

Supplemental Materials

PAR1 pepducin therapy targeting myocardial necrosis in CAD and ACS patients undergoing cardiac catheterization: a randomized, placebo-controlled, phase 2 study

Athan Kuliopulos, Paul A. Gurbel, Jeffrey J. Rade, Carey D. Kimmelstiel, Susan E. Turner, Kevin P. Bliden, Elizabeth K. Fletcher, Daniel H. Cox, Lidija Covic; on behalf of the TRIP-PCI Investigators

From the Center for Hemostasis and Thrombosis Research, Tufts Medical Center, Tufts University School of Medicine, Boston, MA (A.K., S.E.T., E.K.F., D.H.C., L.C.); Inova Center for Thrombosis Research and Translational Medicine, Inova Fairfax Hospital, Falls Church, VA, and Sinai Hospital of Baltimore, MD (P.A.G., K.P.B.); Department of Medicine, Division of Cardiology, University of Massachusetts Memorial Medical Center, University of Massachusetts Medical School, Worcester, MA (J.J.R); Department of Medicine, Division of Cardiology, Tufts Medical Center, Boston, MA (C.D.K.).

Correspondence:

Athan Kuliopulos, MD, PhD, E-mail:athan.kuliopulos@tufts.edu

Expanded Methods

TRIP-PCI Organization

Sponsor

Tufts Medical Center, Boston, MA
Responsible Medical Officer (NHLBI/NIH Principal Investigator): Athan Kuliopulos, MD, PhD
Tufts Medical Center & Tufts University School of Medicine
Federal Award Identifier Number: P50HL110789
Co-Investigator: Lidija Covic, PhD
Trial Manager: Susan E. Turner, BS

Clinical Sites

Inova Fairfax Hospital (Site-1), Falls Church, VA
Number of patients randomized: 62
Principal Investigator: Paul A. Gurbel, MD
Enrolling Investigators: Marjaneh Akbari, MD, Nicholas A. Cossa, MD, Kelly Epps, MD, Nadim Geloo, MD, Matthew W. Sherwood, MD, Hamid Taheri, MD, Benham Tehrani, MD, Alexander Truesdell, MD, Shahram Yazdani, MD
Study Coordinator: Andrea Fitzgerald, MA, RN

Tufts Medical Center (Site-2), Boston, MA
Number of patients randomized: 6
Principal Investigator: Carey D. Kimmelstiel, MD
Study Coordinator: Vilma Castaneda, MD

University of Massachusetts Memorial Medical Center (Site-3), Worcester, MA
Number of patients randomized: 32
Principal Investigator: Jeffrey J. Rade, MD
Enrolling Investigators: Mohammed Akhter, MD, Alvaro Alonso, MD, Nikolaos Kakouros, MD
Study Coordinator: Barbara Smithson, RN

Data Safety and Monitoring Board (DSMB)

David F. Kong, MD (Chair)
Duke University Medical Center & Duke Clinical Research Institute
Durham, NC

William R. Herzog, Jr., MD
Cardiovascular Specialists of Central Maryland & Johns Hopkins University School of Medicine
Baltimore, MD

Victor Hasselblad, PhD, MS
Duke University School of Medicine
Durham, NC

Clinical Events Committee (CEC)

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Johns Hopkins Hospitals & School of Medicine
Baltimore, MD

Rolf P. Kreutz, MD
Indiana University Health Medical Center & School of Medicine
Indianapolis, IN

Institutional Review Boards (IRBs)

Inova Human Research Protection Program (FWA00000573), Falls Church, VA

Tufts Health Sciences Campus IRB (FWA00004449), Boston, MA

University of Massachusetts Medical School (FWA00004009), Worcester, MA.

Central Research Lab

Tufts Medical Center

Center for Hemostasis and Thrombosis Research

Boston, MA

Cardiac Troponin-I Sample Analysis

Tufts Medical Center

Clinical Laboratory, Routine Chemistry

Boston, MA

Pharmacodynamics – Platelet Aggregation Labs

Inova Fairfax Hospital

Inova Center for Thrombosis Research and Drug Development

Fairfax, VA

Tufts Medical Center

Center for Hemostasis and Thrombosis Research

Boston, MA

Pharmacokinetics Analysis

Charles River Laboratories Ashland, LLC

Ashland, OH

Statistical and Data Management Support

RTI International

Research Triangle Park, NC

Chemistry, Manufacturing and Control

Ambiopharm, Inc. (API)

North Augusta, SC

Catalent San Diego, Inc. (Pharmatek)

San Diego, CA

Clinical Supplies Management, Inc. (CSM)

Fargo, ND

Lyophilization Technology, Inc. (LTI)

Ivyland, PA

Inclusion and Exclusion Criteria

Subject Selection

Subjects participating in the study met all the inclusion criteria. Subjects who met any of the exclusion criteria could not be randomized in the study.

Inclusion Criteria

1. The subject is at least 18 years of age and may be of either sex/gender and of any race and ethnicity.
2. The subject is scheduled to undergo non-emergent PCI or non-emergent cardiac catheterization with the intention of performing PCI. The following classifications of the urgency of the procedure at the time the operator decides to perform it will be used for randomization stratification:

Elective: The cardiac catheterization procedure ± PCI can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of MI or death. For stable inpatients, this is a procedure that is performed during the hