the eptifibatide group was obtained by setting a power at 99% and a 1-sided alpha at 0.025. For the second test, a sample size of approximately 350 for the comparison between the short tirofiban and the long tirofiban group was obtained by setting power at 94.5% and a 1-sided alpha at 0.025. For the third test, a sample size of approximately 350 for the comparison between the long tirofiban and the eptifibatide group was obtained by setting power at 94.5% and a 1-sided alpha at 0.025.

DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Aspirin:	As per local practice and physician discretion
$P2Y_{12}$ Receptor Antagonist:	As per local practice and physician discretion
Unfractionated Heparin:	50 U/kg bolus and repeat dosing guided per guidelines in Appendix 4
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
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
Long Tirofiban:	25 µg/kg bolus followed by a 0.15 µg/kg/min infusion for 18 hours post-PCI (minimum 12 hours mandated)

Tirofiban in premixed bags/vials (5 mg per 100 mL) to be supplied by sponsor.

Eptifibatide and all other medications to be supplied by hospital pharmacy.

EFFICACY MEASUREMENTS: The primary endpoint is a composite of events defined as any of the following within 48 hours following PCI or hospital discharge, whichever comes first: death, PPM (defined as ≥3 times the upper limit of normal troponin and at least 20% or greater than the baseline troponin value), uTVR or non-CABG-related major bleeding within 48 hours following PCI or hospital discharge, whichever comes first, quantified according to REPLACE-2 criteria.

SAFETY MEASUREMENTS: The primary safety endpoint will be non-CABG-related major bleeding within 48 hours following PCI or hospital discharge, whichever comes first, quantified according to REPLACE-2 criteria.

DATA ANALYSIS: All efficacy analyses will be performed on the modified intent-to-treat (MITT) population, i.e. all randomized patients who underwent PCI and received study drug. Safety analyses will be performed on the safety population, i.e. patients who received any study drug.

CONTACT INFORMATION

REPORTING OF SERIOUS ADVERSE EVENTS

ANY SERIOUS ADVERSE EVENT, WHICH REQUIRES EXPEDITED REPORTING, MUST BE REPORTED WITHIN 24 HOURS TO THE SPONSOR'S SAFETY SURVEILLANCE. See Protocol Section 8 (Adverse Events) for definitions (8.1), collection and reporting (8.4.2) of serious adverse events.

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1.0 BACKGROUND AND RATIONALE

1.1 Percutaneous Coronary Intervention and Coronary Stents

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 is 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. 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.

1.2 Antiplatelet Therapy

Antiplatelet therapy is relevant during PCI since disruption of the arterial wall results in platelet activation, adhesion and 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.

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., Somerset, 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].

Some important differences exist between the three GPIIb/IIIa inhibitors. For example, abciximab is a large molecule (47,600Da) that binds the GPIIb/IIIa receptor with very high affinity while very little unbound abciximab remains in the circulating bloodstream [20]. In contrast, eptifibatide and tirofiban are both small molecules and their administration results in as many as 200 molecules of circulating drug for every molecule that binds to a receptor

[20]. Tirofiban is a slightly smaller molecule than eptifibatide (495Da vs. 832Da), is more potent (143 nM vs. 810 nM for concentration required to achieve 50% platelet inhibition) and has a slightly shorter half-life (2h vs. 2.5h). It is generally considered that eptifibatide and tirofiban are more alike than either is to abciximab.

1.3 Challenges with the GPIIb/IIIa Inhibitor Therapy Class of Drugs

There have been at least three challenges in the GPIIb/IIIa class. First, suboptimal dosing was a serious challenge for the small-molecule GPIIb/IIIa inhibitors in their early clinical development. Eptifibatide was initially administered using a single bolus dose, 135 μg/kg, followed by a 0.5 or 0.75 μg/kg/min maintenance infusion, which was found to be too low to provide adequate levels of platelet inhibition [21]. The dosing was subsequently increased to a double bolus dose of 180 μg/kg administered 10 min apart, which is then followed by a 2.0 μg/kg/min maintenance infusion for 18 to 24 hours [22]. This dose leads to very high levels of receptor occupancy throughout the infusion. The current double bolus dose of eptifibatide was studied in Enhanced Suppression of the Platelet IIb/IIIa Receptor with INTEGRILIN Therapy (ESPRIT) which compared eptifibatide to placebo in reducing ischemic complications in coronary artery disease patients undergoing elective coronary stent implantation. The trial showed a significant 37% reduction (p=0.0015) in the combined primary endpoint of death, myocardial infarction (MI), urgent target vessel revascularization (uTVR) or "thrombotic bail-out" at 48 hours, with eptifibatide treatment compared to placebo [22]. Eptifibatide is now the most commonly used GPIIb/IIIa inhibitor in the United States. Suboptimal dosing was also a challenge for tirofiban in its clinical development [23]. In recent years, new data have demonstrated that a higher tirofiban dose (25 μg/kg bolus followed by a 0.15 μg/kg/min maintenance infusion) than is currently included in the product's labeling (0.4 μg/kg/min for 30 min followed by a 0.1 μg/kg/min maintenance infusion) is appropriate in the setting of PCI. While both tirofiban dosing regimens achieve similar levels of platelet inhibition (~90-95%), the high-dose bolus achieves maximal inhibition more rapidly (within minutes) compared to the approved dosing regimen (30 minutes) [24,25]. No new safety concerns have been identified with the high-dose bolus [26].

A second challenge with GPIIb/IIIa inhibitor therapy is their extended infusion duration after the initial bolus. The long duration of infusion has several disadvantages such as an increase in bleeding tendencies, increased cost of therapy and the need for overnight hospitalization. Bleeding is an increasing concern for interventional cardiologists since it is associated with worse short- and long-term outcomes, including higher rates of mortality, compared with those who do not experience bleeding complications [27]. One possible solution to lower the bleeding risk associated with GPIIb/IIIa inhibitor therapy is to use a shortened infusion duration. This strategy is particularly attractive given today's PCI practice patterns for several reasons. First, patients today have superior oral anti-platelet medication with the combination of aspirin and clopidogrel, prasugrel or ticagrelor compared to aspirin only protection used in the early GPIIb/IIIa inhibitor clinical studies. With today's more potent oral antiplatelet therapies, patients undergoing PCI reach and sustain a greater degree of platelet inhibition in the immediate post-procedural period. A GPIIb/IIIa inhibitor infusion may therefore be needed for a shorter period following PCI. Second, PCI has evolved over the past 15 years to the point where it is a more common and routine procedure conducted over a shorter period of time. Shorter GPIIb/IIIa infusion durations are becoming increasingly popular and there is increasing demand for optimizing the duration of infusion. Fung and colleagues assessed the safety and efficacy of a bolus plus up to 2h eptifibatide infusion in nonemergent and uncomplicated PCI

versus a bolus plus up to 18h eptifibatide infusion [28]. Rates of REPLACE-2 major bleeding were found to be less frequent in the <2h group (1.0% vs. 4.2%; p=0.02) and the incidence of periprocedural myonecrosis (defined as troponin-I ≥3x ULN) was non-inferior between the two groups (30.1% in the <2h group vs. 28.3% in the 18h group; p<0.012 for noninferiority). The authors concluded following uncomplicated PCI, eptifibatide infusion can be abbreviated safely to <2h [28].

A third challenge with the GPIIb/IIIa inhibitor therapies is that the endpoint definitions, background medical therapies, and procedural approaches used to establish their label dosing are no longer considered contemporary. For example, CK-MB was the enzyme biomarker used to measure MI rates in GPIIb/IIIa inhibitor registration studies. The contemporary definition of MI (according to a recent Task Force involving the AHA, ACC, ESC, and WHF) in the setting of PCI is, however, based on the enzyme biomarker troponin [29a]. In the SAVI-PCI study, the term MI was originally used to describe ≥3x ULN troponin elevation but was changed to the term periprocedural myonecrosis in light of the recently updated Task Force publication [29b] and considerably higher than expected event rates in the first 159 patients. With respect to medical therapy, high-dose clopidogrel, prasugrel and bivalirudin are all routinely used today in the setting of PCI but were not studied in the early GPIIb/IIIa inhibitor registration trials. The efficacy and safety of a GPIIb/IIIa inhibitor on top of contemporary agents is therefore not fully understood. Measuring the clinical effectiveness of GPIIb/IIIa inhibitor therapies using modern endpoint definitions and pharmacotherapies is therefore of clear medical and scientific interest.

1.4 Tirofiban

Tirofiban 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 [10,16,17,23,30,31] demonstrated its efficacy and safety in reducing 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 [26, 33-56]. The tirofiban high-dose bolus regimen is approved for use in the setting of PCI in Europe, but not in the United States.

Three large-scale clinical trials, RESTORE [10], PRISM [17], and PRISM-PLUS [16], supported the current label-dosing of tirofiban in the management of patients with ACS undergoing percutaneous transluminal coronary angioplasty or atherectomy.

TARGET, the only head-to-head comparison of GP IIb/IIIa inhibitors sponsored by a pharmaceutical company, was designed to test whether tirofiban, using a bolus dose of 10 μg/kg followed by a 0.15 μg/kg/min maintenance infusion for 18 to 24 hours, was non-

inferior to abciximab among PCI patients receiving a coronary stent [23]. At 30 days the primary efficacy endpoint of death, MI, and urgent TVR occurred more frequently in the tirofiban group (7.6%) than in the abciximab group (6.0%; p=0.038). The rate of major bleeding was similar between the 2 study groups, although minor bleeding and thrombocytopenia occurred less frequently among tirofiban-treated patients. The reason for the higher event rate in the tirofiban group was primarily due to procedure-related myocardial infarctions occurring immediately after the PCI procedure, suggesting the potency of the tirofiban bolus injection at the time of intervention was suboptimal.

1.4.1 Rationale for Tirofiban High-Dose Bolus Regimen

Several studies performed following the completion of TARGET strongly suggested that the 10 µg/kg bolus dose of tirofiban was inadequate. The TARGET dosing regimen of tirofiban inhibited 20 µM ADP-mediated platelet aggregation only by 60-66% from 15-60 minutes after onset of treatment when tested with PPACK as a sample anticoagulant, and as a result of rapid tissue redistribution yielded a tirofiban plasma level of 35-40 ng/mL [24]. Abciximab, as it was dosed in the TARGET trial, produced a 90-95% inhibition of platelet aggregation in this same time period. This difference in extent of platelet aggregation inhibition was proposed as the reason why more procedure-related ischemic events occurred more frequently among patients receiving tirofiban in the TARGET trial.

Schneider and co-workers evaluated bolus doses of tirofiban that were higher than the bolus dose used in the TARGET trial, comparing the results with the extent of inhibition provided by abciximab [24, 25]. They tested tirofiban bolus doses of 20 µg/kg and 25 µg/kg in 30 patients undergoing PCI primarily for an acute coronary syndrome. The tirofiban infusion dose was 0.15 µg/kg/min. The authors found that the 20 µg/kg bolus inhibited platelet aggregation by 84-89% (Figure 1) and produced a 67-82 ng/mL plasma level (Figure 2) of tirofiban [24, 25]. The 25 µg/kg dose consistently provided a level of inhibition, similar to that provided by abciximab. Importantly, during the first hour of treatment, the lower limit of the 95% confidence interval for platelet inhibition with this tirofiban dosing regimen was >85% during the first hour of treatment. At 15 to 60 minutes following the 25 µg/kg bolus dose of tirofiban, the inhibition of platelet aggregation was 92-95%, and the plasma level of tirofiban ranged 80-99 ng/mL [24, 25] (Figure 2).

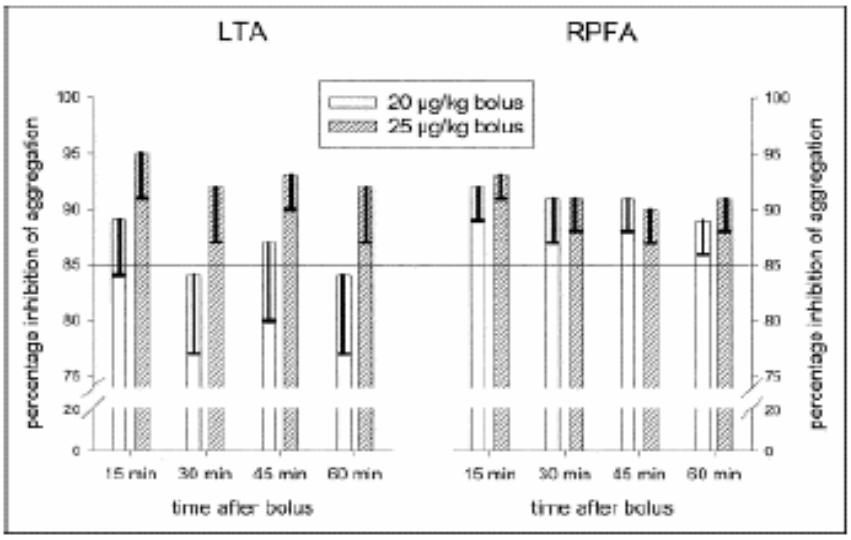

Figure 1. Inhibition of turbidometric platelet aggregation (LTA) in response to 20 µM ADP (left) and in response to thrombin receptor agonist peptide (TRAP) and measured by rapid platelet function assay (RPFA) (right). Patients were treated with either 20 µg/kg or 25 µg/kg bolus of tirofiban followed by an infusion of 0.15 µg/kg/min. Values are the means and the lower bounds of the 95% confidence interval. [25]

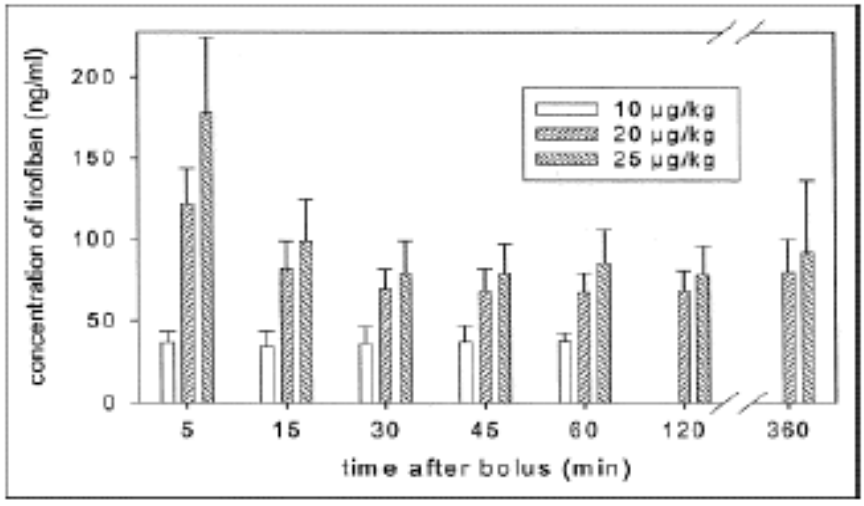

Figure 2. The concentration of tirofiban in blood from patients treated with a 10, 20, or 25 µg/kg bolus of tirofiban followed by a 0.15µg/kg/min infusion. The concentration of tirofiban, evaluated by radioimmunoassay, was found to be consistently >80 ng/mL with the 25 µg/kg bolus. [24]

Schneider and co-workers collected blood from patients with acute coronary syndrome undergoing PCI and was spiked (ex vivo) with tirofiban, resulting in concentrations of 0, 50, 100, or 150 ng/mL of drug. Inhibition of platelet aggregation to 20 µM ADP was found to plateau (on average) at greater than 95% once reaching a plasma concentration beyond 80 ng/mL [24] (Figure 3). When pursuing yet higher plasma concentrations, the residual ability of platelets to bind fibrinogen was not significantly different (18% to 16%) between the 100 ng/mL and 150 ng/mL samples.

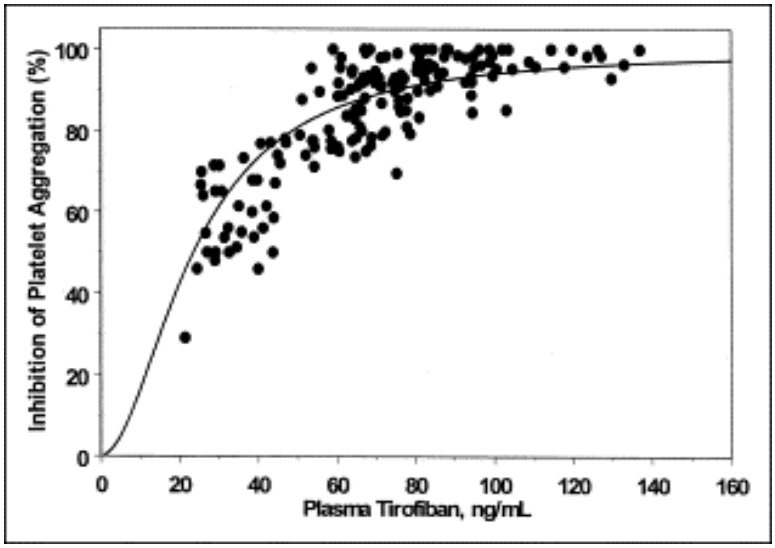

Figure 3. The association between the concentration of tirofiban and the turbidometric platelet aggregation induced by 20 μM ADP. Each point depicts results during the first 2 hours of therapy from patients treated with a 10, 20, or 25 μg/kg bolus of tirofiban followed by a 0.15μg/kg/min infusion. The sigmoidal dose-response relationship shows limited additional aggregation inhibition provided by concentrations of tirofiban >90 ng/mL. [24]

The above-referenced studies demonstrated that a single 25 μg/kg bolus followed by a 0.15 μg/kg/min infusion of tirofiban consistently and effectively inhibits platelet function to a high degree and that this dosing regimen provided the peak inhibitory effects most similar to those produced by the abciximab-labeled dosing regimen.

1.4.2 Clinical Studies Conducted with Tirofiban High-Dose Bolus Regimen

Based on the published findings demonstrating that a higher bolus dose of tirofiban provided platelet inhibition on par with abciximab during the PCI peri-procedural period, the TENACITY trial was initiated by Guilford Pharmaceuticals. Unfortunately, due to financial constraints, TENACITY was halted in June 2005, after enrolling 383 patients out of a planned 8000.

TENACITY was a double-blind, randomized active-comparator study comparing the high-dose bolus regimen of tirofiban to abciximab in intermediate to high-risk ACS patients. A second randomization assigned patients to receive either unfractionated heparin or bivalirudin as their direct thrombin inhibitor. All patients received clopidogrel and aspirin prior to randomization.

The results of the TENACITY study were analyzed with the 383 patients enrolled in the study and recently published [62]. At 30-days there was a non-significant difference between high-dose bolus tirofiban and abciximab, and the percent of patients with death, non fatal MI or urgent target vessel revascularization was 6.9% in the high-dose bolus tirofiban group versus 8.8% in the abciximab group (P=NS). This difference was driven primarily by an almost 2% absolute difference in rates of non-fatal myocardial infarction between high-dose bolus tirofiban and abciximab (5.9% vs. 7.7%; P=NS). There were no differences in bleeding between the two groups. When analyzed for combined death, MI, urgent TVR and major bleeding at 30-days, the combination of high-dose bolus tirofiban

and bivalirudin (5.6%) was non-significantly lower than abciximab and UFH (9.1%), abciximab and bivalirudin (10.5%), and high-dose bolus tirofiban and UFH (10.1%).

The ADVANCE trial evaluated the efficacy and safety of HDB tirofiban compared with placebo in treating high-risk patients [35]. The study enrolled 202 patients with either a single coronary artery occlusion or diabetes, diagnosed NSTEMI, or multivessel coronary artery disease. This trial demonstrated a statistically significant decrease in 6-month MACE or bailout GPIIb/IIIa inhibitor use for patients treated with HDB tirofiban versus placebo (19.8% vs. 34.7%; P=0.01). HDB tirofiban was shown to significantly reduce the increase in cardiac markers (both troponin I and CK-MB) associated with ischemic events. Subgroup analysis showed a statistically significant decrease in the primary endpoint for diabetic and ACS patients treated with HDB tirofiban. Finally, there was no major bleeding, no need for red blood cell transfusion, or severe thrombocytopenia, and there was no significant difference in even minor bleeding rates between HDB tirofiban-treated patients and those treated with placebo (4% vs. 1%; P = 0.19).

The 3T/2R trial evaluated the effect of tirofiban in patients with aspirin and/or clopidogrel resistance [52]. 263 patients who were non-responders to either aspirin or clopidogrel or both underwent double-blind randomization to receive HDB tirofiban (25 µg/kg in three minutes, followed by 12-24 hour infusion at 0.15 µg/kg/min) or placebo on top of standard aspirin and clopidogrel therapy. The primary end point was the rate of periprocedural myocardial infarction defined as an elevation of troponin I or T at least three times the upper limit of normal within 48 hours after the procedure. The primary endpoint was observed in 20.4 percent of patients in the tirofiban group, compared to 35.1 percent of patients in the placebo group (P=0.009; RRR=0.42). The benefit seen in the tirofiban group was maintained at 30 days, with a 21.2 percent incidence of major adverse cardiovascular events, compared to 36.6 percent in the placebo group (P=0.0065). The incidence of bleeding was low and did not differ significantly between the two groups [52].

The On-TIME 2 trial evaluated whether patients undergoing primary coronary angioplasty (PCI) would benefit from early administration of high-dose tirofiban [48]. The study enrolled 984 patients with ST-elevation myocardial infarction (STEMI) who were indicated for primary PCI. Once enrolled, patients were randomly assigned to receive tirofiban (25 µg/kg bolus dose followed by a 0.15 µg/kg/min infusion for 18 hours) or placebo.

The primary endpoint, residual ST deviation one hour after PCI, favored tirofiban (3.6 mm) over placebo (4.8 mm); P=0.003). Major bleeding rates were similar between the two groups (4% vs. 3%; P=0.36). The authors concluded that early administration of high-dose tirofiban improved ST-segment resolution and clinical outcomes after PCI.

Schiariti and co-workers published a clinical study investigating the efficacy and safety profile of HDB tirofiban (N=1,578) [54]. The study compared, as a primary endpoint, the combination of bleeding and access site complications of patients undergoing PCI under double anti-aggregating drugs (i.e. any two of ASA, clopidogrel, or ticlopidine) in the absence or presence of intravenous high-dose tirofiban given just before PCI followed by an 18 hour infusion. Based on the rates of blood transfusions (2.2% tirofiban vs. 2.1%; P=NS) and in-hospital complications (5.3% tirofiban vs. 5.9%; P=NS) the authors concluded the that high-dose tirofiban did not increase the complication risk for patients undergoing elective, primary or rescue PCI.

Schiariti and co-workers also compared the use of tirofiban HDB and eptifibatide in patients (N=666) undergoing PCI when added to standard antiaggregating drugs (aspirin and clopidogrel or ticlopidine) to prevent ischemic events within 1 year [56]. Adjusted hazard ratios showed that eptifibatide use, as compared to tirofiban (hazard ratio 1.85, 95% CI 1.04–3.29, P=0.04), was a significant risk factor and it seems these effects are due to a lower efficacy of eptifibatide on CK-MB levels. Additional risk factors identified were age, chronic renal failure, pre-PCI values of CK-MB, and intra-aortic balloon pump.

A meta-analysis of 31 studies involving 20,006 patients was published by Valgimigli and co-workers in 2010. The analysis showed tirofiban to be an efficacious treatment option in reducing ischemic events in patients with acute coronary syndromes and/or those undergoing PCI [26]. When employed as a high-dose bolus just prior to PCI, the authors concluded tirofiban provides similar efficacy but with an improved safety profile when compared to abciximab. In the 4,076 patients enrolled in studies employing the tirofiban high-dose bolus regimen, 1,863 were controlled with placebo and 2,213 were controlled with abciximab. For the HDB tirofiban versus placebo comparison, a reduction in short-term (30 days) mortality (P = 0.07) and mortality or MI (P = 0.006) were observed. For the HDB tirofiban versus abciximab comparison, mortality (P = 0.38), the composite of death or MI (P = 0.54) or long-term death or MI rate (P = 0.35), or MACE rate (P = 0.51) were similar [26].

These trials represent a significant clinical experience demonstrating the safety and efficacy of the HDB tirofiban administered at the time of PCI. The HDB tirofiban regimen is approved in Europe, however, has not been approved in the United States.

1.4.3 Rationale for a GPIIb/IIIa Shortened Infusion Duration

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 [58] 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 [28] 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 [59] 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 [60]. These studies suggest a bolus plus a shortened infusion of GPIIb/IIIa inhibitor therapy can be safe and effective in the setting of PCI.

In order to further investigate this hypothesis, the SAVI-PCI study will provide a comparison of tirofiban using a shortened infusion duration versus eptifibatide using a 12-18 hour infusion duration. In addition, to further isolate and distinguish the specific effects of the duration of dosing, a comparison of shortened infusion tirofiban versus regular (12-18 hr) infusion tirofiban will be conducted in the study. Lastly, to further isolate and compare the clinical differences between the two small molecule agents, tirofiban and

eptifibatide will be compared using the same duration of infusion (12-18 hour infusion duration for both treatment arms).

1.4.4 Tirofiban Dosing in Patients with Renal Insufficiency

A pharmacokinetic modeling study, based on the available tirofiban pharmacokinetic literature, was conducted to determine the optimal tirofiban dosing regimen for patients with renal insufficiency (i.e., creatinine clearance <30 mL/min) [63a]. The study concluded that patients with renal insufficiency would have a tirofiban exposure profile (i.e., plasma concentration time profile) similar to that observed in patients with normal renal function when tirofiban is administered as a 25 µg/kg bolus plus a reduced infusion rate of 0.10 µg/kg/min infusion instead of the usually recommended 0.15 µg/kg/min rate. The modeling results also indicate that the estimated low and high tirofiban plasma concentration ranges for this dosing regimen would be similar (or slightly greater) compared to the low and high ranges of patients with normal renal function. Thus, patients with renal impairment would most likely not reach elevated tirofiban plasma concentrations (after either the IV bolus or IV infusion doses of tirofiban) that could result in any adverse event that has not already been observed in patients with normal renal function. In addition, the PK modeling of low and high dose ranges indicates that tirofiban plasma concentrations in patients with renal impairment are sufficient to produce and maintain the desired pharmacological activity.

During the course of SAVI-PCI, the FDA requested Medicure conduct a Phase 1 study in healthy volunteers with varying degrees of renal insufficiency to evaluate the impact of renal function on the PK profile of tirofiban administered using a single high-dose bolus (25 µg/kg). The study showed that patients with renal insufficiency (i.e. creatinine clearance <60 mL/min) should receive the 25 µg/kg bolus followed by a reduced infusion rate of 0.10 µg/kg/min infusion, instead of the recommended 0.15 µg/kg/min rate. This change in dosing for patients with renal insufficiency was implemented after 159 patients were enrolled [63b].

On October 11, 2013 the FDA approved the 25 µg/kg bolus followed by a reduced infusion rate of 0.075 µg/kg/min for patients with creatinine clearance ≤60 mL/min [69]. For patients with creatinine clearance >60 mL/min, the approved Aggrastat dosing regimen is a 25 µg/kg bolus followed by an infusion rate of 0.15 µg/kg/min [69].

A shortened infusion duration of tirofiban should further reduce safety concerns for patients with renal insufficiency. If an average PCI procedure takes 45 minutes [60], then according to the SAVI-PCI protocol, tirofiban will be infused for a total of 165 minutes. This is a substantial reduction in tirofiban dosing compared to recent clinical studies ON-TIME 2 [48], MULTISTRATEGY [46] and 3T/2R [52]. For example, the total amount of tirofiban drug used in a HDB tirofiban followed by a 165 minute infusion regimen is 4478 µg (for a 90kg patient). In comparison, for the same 90kg patient, the total amount of tirofiban drug administered in 3T/2R was between 13590 µg (for a 14h infusion) and 21690 µg (for a 24h infusion) representing a relative reduction in tirofiban dosing of 67% and 79%, respectively. A substantial reduction in tirofiban dosing should reduce tirofiban dosing safety concerns for patients with renal insufficiency.

1.5 Summary

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 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 [65,66]. 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. Approximately 550 patients will be enrolled into the study.

2.0 OBJECTIVES

2.1 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 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: (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.

2.2 Secondary Objective

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.

3.0 PRIMARY HYPOTHESIS

The first primary hypothesis is a 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.

The co-primary hypotheses include: (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, among patients undergoing PCI with respect to death, PPM, uTVR or major bleeding within 48 hours following PCI or hospital discharge, whichever comes first.

4.0 POPULATION

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.

4.1 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.

4.2 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
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.

5.0 STUDY DESIGN

5.1 Summary of Study Design

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.

Physician-directed standard background therapies will include dual oral antiplatelet therapy with aspirin and an approved oral $P2Y_{12}$ antagonist as well as antithrombotic therapy with unfractionated heparin. Physician-directed $P2Y_{12}$ 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].

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

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.

Patients will sign an informed consent form and a HIPAA authorization form prior to initiation of study procedures. Patients will be assessed by the Investigator according to the selection criteria for the study. A patient who signs the consent and authorization forms, meets the inclusion criteria, and does not meet any of the exclusion criteria is eligible for inclusion into the study.

Study drug administration will begin prior to initiation of the PCI procedure as described in Section 5.2.5.

At the end of the PCI procedure, all patients experiencing an intraprocedural thrombotic complication will be recorded. If a patient randomized to short tirofiban is experiencing an intraprocedural thrombotic complication, then the infusion is to be continued for a minimum of 12 hours. If a patient is randomized to eptifibatide and is experiencing an intraprocedural thrombotic complication, then no change is to be made to the infusion duration (i.e. the infusion continues for 18 hours post-PCI [minimum 12 hours mandated]).

Initiation of the PCI procedure is defined as advancement of the guidewire out of the guiding catheter. Completion of the PCI procedure is defined as final removal of the guiding catheter.

If femoral access is used, the sheath should be removed when the ACT is ≤180 seconds (or aPTT ≤50 seconds if ACT unavailable). If radial access is used, the sheath should be removed based on the discretion of the treating physician.

Troponin (either troponin I or troponin T) will be sampled immediately prior to PCI, preferably from the PCI access sheath or guiding catheter, at 9±3 hours after PCI, and at 21±3 hours after PCI. If the patient remains in the hospital longer than 36 hours after PCI, a third post-PCI troponin will be sampled at 42±6 hours after PCI. All troponin samples will be analyzed by the local laboratory. It is **mandated** that patients be observed for a minimum of 18 hours following PCI to allow for at least two post-PCI troponin samples.

Hemoglobin, hematocrit and platelet count will be sampled at the same time as the troponin draws, i.e., immediately prior to PCI, preferably from the PCI access sheath or guiding catheter, at 9±3 hours following PCI, and at 21±3 hours. If the patient remains in the hospital longer than 36 hours after PCI, a third hemoglobin, hematocrit and platelet count post-PCI draw will be sampled at 42±6 hours after PCI. All hemoglobin, hematocrit and platelet count samples will be analyzed by the local laboratory.

Patients will be assessed for serious adverse experiences (including serious bleeding events) that occur within 48 hours following PCI or hospital discharge, whichever comes first. Patients will be assessed for non-serious adverse experiences that occur within 48 hours following PCI or hospital discharge, whichever comes first.

5.2 Sequence of Procedures

A Schedule of Evaluations and Procedures is shown in Appendix 1.

5.2.1 Baseline/Pretreatment Period

The Investigator has the ultimate responsibility for obtaining written informed consent and HIPAA authorization. This process will be completed for a patient before performing any protocol-specific procedure. No sedation shall be administered to the patient within reasonable proximity, consistent with local IRB rules, to exert a meaningful pharmacologic effect before written informed consent and HIPAA authorization is obtained. Consent will include HIPAA authorization.

The following procedures must be performed prior to randomization (maximum timing prior to randomization in parenthesis):

a. brief medical history (within 7 days)
b. brief physical examination (within 7 days)
c. vital signs (height, weight, body temperature, heart rate, systolic and diastolic blood pressure) (within 7 days)
d. serum or urine pregnancy if of child bearing potential (within 7 days)
e. serum creatinine (within 24 hours)
f. 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)
g. hematology: hemoglobin, hematocrit and platelet count (within 24 hours)

The following baseline sampling will be performed immediately prior to PCI:

a. Baseline blood sample for troponin
b. Baseline blood sample for hemoglobin, hematocrit and platelet count
c. ACT (see Appendix 4)

Whenever institutional policies allow, blood sampling can be obtained from sheaths, catheters, or central lines (including arterial lines) if available. Otherwise, an additional peripheral in-dwelling catheter may be inserted for venous blood sampling (e.g. heparin lock).

Blood pressure will be assessed per institutional policy.

5.2.2 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 $P2Y_{12}$ 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 $P2Y_{12}$ antagonist agent used post-randomization is pre-specified, AND
c. access site for PCI is pre-specified, AND
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.

5.2.3 Timing of Oral Antiplatelet Therapy, PCI & Study Drug Administration

PCI will be performed according to institutional guidelines and standards. The index PCI procedure will be completed as clinically appropriate. Any PCI device approved by the FDA may be used (investigational stents may not be used in this study).

All clinical events from the time of study drug administration will be recorded. The number and position of coronary stents placed as well as the outcome of the procedure will be recorded.

All patients must receive aspirin (81 - 325 mg daily is recommended) and oral $P2Y_{12}$ antagonist therapy throughout the course of the study.

Patients who are on a $P2Y_{12}$ antagonist at time of randomization should remain on that same $P2Y_{12}$ agent post-randomization.

Patients who have not received any oral $P2Y_{12}$ antagonist therapy within 24 hours prior to randomization must receive a loading dose between randomization and 15 minutes after completion of the PCI (defined as final removal of the guiding catheter), preferably as close to time of randomization as possible.

Recommended loading doses for the oral $P2Y_{12}$ antagonist therapies are the following: clopidogrel 600 mg; prasugrel 60 mg; and ticagrelor 180 mg.

Patients will be administered unfractionated heparin as an initial I.V. bolus of 50 U/kg prior to PCI. Additional heparin boluses will be administered according to the suggested guidelines in Appendix 4.

Study drug will be prepared and labeled accordingly for each patient as described in the pharmacy manual. Tirofiban will be provided by Sponsor and packaged in 100 mL bags/vials containing 5.0 mg of tirofiban. Eptifibatide will be provided by the Institution and packaged in 10 mL bolus vials containing 20 mg eptifibatide and 100 mL infusion vials containing 75 mg of eptifibatide. See Pharmacy Manual for details of study drug preparation.

Patients assigned to short tirofiban will receive a 25 µg/kg bolus administered by I.V. push 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. Sites have the option of administering the tirofiban 25 µg/kg bolus via I.V. pump over approximately 3 minutes or

bolus push with syringe. Sponsor will supply T-ports (Trudell Medical Marketing) to use for filling syringe for bolus administration.

Patients assigned to short tirofiban with renal insufficiency (creatinine clearance ≤60 mL/min) will receive a 25 µg/kg bolus followed by a 0.075 µg/kg/min 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.

Patients assigned to eptifibatide will receive a 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.

Patients assigned to eptifibatide with renal insufficiency (creatinine clearance <50 mL/min) will receive a 180 µg/kg bolus followed by a 1.0 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.

Patients assigned to long tirofiban received a 25 µg/kg bolus administered by I.V. push followed by a 0.15 µg/kg/min infusion for 12-18 hours post-PCI.
Patients assigned to long tirofiban with renal insufficiency (creatinine clearance ≤60 mL/min) received a 25 µg/kg bolus followed by a 0.075 µg/kg/min maintenance infusion for 12-18 hours post-PCI.

The study drug boluses of tirofiban or eptifibatide will be administered intravenously by volume according to patient weight (see Appendix 3 for dosing tables). The bolus volume and infusion rate increases with increasing patient weight, but is capped at the patient weight of 153 kg and 121 kg for tirofiban and eptifibatide, respectively. Therefore, any patient randomized to tirofiban weighing over 153 kg will receive the same bolus volume and infusion rate as a patient randomized to tirofiban weighting 153 kg. Similarly, any patient randomized to eptifibatide weighing over 121 kg will receive the same bolus volume and infusion rate as a patient randomized to eptifibatide weighting 121 kg. Administration of the bolus will begin prior to the initiation of the PCI procedure. Initiation of the PCI procedure is defined as advancement of the guidewire out of the guiding catheter.

In patients with known coronary anatomy (i.e., a baseline angiogram was previously performed), the bolus will be administered after arterial access is achieved, prior to advancement of the guidewire out of the guiding catheter. In patients without a baseline angiogram, the bolus will be administered after completion of the initial angiography, once the decision has been made to proceed with PCI, prior to advancement of the guidewire out of the guiding catheter. The study drug infusion will be started immediately after completion of the bolus (first bolus in the case of eptifibatide). Upon completion of the study drug bolus administration and initiation of study drug infusion, advancement of the guidewire out of the guiding catheter and PCI may proceed.

5.2.4 In The Event of Thrombotic Complications

At the end of the PCI procedure all patients will be assessed to determine if a thrombotic complication persists according to the following criteria:

1. abrupt or threatened closure, with reduced flow, and/or
2. no reflow or slow flow, due to distal embolization, and/or

3. visible thrombus.

Determination of whether one or more of these criteria has been satisfied will be at the determination of the investigator.

Patients administered short tirofiban experiencing a thrombotic complication will continue to receive an infusion of tirofiban at a dose of 0.15 µg/kg/min (or 0.075 µg/kg/min for patients with renal insufficiency (creatinine clearance ≤60 mL/min)) for a minimum of 12 hours following PCI. See Appendix 3 for dosing tables.

Patients administered eptifibatide experiencing a thrombotic complication will continue to receive an infusion of eptifibatide at a dose of 2.0 µg/kg/min (or 1.0 µg/kg/min for patients with renal insufficiency (creatinine clearance <50 mL/min)) for 18 hours following PCI (minimum 12 hours mandated, no maximum infusion duration). See Appendix 3 for dosing tables.

Patients administered long tirofiban experiencing a thrombotic complication continued to receive an infusion of tirofiban at a dose of 0.15 µg/kg/min (or 0.075 µg/kg/min for patients with renal insufficiency (creatinine clearance ≤60 mL/min)) for 18 hours following PCI (minimum 12 hours mandated, no maximum infusion duration). See Appendix 3 for dosing tables.

5.2.5 Following the Procedure

Short tirofiban will be infused for the duration of the procedure plus a minimum of one hour and up to a maximum of two hours post-PCI. For example, if the procedure takes 25 minutes (i.e. 25 minutes from the time of advancement of the guidewire out of the guiding catheter to final removal of the guiding catheter) then tirofiban will be infused for a total of 25 minutes plus a minimum of one hour (for a total infusion time of 85 minutes) and up to a maximum of two hours (for a total infusion time of 145 minutes). For another example, if the PCI procedure takes 55 minutes, then tirofiban will be infused for a total of 55 minutes plus a minimum of one hour (for a total infusion time of 115 minutes) and up to a maximum of two hours (for a total infusion time of 175 minutes).

Eptifibatide will be infused for a total of 18 hours following PCI (minimum 12 hours mandated).

Long tirofiban was infused for a total of 18 hours following PCI (minimum 12 hours mandated).

During study drug administration and following discontinuation of study drug, the patient will be observed for signs of bleeding. Blood pressure and heart rate will be monitored according to the institution’s standard procedures.

For the definition of procedure duration, final removal of the guiding catheter will define procedure completion.

5.2.5.1 Antithrombin Use

Routine use of unfractionated heparin post-procedure is not recommended.

5.2.5.2 Sheath Removal

If femoral access is used, the sheath should be removed when the ACT is ≤180 seconds (or aPTT ≤50 seconds if ACT unavailable). If radial access is used, the sheath should be removed based on the discretion of the treating physician.

If a closure device is utilized, it will not be necessary to wait until the ACT or aPTT reaches the prescribed levels. Institutional guidelines for ambulating following sheath removal should be followed. Patients may be ambulated while study drug infusions continue if institutional guidelines permit it.

5.2.5.3 Blood Sampling

Whenever institutional policies allow, blood sampling can be obtained from sheaths, catheters, or central lines (including arterial lines) if available. Otherwise, an additional peripheral in-dwelling catheter may be inserted for venous blood sampling (eg, heparin lock).

The following evaluations will be performed at the times indicated (see Schedule of Evaluations and Procedures, Appendix 1; all evaluations and laboratory measurements should be performed within the time specified, unless otherwise specified):

a. Hemoglobin, hematocrit and platelet count will be sampled at the same time as the troponin draws (see below), i.e., immediately prior to PCI, preferably from the PCI access sheath or guiding catheter, at 9±3 hours following PCI, and at 21±3 hours. If the patient remains in the hospital longer than 36 hours after PCI, a third hemoglobin, hematocrit and platelet count post-PCI draw will be sampled at 42±6 hours after PCI. All hemoglobin, hematocrit and platelet count samples will be analyzed by the local laboratory.

b. If a platelet count falls below 100,000 cells/μL and decreases at least 25% from the baseline value in any sample compared to any previous sample, additional repeat platelet counts and/or further laboratory analyses (i.e., microscopic) per local institution guidelines must be performed to exclude laboratory error (clumping, etc.). The repeat platelet counts should be performed according to the specific practice at each institution. See Appendix 7 for guidelines for management of thrombocytopenia.

c. Troponin (troponin I or troponin T) will be sampled immediately prior to PCI, preferably from the PCI access sheath or guiding catheter, at 9±3 hours following PCI, and at 21±3 hours. If the patient remains in the hospital longer than 36 hours after PCI, a third post-PCI troponin will be sampled at 42±6 hours after PCI. All troponin samples will be analyzed by the local laboratory. It is **mandated** that patients be observed for a minimum of 18 hours following PCI to allow for at least two post-PCI troponin samples.

See Appendix 2 for a complete listing of local laboratory evaluations.

5.2.6 Safety Evaluation, Discharge and Follow-Up

Patients will be assessed for serious adverse events (including serious bleeding events) and non-serious adverse events of interest that occur from the time of study drug initiation

through 48 hours following PCI or hospital discharge, whichever comes first. These events will be documented on the CRF. Some serious adverse events will require expedited reporting (see Adverse Events Section 8.0).

Patients are **mandated** to stay a minimum of 18 hours following PCI to allow for at least two post-PCI troponin samples to be obtained at time-points 9±3 hours and 21±3 hours following PCI. If the patient remains in the hospital longer than 36 hours after PCI, a third post-PCI troponin will be sampled at 42±6 hours after PCI.

5.2.7 Evaluation of Endpoints

Evaluation of death, PPM uTVR and REPLACE-2 Major bleeding and other endpoints will not be adjudicated.

5.2.8 Criteria for Discontinuation of Study Drug

If at any time during the study the Investigator responsible for the clinical care of the patient decides that continued use of the study drug is contraindicated, administration of the study drug should be stopped. Study drug should be discontinued if any of the following develop:

a. Unusual or excessive bleeding;
   Signs or symptoms of abnormal, pathological bleeding from any source that cannot be controlled without discontinuation of the study drug. Hematoma at the site of the vascular sheath insertion is expected and should not serve as a reason to discontinue study drug, unless the bleeding cannot be controlled with normal measures.

b. Development of a new, neurologic deficit or significant alteration in mental status.

c. Development of a platelet count <50,000/mm^3.

d. Any serious adverse event possibly related to or exacerbated by study drug administration.

e. Need for urgent CABG. Appropriate measures should be taken to minimize surgical risk (see Appendix 5 Guidelines for Management of Urgent Target Vessel Revascularization).

f. Any need for a surgical procedure with the exception of those procedures performed under local anesthesia.

If the study drug is discontinued prematurely, the Sponsor will be notified as soon as possible. A patient for whom study drug is discontinued will continue to be monitored according to the protocol tests and procedures after study drug has been discontinued.

5.2.9 Concomitant Medication(s)/Treatment(s)

Only FDA-approved drugs may be administered in this study. Concomitant oral $P2Y_{12}$ antagonist medications must be pre-specified prior to randomization.

5.2.9.1 Permitted

Antiplatelet/Anticoagulant agents

The following concomitant antiplatelet/anticoagulant agents are permitted in the study:

- aspirin
- clopidogrel
- prasugrel

- ticagrelor
- unfractionated heparin

The name, timing and dosing of the above antiplatelet/anticoagulant agents should all be recorded on the CRF.

Clopidogrel is contraindicated with prasugrel and ticagrelor; prasugrel is contraindicated with clopidogrel and ticagrelor; and ticagrelor is contraindicated with clopidogrel and prasugrel.

Oral, sublingual, topical, or I.V. nitrates
Any of these medications may be given if necessary based on the discretion of the treating physician. These medications received during the procedure and for 48 hours following PCI or until hospital discharge, whichever comes first will be recorded on CRFs, according to drug class (recording of name, dosage and timing is not required).

Ace-inhibitors, calcium channel blockers, beta-blockers, lipid-lowering therapy, angiotensin receptor blockers, diuretics, digoxin and diabetes medications.
Any of these medications may be given if necessary based on the discretion of the treating physician. These medications received during the procedure and for 48 hours following PCI or until hospital discharge, whichever comes first will be recorded on CRFs, according to drug class (recording of name, dosage and timing is not required).

Nonsteroidal anti-inflammatory agents
Any of these medications may be given if necessary based on the discretion of the treating physician. These medications received during the procedure and for 48 hours following PCI or until hospital discharge, whichever comes first will be recorded on CRFs, according to drug class (recording of name, dosage and timing is not required).

5.2.9.2 Prohibited

Oral anticoagulation
Oral anticoagulation medications (warfarin derivatives) should not be administered until at least 12 hours after completion of the study drug infusions unless INR ≤1.3.

Antiplatelet/Anticoagulant agents
No other antiplatelet agents (except aspirin, clopidogrel, prasugrel or ticagrelor) or anticoagulant agents (except unfractionated heparin) should be administered until completion of the study drug infusion. Low-molecular-weight heparin should not be administered during infusion of study drug. Dextran may not be used during or prior to study drug infusion.

Thrombolytic agents
Thrombolytic agents must be discontinued for at least 24 hours prior to randomization and may not be used until at least 12 hours after completion of the study drug infusion.

Bivalirudin
Bivalirudin must be discontinued for at least 12 hours prior to randomization and may not be used until at least 12 hours after completion of the study drug infusion.

Ticlopidine

Ticlopidine should not be administered in this study.

Unapproved agents
Therapeutic agents not approved by the FDA at the time of the protocol finalization should be discontinued at least 48 hours prior to randomization and may not be used until after 24 hours following PCI.

5.2.10 Patient Withdrawal

Patients may withdraw at any time during the study without prejudice, or be discontinued from the study at the discretion of the Investigator if medically necessary or if any untoward effects occur. In addition, a patient may be withdrawn by the Investigator or the Sponsor if the patient violates the study plan or for administrative and or other safety reasons. The Investigator or study coordinator must notify the Sponsor immediately (via telephone or fax) when a patient has been discontinued or withdrawn because of an adverse experience. When a patient discontinues or withdraws prior to study completion, all applicable activities scheduled for the end of study should be performed at the time of discontinuation. Any adverse experiences that are present at the time of discontinuation/withdrawal should be reported and followed-up in accordance with the safety requirements outlined in the Adverse Events Section 8.0.

Unless the patient has explicitly withdrawn consent for further data collection, it is important that complete data are obtained for all patients whether or not they receive their assigned treatment or have discontinued study drug. Every attempt should be made to collect information. All procedures and laboratory specimens or tests requested for evaluation following administration of the study drug should be carried out when possible whether or not a patient continues to receive treatment according to the protocol. Discontinued patients will not be replaced.

6.0 PRIMARY EFFICACY MEASUREMENTS

The primary endpoint will be the composite of death, PPM, uTVR or major bleeding (where major bleeding is defined in Section 7.1 and discussed further in Section 9) within 48 hours following PCI or hospital discharge, whichever comes first.

All clinical events from the time of study drug administration will be recorded. The number, type and length of coronary stents placed as well as the outcome of the procedure will be recorded on the CRF.

After study drug administration, the development of any of the following events will be recorded on the appropriate CRF.

6.1 Death

Death due to any cause will be assessed through to 48 hours following PCI or hospital discharge, whichever comes first.

Death will <u>not</u> be adjudicated.

6.2 Periprocedural Myonecrosis

The definition of periprocedural myonecrosis is the following:

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.

Periprocedural myonecrosis will not be adjudicated.

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.

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.

6.3 Urgent Target Vessel Revascularization

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).

uTVR will not be adjudicated.

7.0 SAFETY MEASUREMENTS

The following adverse events will be monitored closely from study drug administration through 48 hours following PCI or hospital discharge, whichever comes first.

7.1 Bleeding

Bleeding complications will be closely monitored clinically and by serial determinations of hemoglobin and hematocrit. All bleeding events from study drug administration through 48 hours following PCI or hospital discharge, whichever comes first, will be collected and categorized by site and quantified according to REPLACE-2 Major bleeding criteria. While other bleeding definitions will also be applied, REPLACE-2 Major bleeding criteria will be

used in the primary safety analysis and in the bleeding component of the primary composite endpoint.

Hemoglobin, hematocrit and platelet count will be sampled at the same times as the troponin draws. i.e., immediately prior to PCI, preferably from the PCI access sheath or guiding catheter, and at 9±3 hours following PCI, and at 21±3 hours. If the patient remains in the hospital longer than 36 hours after PCI, a third hemoglobin, hematocrit and platelet count post-PCI draw will be sampled at 42±6 hours after PCI.

Bleeding events will not be adjudicated.

7.1.1 Bleeding Site

Each site will be recorded on the CRF and evaluated separately. Bleeding sites include intracranial, retroperitoneal, sheath puncture site, other puncture site, ENT bleed, GI bleed, GU bleed, cardio/pulmonary bleed, other, and unknown. Microscopic hematuria and positive fecal occult blood will be recorded as laboratory adverse events only and will not be captured as bleeding events. Information on whether the bleeding event was a result of CABG will be collected on the CRF.

7.1.2 Primary Safety Measurement Non-CABG REPLACE-2 Major Bleeding Definition

Major bleeding is defined using the criteria from the REPLACE-2 trial. Major bleeding is defined as follows [57]:

a. transfusion of ≥2 units whole blood or packed red blood cells, or
b. intracranial hemorrhage, or
c. retroperitoneal hemorrhage, or
d. a fall in Hgb < 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.

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 [68]:

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

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

7.1.3 Other Bleeding Definitions

While not part of the primary safety analysis and composite endpoint, bleeding will be evaluated using alternate definitions as described below.

7.1.3.1 TIMI Major Bleeding Definition

Major bleeding is defined using the criteria from the trials of Thrombolysis in Myocardial Infarction (TIMI criteria). Major bleeding is defined as follows [64]:

a. if there was a reduction of hemoglobin of 5 g/dl or more (or >15% in hematocrit); or
b. any intracranial bleeding.

The TIMI 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 [68]:

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

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

7.1.3.2 TIMI Minor Bleeding Definition

Minor bleeding is defined using the criteria from the trials of Thrombolysis in Myocardial Infarction (TIMI criteria). Minor bleeding is defined as follows [64]:

a. If there is an observed blood loss and a drop in hemoglobin of 3 to 5 g/dl (or in hematocrit from 10% to 15%) from study entry to the time of the lowest hemoglobin (hematocrit); or

b. if there was spontaneous gross hematuria or hematemesis (>120 mL), even if the hemoglobin or hematocrit drop was less than 3 g or less than 10%, respectively; or

c. if there was an unobserved blood loss 4 g/dl or more in hemoglobin or 12% or more in hematocrit.

The TIMI Minor 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 [68]:

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

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

7.1.3.3 REPLACE-2 Minor Bleeding Definition

Minor bleeding is defined as any observed bleeding event that does not meet the criteria for a major hemorrhage.

7.1.3.4 REPLACE-2 Plus Major Bleeding Definition

REPLACE-2 Plus Major bleeding is defined using criteria from the REPLACE-2 trial, with the exception of transfusion. REPLACE-2 Plus Major bleeding is defined as follows:

a. any transfusion of whole blood or packed red blood cells, or
b. intracranial hemorrhage, or
c. retroperitoneal hemorrhage, or
d. a fall in Hgb < 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.

The REPLACE-2 Plus 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 [68]:

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

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

7.1.3.5 TIMI Plus Major Bleeding Definition

TIMI Plus Major bleeding is defined using the criteria from the trials of Thrombolysis in Myocardial Infarction (TIMI criteria) with the exception of transfusion [64]:

a. any transfusion of whole blood or packed red blood cells, or
b. if there was a reduction of hemoglobin of 5 g/dl or more (or >15% in hematocrit); or
c. any intracranial bleeding.

The TIMI Plus 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 [68]:

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

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

7.2 Thrombocytopenia

If a platelet count falls below 100,000 cells/µL and decreases at least 25% from the baseline value in any sample compared to any previous sample, additional repeat platelet

counts and/or further laboratory analyses (i.e., microscopic) per local institution guidelines must be performed to exclude laboratory error (clumping, etc.). The repeat platelet counts should be performed according to the specific practice at each institution. See Appendix 7 for guidelines for management of thrombocytopenia.

7.2.1 Moderate Thrombocytopenia

Moderate thrombocytopenia is defined as a platelet count <50,000 cells/μL.

7.2.2 Severe Thrombocytopenia

Severe thrombocytopenia is defined as a platelet count <20,000 cells/μL.

8.0 ADVERSE EVENTS

8.1 Definitions

An adverse event (AE) is any untoward new medical problem or exacerbation of an existing problem, experienced by a patient while enrolled in the study, whether or not it is considered drug-related by the Investigator.

Expected complications of percutaneous procedures as well as study endpoints that are not felt to be related to study drug are not to be considered adverse events, although any bleeding endpoint will still be recorded.

In addition, planned hospital admissions and/or surgical operations for an illness or disease which existed before the drug was given or the patient was randomized in a clinical study are not to be considered adverse events.

A serious adverse event (SAE) is any adverse event occurring within 48 hours that:

- Results in death; or
- Is life threatening (places the patient, in the opinion of the Investigator, at immediate risk of death from the experience as it occurred. [This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]); or
- Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or
- Results in or prolongs an existing in-patient hospitalization (hospitalization is defined as an in-patient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation); or
- Is a congenital anomaly/birth defect (in offspring of patient taking the product regardless of time to diagnosis); or
- Is medically significant: requires medical or surgical interventions to prevent one or more of the outcomes above.

8.2 Study Drug Causality

The relationship of an AE to treatment will be assessed by the Investigator as one of the following:

- **Probably related**: There is a reasonable causal relationship between the study drug and the AE. The event responds to de-challenge.
- **Possibly related**: There is a reasonable causal relationship between the study drug and the AE.
- **Unlikely related**: There is not a temporal or causal relationship to the study drug administration.

8.3 Severity

The intensity of adverse events will be graded by the Investigator on a 3-point scale as indicated on the CRF. The intensity of an adverse event is defined as follows:

- **Mild**: Discomfort noticed, but no disruption to daily activity
- **Moderate**: Discomfort sufficient to reduce or affect normal daily activity
- **Severe**: Inability to work or perform normal daily activity

8.4 Collection of Adverse Events

The Investigator will periodically assess patients for the occurrence of adverse events. To avoid bias in eliciting adverse events, patients should be asked the following non-leading question: “How are you feeling?” All adverse events (serious and non-serious) reported by the patient will be followed until the event has resolved or has stabilized.

8.4.1 Collection and Reporting of Nonserious Adverse Events

Nonserious adverse events will be collected from study drug initiation through to 48 hours following PCI or hospital discharge, whichever comes first on the CRF but will not require urgent expedited reporting.

8.4.2 Collection and Reporting of Serious Adverse Events

Serious adverse events (including serious bleeding events) will be collected on the CRF. The Investigator is responsible for following all SAEs until the event has resolved or has stabilized.

In the event of an SAE, or in the event of death due to any cause, immediately (within 24 hours) the SAE form is to be completed and submitted to:

Name: Monique Vonk
Title: Clinical Safety Officer
Fax: 204-489-0175
Email: safety@gvicds.com
Phone: 204-928-7208

If details of the event are not known submit the SAE form within 24 hours and update the information as it becomes available.

8.4.3 Collection and Reporting of Endpoints

Endpoints will be collected on the case report form from study drug administration through 48 hours following PCI or hospital discharge, whichever comes first. Any coronary ischemic or anginal event will be collected on the CRF but will not require urgent/expedited reporting. Endpoints will not be reported as SAEs.

8.5 Submission of Follow-up Data

The Investigator is responsible for following all SAEs until the event has resolved or has stabilized. The Sponsor's Safety Surveillance Contact will follow all SAEs with outcomes pending until the last patient enrolled has completed the study**.**

8.6 Ethics Committee SAE Reporting

The Investigator will be responsible for reporting adverse events to the Independent Review Board (IRB) and their local regulatory authorities in accordance with their local guidelines.

9.0 STATISTICAL CONSIDERATIONS

This section summarizes the statistical aspects of the protocol. A final statistical analysis plan (SAP), which will provide detailed descriptions of the statistical methodology and mock tables, listings and figures (TLFs), will be completed prior to any blinded sample size reassessment or final analysis.

9.1 Study Design

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. After 159 patients were randomized, a 1:1:1 randomization was initiated, randomizing patients to short tirofiban, eptifibatide or long tirofiban. Randomization in the long tirofiban arm is completed, changing the allocation ratio back to 1:1. Patients are mandated to stay a minimum of 18 hours following PCI.

Physician-directed standard background therapies will include dual oral antiplatelet therapy with aspirin and an approved oral $P2Y_{12}$ antagonist as well as antithrombotic therapy with unfractionated heparin. Physician-directed $P2Y_{12}$ 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].

Enrolment in the Long Tirofiban arm is completed. Enrolment continues in the Short Tirofiban and Eptifibatide arms as outlined above.

Approximately 550 patients will be enrolled into the study.

9.2 Statistical Alternative Hypothesis (Ha)

The first primary test is that short tirofiban is non-inferior to eptifibatide for death, PPM, uTVR or REPLACE-2 Major bleeding within 48 hours following PCI or hospital discharge, whichever comes first. The original non-inferiority margin was 12.4% (with an expected pooled rate of 32.5%), but based on the higher observed pooled event rate of 51% after 159 randomized patients, the non-inferiority margin was revised to be 19.1% in order to maintain the same relative margin (i.e. 12.4% / 32.5% = 19.1% / 51% = 0.38) For the co-primary tests, the same non-inferiority margin (19.1%) will be used.

9.3 Study Endpoints, Covariates, and Subgroups

9.3.1 Primary Endpoint and Associated Tests

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: (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.

9.3.2 Secondary Endpoint and Associated Tests

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 non-inferiority 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.

9.3.3 Safety Endpoints

- 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

9.3.4 Potential Covariates and/or Subgroups

- Patient with acute coronary syndromes
- STEMI >48 hours
- Stable angina
- Troponin baseline negative
- Troponin baseline positive
- Femoral access PCI
- Radial access PCI
- Total stent length
- Use of a closure device
- Number of stents implanted
- Single vessel
- Multivessel
- Number of vessels treated
- Total infusion time

- Patients receiving $P2Y_{12}$ antagonist therapy between 24 and 6 hours prior to randomization
- Patients receiving $P2Y_{12}$ antagonist therapy between 6 and 1 hours prior to randomization
- Patients receiving $P2Y_{12}$ antagonist therapy between 1 hour prior to randomization and 15 minutes after completion of the PCI procedure
- Type 1 diabetes mellitus
- Type 2 diabetes mellitus
- Prior use of GPIIb/IIIa inhibitor therapy
- Indication for PCI
- Age < 65 years, ≥65 years and ≥75 years
- Sex
- Race
- Clopidogrel
- Prasugrel
- Ticagrelor
- Elective PCI
- Urgent PCI

9.4 Analysis Population

All efficacy analyses will be performed on the modified intent-to-treat population (MITT) (i.e. randomized patients who underwent PCI and received study drug) and on the per-protocol population (i.e. patients who completed the full course of the study without major protocol violations). Safety analyses will be performed on the safety population (i.e. patients who received any study treatment).

9.5 Sample Size Calculations

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% will be assumed for the active control and test group which was then later assumed 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 non-inferiority 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.

The trial may be terminated for futility at an interim point in time. Details of the methodology and stopping boundaries will be provided in the Statistical Analysis Plan.

9.6 Planned Methods of Analysis

General Principles

For continuous variables, descriptive statistics (mean, SD, median, and quartiles) will be tabulated by treatment group. For categorical variables, the number and proportion of patients in each category will be tabulated.

The primary and secondary endpoints will be analyzed using the MITT population. Safety endpoints will be analyzed using the safety population. Demographics, baseline characteristics, and other study assessments will be analyzed using the MITT and intent-to-treat (ITT) population.

Confidence intervals will be used to assess hypotheses of non-inferiority and superiority. Details of the statistical methods will be developed in the Statistical Analysis Plan (SAP).

Demography and Baseline Characteristics

All appropriate background data will be summarized for each treatment group. If there are heterogeneities between two groups in any of the patient characteristics that are of clinical importance or could affect the study outcome, the impact of the imbalances will be investigated. If necessary, adjustments may be made in the efficacy and safety analysis and will be documented in the study report.

Primary Endpoint

The first primary and co-primary endpoints will be analyzed by the use of a one-sided 97.5% confidence interval

Subgroup/Covariate Analyses

Formal subgroup analyses will be performed by including the appropriate interaction terms in multivariable logistic regression models. The effects of potential covariates (see Section 9.3.4) will be assessed using multi-variable logistic regression.

Secondary Endpoints

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

Safety Endpoints

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, using the Fisher's mid-p (Berry and Armitage, 1995). Serious adverse events will also be tabulated overall and by severity for each treatment group.

Multiplicity (Multiple Endpoints)

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.

Missing Data
Imputation methods will not be used for missing data.

9.7 Timing of Final Analyses

The final analysis will be conducted when all patients have completed their assessment (within 48 hours following PCI or hospital discharge whichever comes first) This database will include all patients' data up to this timepoint from the date of study drug administration. The database will be cleaned, locked, and unblinded before the commencement of the statistical analysis.

10.0 STUDY DRUG MANAGEMENT

See the Pharmacy Manual for complete details and requirements for Study Drug packaging, labeling, storage, preparation, administration and accountability.

10.1 Packaging and Labeling

10.1.1 Tirofiban

Supply of open-label tirofiban will be the responsibility of the Sponsor.

10.1.2 Eptifibatide

Supply of open-label eptifibatide will be the responsibility of the hospital pharmacy.

10.2 Storage

Store tirofiban at 25°C (77°F) with excursions permitted between 15°-30°C (59°F-86°F). Do not freeze. Protect from exposure to light until used.

10.3 Accountability

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the research pharmacist, Investigator and/or designated assistants have access. Clinical supplies are to be dispensed only in accordance with the protocol. The research pharmacist and/or Investigator and/or designate is responsible for keeping accurate records of the clinical supplies received from the Sponsor, the amount dispensed and returned, and the amount remaining at the conclusion of the study. The above accountability is not required for eptifibatide (which is supplied by the hospital pharmacy).

11 STUDY DOCUMENTATION

Study documentation includes all electronic and paper case report forms, data correction forms, source documents, monitoring logs and appointment schedules, Sponsor-Investigator correspondence and regulatory documents (e.g., signed protocol and amendments, Ethics or Institutional Review Committee correspondence and approval, approved and signed patient consent forms, Statement of Investigator form, and clinical supplies receipts and distribution records).

This study will use web-based electronic CRFs (e-CRFs) developed through a validated, ERES-compliant platform (21 CFR Part 11). Prior to initiation of the trial, each site will be contacted as to computer availability, hardware specifications, internet connectivity, to evaluate their capacity to use this type of data collection system. The Investigator's site

staff who will be entering data into this system will receive training on the system, after which each person will be issued a unique user identification and password.

For security reasons, and in compliance with regulatory guidelines, it is imperative that only the person who owns the user identification and password access the system using their own unique access codes. Access codes are non-transferable. Site personnel who have not undergone training may not use the system and will not be issued user identification and password until appropriate training is completed.

During monitoring visits the site will make their computer and/or high speed Internet access available to the CRA so that he/she may verify the data entries with the source documentation. At the conclusion of the study, each enrolling site will be provided with a compact disc (CD), or equivalent electronic storage device, containing PDF files of both the data for each individual patient enrolled at the site and the audit trail (changes made to the database). This will be maintained at the site according to the requirements for records retention.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, X rays, radiologist reports, patient diaries, biopsy reports, ultrasound photographs, patient progress notes, hospital charts or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each patient participating in the study, promptly complete all original case report forms and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and case report forms.

12 RECORDS RETENTION

As this study is being conducted under a US Investigational New Drug application, FDA regulations require all Investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years following the date on which a New Drug Application is approved by the FDA (for this dose/concomitant use);

- A period of 2 years after the Sponsor notifies the Investigator that no further application is to be filed with the FDA.

The Investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is patient to inspection by the Sponsor and its agents as well as the FDA and other regulatory agencies.

13 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

14 MONITORING

The Sponsor has ethical, legal and scientific obligations to follow this study in a detailed and orderly manner in accordance with established research principles and applicable regulations. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the study), the Sponsor or its designee will visit the center(s) during the study in addition to maintaining frequent telephone and written communication.

15 AUDITING

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to the following: audit trail of data handling and processes, SOPs, drug supply, presence of required documents, the informed consent process, and comparison of case report forms/database with source documents. The Investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with governmental (e.g. FDA) audits conducted at a reasonable time in a reasonable manner.

16 ETHICS AND RESPONSIBILITY

By signing this protocol, the Investigator agrees to conduct the study in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the United States Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) GCP guidelines, the Declaration of Helsinki, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

17 INFORMED CONSENT

Written informed consent will be obtained from all patients (or their legal representative) before any study-related procedures (including any pre-treatment procedures, such as pre-procedure sedation) are performed or given. The Investigator(s) has both ethical and

legal responsibility to ensure that each patient being considered for inclusion in this study is given a full explanation of the study. This shall be documented on a written informed consent form, which shall be approved by the same Ethics Committee responsible for approval of this protocol. Each informed consent form shall include the elements required by FDA regulations in 21 CFR Part 50 and ICH GCPs. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, prior to submission to the IRB.

Once the appropriate essential information has been provided to the patient and fully explained by the Investigators (or a qualified designee) and it is felt that the patient understands the implications of participating, the patient and the Investigator (or designee) shall sign and date the Ethics Committee approved written informed consent form. The patient shall be given a copy of the signed informed consent form, and the original shall be kept in the site's regulatory file. A second copy may be filed in the patient's medical record, if allowed by the institution.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., study staff personnel).

The initial informed consent form, any subsequent revised written informed consent form, and any written information given to the patient must receive the Ethics Committee approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information should be documented.

18 AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION (HIPAA)

An authorization for use and disclosure of protected health information under the HIPAA Privacy Rule [45 CFR § 164.102 *et seq*] will be obtained from every trial patient prior to, or at the time of, enrollment. It will be presented to, and signed by, the trial patient at the same time as the Informed Consent Form (ICF). The Investigator is responsible for obtaining trial patients' (or their legal representatives') authorizations and signatures, and for explaining the elements of the HIPAA Authorization form if necessary.

HIPAA Authorization may either be a separate form or included in the study ICF, dependent upon local requirements. If a separate HIPAA document is signed, the Investigator will append one signed original of each executed HIPAA Authorization to the trial patient's signed ICF, and file it in the site's regulatory file. If a second copy of the signed ICF is filed in the patient's medical records, an additional copy of the signed HIPAA Authorization form will be appended. Trial patients will be given the other signed duplicate for their personal records.

The HIPAA Authorization form will contain all elements required under the HIPAA Privacy Rule. By law, site Ethics Committee approval of the Sponsor-provided Authorization form for use in this study is not required, and no such approval will be sought or requested. However, the Sponsor, upon request, will provide advance copies of its HIPAA

Authorization form to the Investigator or the site's privacy board or privacy official, and will work with the site to eliminate any concerns.

The Investigator or the site will promptly inform the Sponsor of any restrictions on the use or disclosure of Protected Health Information of any trial patient to which the site or the investigator have agreed under the Privacy Rule. The investigator or the site will also promptly inform the Sponsor of any written revocation of any trial patient's HIPAA Authorization.

19 INSTITUTIONAL REVIEW BOARD (IRB)

The Investigator is responsible for obtaining initial and continuing review of the study by an IRB. Written approval from the IRB must be forwarded to the Sponsor before clinical supplies will be shipped. This protocol and the written informed consent form shall be submitted to the IRB identified with this responsibility at the Institution. Notification in writing of approval must come from the IRB chairman or secretary to the investigator, either as a letter or as a copy of the appropriate section of the IRB meeting minutes where this protocol and associated informed consent form were discussed. The Investigator will not participate in the decision to approve the protocol. If the Investigator is an IRB member, the written approval must indicate such non-participation. The Investigator will submit status reports to the IRB at least annually (when applicable). The IRB must be notified by the Investigator in writing of the interruption and/or completion of the study; the Investigator must promptly report to the IRB all changes in research (protocol amendments) and will not make such changes without IRB approval except where necessary to eliminate apparent immediate hazards to human patients. In these cases, the IRB must be notified within five days of the change. The Investigator will promptly report to the IRB all unanticipated problems involving risk to patients or others. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB and must agree to share all such documents and reports with the Sponsor.

The IRB will comply with all federal, state, and local laws. Particular attention is drawn to the Food and Drug Administration Regulations for Institutional Review Boards (21 CFR, Part 56), and the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices for IRB Committees.

The Sponsor will promptly be advised of any regulatory inspection (relating to this study), of either the institution or the IRB. The Investigator will promptly provide the Sponsor with a copy of any inspection report.

20.0 CONFIDENTIALITY

20.1 Confidentiality of Data

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical Investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical Investigator and Institutional Review Board.

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information

will be divulged to the Institutional Review Board, Ethics Review Committee, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication.

20.2 Confidentiality of Patient Records

By signing this protocol, the Investigator agrees that the Sponsor (or Sponsor representative), Institutional Review Board (IRB) or Regulatory Agency representatives may consult and/or copy study documents in order to verify case report form data. By signing the consent form, the patient agrees to this process. If study documents will be photocopied during the process of verifying case report form information, the patient will be identified by unique code only; full names/initials will be masked. Notwithstanding the foregoing, to the extent that Protected Health Information is used and/or disclosed in the course of this study, all applicable provisions of the HIPAA Privacy Rule [45 CFR § 164.102 *et seq*] will be complied with.

20.3 Confidentiality of Investigator Information

By signing this protocol, the Investigator recognizes that certain personal identifying information (e.g., name, hospital or clinic address, curriculum vitae) may be made part of a regulatory submission and may be transmitted (either in hardcopy or electronically) to all Medicure International affiliates/agents worldwide for internal study management purposes or as required by individual regulatory agencies. Additionally, the Investigator's name, hospital/clinic address/phone number may be included when reporting certain serious adverse events to regulatory agencies or to other Investigators.

21 DEBARMENT

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The Investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred, or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that site's IRB.

22 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the Investigator agrees to provide to the Sponsor accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). This requirement also extends to sub-investigators.

23 PUBLICATIONS

Members of the Steering Committee will be primarily responsible for the creation, review and submission of publications and presentations relating to the major aspects of the study (design, baseline data, mortality and safety data) and approved sub-study, ancillary analyses within a timely fashion after completion of the study.

The Investigator agrees that all data regarding the study will be the property of the Sponsors. The Investigator agrees to consider the results as information patient to confidentiality and use restrictions until the results are presented in the public domain.

The underlying principles by which clinical study publication of safety and efficacy data will be managed are as follows:

- Manuscripts for publication will be submitted to the Steering Committee with representation from the Sponsor.

- Members of the Steering Committee will determine the focus of the manuscript and will also select the appropriate journal(s) in which to publish, and will determine the appropriate tables and figures for inclusion.

PROTOCOL SIGNATURE PAGE

IND# 38,899; Protocol #11002; Version 3.0 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

SITE PRINCIPAL INVESTIGATOR

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Adverse Events Section of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol.

_____
Site Principal Investigator (Printed Name)

_____
Site Principal Investigator (Signature)

_____
Date

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69. Aggrastat Prescribing Information.

LIST OF APPENDICES

APPENDIX 1

Schedule of Evaluations and Procedure

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.

[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.

APPENDIX 2

Laboratory Evaluations

Local Laboratory
The following laboratory evaluations will be performed by a local laboratory according to local practice standards:

- **Serum or Urine Pregnancy**
  If per institutional policy (within 7 days prior to randomization).

- **Serum Creatinine**
  Baseline assessment (within 24 hours prior to randomization).

- **PT-INR**
  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).

- **Troponin**
  Troponin (either troponin I or troponin T) will be sampled immediately prior to PCI, preferably from the PCI access sheath or guiding catheter, and at 9±3 hours after PCI, and at 21±3 hours after PCI. If the patient remains in the hospital longer than 36 hours after PCI, a third post-PCI troponin will be sampled at 42±6 hours after PCI. All troponin samples will be analyzed by the local laboratory. It is **mandated** that patients be observed for a minimum of 18 hours following PCI to allow for at least two post-PCI troponin samples.

- **Hemoglobin, Hematocrit and Platelet Count**
  Hemoglobin, hematocrit and platelet count will be sampled at the same time as the troponin draws (see above), i.e., immediately prior to PCI, preferably from the PCI access sheath or guiding catheter, and at 9±3 hours following PCI, and at 21±3 hours. If the patient remains in the hospital longer than 36 hours after PCI, a third hemoglobin, hematocrit and platelet count post-PCI draw will be sampled at 42±6 hours after PCI. All hemoglobin, hematocrit and platelet count samples will be analyzed by the local laboratory. It is **mandated** that patients be observed for a minimum of 18 hours following PCI to allow for at least two post-PCI hemoglobin, hematocrit and platelet count samples.

- **PT/aPTT**
  If/as indicated for bleeding or sheath removal.

Note no central laboratory work is required for this study.

APPENDIX 3

Study Drug Dosing Tables

Refer to Pharmacy Manual for detailed dosing and drug preparation description.

Short Tirofiban will be administered as a 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.

Eptifibatide will be administered as a 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.

Long Tirofiban was administered as a 25 µg/kg bolus followed by a 0.15 µg/kg/min infusion for 18 hours post-PCI (minimum 12 hours mandated).

The study drug boluses of tirofiban or eptifibatide will be administered intravenously by volume according to patient weight (see Appendix 3 for dosing tables). The bolus volume and infusion rate increases with increasing patient weight, but is capped at the patient weight of 153 and 121 kg for tirofiban and eptifibatide, respectively. Therefore, any patient randomized to short or long tirofiban weighing over 153 kg will receive the same bolus volume and infusion rate as a patient randomized to tirofiban weighting 153 kg. Similarly, any patient randomized to eptifibatide weighing over 121 kg will receive the same bolus volume and infusion rate as a patient randomized to eptifibatide weighting 121 kg. See **Tables 1** and **2** for study-drug dosing information.

In The Event of Thrombotic Complications

The following six paragraphs refer ONLY to patients assessed a thrombotic complication (according to the criteria defined in section 5.2.4) persisting at the end of the PCI procedure:

Patients administered short tirofiban with normal renal function shall receive a continuing infusion of 0.15 µg/kg/min maintenance infusion of tirofiban for a minimum of 12 hours following PCI. See **Table 1** for study-drug dosing table. After 159 patients were randomized, a 1:1:1 randomization was initiated, randomizing patients to short tirofiban, eptifibatide or long tirofiban.

Patients administered short tirofiban with renal insufficiency (creatinine clearance ≤60 mL/min) shall receive a continuing infusion of 0.075 µg/kg/min maintenance infusion (i.e. 1/2 the usual rate) of tirofiban for a minimum of 12 hours following PCI. See **Table 1** for study-drug dosing table. The change in dosing for patients with renal insufficiency (<30 mL/min to <60 mL/min creatinine clearance) randomized to either short or long tirofiban was implemented after 159 patients were enrolled. The second change in dosing for patients with creatinine clearance ≤60 mL/min (0.10 to 0.075 µg/kg/min was implemented after 167 patients were enrolled.

Patients administered eptifibatide with normal renal function shall continue to receive a 2.0 µg/kg/min maintenance infusion of eptifibatide for 18 hours following PCI

(minimum 12 hours mandated, no maximum infusion duration). See **Table 2** for study-drug dosing table.

Patients administered eptifibatide with renal insufficiency (creatinine clearance <50 mL/min) shall continue to receive a 1.0 µg/kg/min maintenance infusion (i.e. 1/2 the usual rate) of eptifibatide for 18 hours following PCI (minimum 12 hours mandated, no maximum infusion duration). See **Table 2** for study-drug dosing table.

Patients administered long tirofiban with normal renal function received a continuing infusion of 0.15 µg/kg/min maintenance infusion of tirofiban for 18 hours following PCI (minimum 12 hours mandated, no maximum infusion duration). See **Table 1** for study-drug dosing table.

Patients administered long tirofiban with renal insufficiency (creatinine clearance ≤60 mL/min) received a continuing infusion of 0.075 µg/kg/min maintenance infusion (i.e. 1/2 the usual rate) of tirofiban for 18 hours following PCI (minimum 12 hours mandated, no maximum infusion duration). See **Table 1** for study-drug dosing table.

Table 1. Tirofiban dosing table using 100 mL injection premixed bags.

Patient Weight (kg)	Bolus Volume (mL)	0.15 μg/kg/min Infusion Rate (mL/hr)	0.075 μg/kg/min Infusion Rate (mL/hr)
30-37	17	6	3
38-45	21	7.5	3.75
46-54	25	9	4.5
55-62	29	10.5	5.25
63-70	33	12	6
71-79	37.5	13.5	6.75
80-87	42	15	7.5
88-95	46	16.5	8.25
96-104	50	18	9
105-112	54	19.5	9.75
113-120	58	21	10.5
121-128	62	22.5	11.25
129-137	66.5	24	12
138-145	71	25.5	12.75
146-153	75	27	13.5

Table 2. Eptifibatide dosing table [67].

Patient Weight		180-mcg/kg Bolus Volume	2.0-mcg/kg/min Infusion Volume		1.0-mcg/kg/min Infusion Volume	
(kg)	(lb)	(from 2-mg/mL vial)	(from 2-mg/mL 100-mL vial)	(from 0.75-mg/mL 100-mL vial)	(from 2-mg/mL 100-mL vial)	(from 0.75-mg/mL 100-mL vial)
37-41	81-91	3.4 mL	2.0 mL/h	6.0 mL/h	1.0 mL/h	3.0 mL/h
42-46	92-102	4.0 mL	2.5 mL/h	7.0 mL/h	1.3 mL/h	3.5 mL/h
47-53	103-117	4.5 mL	3.0 mL/h	8.0 mL/h	1.5 mL/h	4.0 mL/h
54-59	118-130	5.0 mL	3.5 mL/h	9.0 mL/h	1.8 mL/h	4.5 mL/h
60-65	131-143	5.6 mL	3.8 mL/h	10.0 mL/h	1.9 mL/h	5.0 mL/h
66-71	144-157	6.2 mL	4.0 mL/h	11.0 mL/h	2.0 mL/h	5.5 mL/h
72-78	158-172	6.8 mL	4.5 mL/h	12.0 mL/h	2.3 mL/h	6.0 mL/h
79-84	173-185	7.3 mL	5.0 mL/h	13.0 mL/h	2.5 mL/h	6.5 mL/h
85-90	186-198	7.9 mL	5.3 mL/h	14.0 mL/h	2.7 mL/h	7.0 mL/h
91-96	199-212	8.5 mL	5.6 mL/h	15.0 mL/h	2.8 mL/h	7.5 mL/h
97-103	213-227	9.0 mL	6.0 mL/h	16.0 mL/h	3.0 mL/h	8.0 mL/h
104-109	228-240	9.5 mL	6.4 mL/h	17.0 mL/h	3.2 mL/h	8.5 mL/h
110-115	241-253	10.2 mL	6.8 mL/h	18.0 mL/h	3.4 mL/h	9.0 mL/h
116-121	254-267	10.7 mL	7.0 mL/h	19.0 mL/h	3.5 mL/h	9.5 mL/h
>121	>267	11.3 mL	7.5 mL/h	20.0 mL/h	3.7 mL/h	10.0 mL/h

APPENDIX 4

ACT Measurements and Unfractionated Heparin Dosing Algorithm

For Patients Administered Background Unfractionated Heparin Therapy

In this study, the recommended target for the ACT is 200-300 seconds for patients administered background unfractionated heparin and randomized to either short or long tirofiban or eptifibatide. The following sequence of events is recommended for all patients administered background unfractionated heparin and randomized to either tirofiban or eptifibatide in this study:

If unfractionated heparin therapy was used pre-procedure, the infusion must be turned off before the start of the index procedure.

The following sequence of events is recommended for all patients administered background unfractionated heparin and randomized to either tirofiban or eptifibatide in this study:

- Establish vascular access.

- If the patient is not receiving intravenous unfractionated heparin, administer 50 U/kg of heparin and then proceed to the next step. If the patient has received an intravenous unfractionated heparin infusion within the previous 6 hours, proceed directly to the next step.

- Obtain ACT, perform guide shot angiograms.

- If ACT is $\geq$ 200 seconds, the intervention may begin.

- If ACT is $<$ 200 seconds, administer additional heparin per the following dosing guidelines.

Baseline ACT (seconds)	Unfractionated Heparin dose (U/kg)
<150	40
150-174	25
175-199	10

- The initial bolus dose should not exceed 6,000 units.

- An ACT should be checked a minimum of 2 minutes after the initial unfractionated heparin bolus. If the ACT is $\geq$ 200 seconds, the intervention may begin.

- If the ACT is <200 seconds, an additional bolus should be administered as in the table above. An ACT should then be checked a minimum of 2 minutes after this additional bolus.

- Additional boluses of unfractionated heparin may be given as in the table above until an ACT of ≥ 200 seconds is achieved.

These recommendations are to serve as guidelines. Additional boluses of unfractionated heparin may also be administered according to the discretion of the operator to achieve and maintain the ACT in the target range of 200-300 seconds.

<u>During the procedure:</u>

- After an initial ACT of 200-300 seconds is obtained, the ACT should be re-checked 30 minutes later, and every 30 minutes thereafter for the duration of the procedure.

- If the ACT is ≥ 200 seconds, no additional unfractionated heparin should be given.

- If the ACT is <200 seconds, an additional bolus may be administered as in the table above. An ACT should then be checked a minimum of 2 minutes after this additional bolus.

These recommendations are to serve as guidelines. Additional boluses of unfractionated heparin may also be administered according to the discretion of the operator to maintain the ACT in the target range of 200-300 seconds.

APPENDIX 5

Guidelines for Management of Urgent Target Vessel Revascularization

If the PCI procedure is unsuccessful and the patient requires urgent CABG (within 24 hours post-procedure), study drug should be discontinued and appropriate measures be taken to minimize the surgical risk. Both short and long tirofiban and eptifibatide treated patients will generally recover platelet function within 4 to 8 hours, although platelet and/or fresh frozen plasma transfusions might be considered for bleeding. There is limited experience with the efficacy of either of these interventions, though cryoprecipitate or FFP has been suggested for urgent reversal of tirofiban's effect.

Delayed Elective CABG

If the patient is scheduled for delayed elective CABG, study drug infusions should continue if clinically appropriate. Optimally, elective CABG should be deferred for 3-5 days to allow for normalization of platelet function among patients who have received study drug and clopidogrel.

APPENDIX 6

Guidelines for Management of Serious Bleeding

Should a major bleeding complication occur during study drug infusion, the first step in treatment should be to immediately discontinue the study drug. Packed red blood cells should be transfused as clinically indicated (see Transfusion Guidelines appended in this Appendix). Transfusion of platelets may also be considered, especially in the presence of severe thrombocytopenia (see Appendix 7).

Any patient experiencing clinically significant bleeding which does not warrant immediate discontinuation of study drug must have a complete blood count (CBC) including platelet count and a PT/PTT repeated within four (4) hours of the observed blood loss or the last CBC. Based upon the results of this CBC and platelet count and subsequent clinical events either:

a. In the opinion of the Investigator the patient is clinically stable; then study drug infusions may continue and another repeat CBC/platelet and PT/PTT must be obtained 4 hours later to confirm patient stability, OR

b. In the opinion of the Investigator the patient is considered unstable as determined by clinical symptoms or assessment of labs, then the study drugs should be discontinued.

Consideration should be given to transfusion of fresh frozen plasma in the event of serious bleeding. Platelet function should return to near baseline in approximately 90% of patients in 4 to 8 hours.

A decision to administer platelets should be based on clinical judgment, taking into account the site and severity of bleeding and time of discontinuation of study drug. In the case of documented or suspected central nervous system (CNS) hemorrhage, platelet transfusions are strongly recommended regardless of treatment assignment. If a decision is made to administer platelets, it is recommended that 10 units of platelets be given initially. If platelet function does not return to normal or cannot be measured, repeat platelet transfusions should be considered within 1 to 2 hours if there is evidence of progressive CNS hemorrhage or uncontrollable gastrointestinal, genitourinary, or retroperitoneal hemorrhage. If serious bleeding occurs in the setting of thrombocytopenia, platelet transfusions should be administered.

Transfusion Guidelines

Guidelines for Transfusion in Asymptomatic Patients:

a) Assess the patient's intravascular volume status. All asymptomatic patients should be normovolemic. Normovolemic anemia (hemoglobin 7 –10 g/dl) can be well tolerated in asymptomatic patients.

b) If hypovolemic, intravascular volume of patients should be adequately restored with crystalloids.

c) In asymptomatic, normovolemic patients transfusion is not indicated unless the hgb is ≤7 g/dl or a deterioration in vital signs is seen or unless the patient develops signs and symptoms, as described below.

Guidelines for Transfusion in Symptomatic Patients:

If the following signs and symptoms occur, syncope, dyspnea, postural hypotension, tachycardia, angina, transient ischemic attack:

a) Use crystalloids to replace intravascular volume.

b) If symptoms persist after volume repletion, the patient should receive transfusion(s) with autologous blood (if available).

c) If autologous blood is not available, the patient should receive transfusion(s) with homologous blood on a unit-by-unit basis to relieve symptoms. Remember: One unit may be sufficient.

APPENDIX 7

Guidelines for Management of Thrombocytopenia

< 100,000 cells/μL and a decrease of at least 25% from the baseline
If a platelet count falls below 100,000 cells/μL and decreases at least 25% from the baseline value in any sample compared to any previous sample, additional repeat platelet counts and/or further laboratory analyses (i.e., microscopic) per local institution guidelines must be performed to exclude laboratory error (clumping, etc.). The repeat platelet counts should be performed according to the specific practice at each institution.

If thrombocytopenia is verified and determined not to be an artifact caused by the interaction with anticoagulants (pseudothrombocytopenia), a daily platelet count is to be obtained until the platelet count steadily and adequately increases or returns to within normal range.

< 50,000 cells/μL
In addition to the above, if a patient's platelet count drops to less than 50,000 cells/μL, aspirin and the study drug infusions should be discontinued.

< 20,000 cells/μL
In addition to the above, if a patient's platelet count drops below 20,000 cells/μL, transfusion should be considered to maintain a platelet count greater than 50,000 cells/μL.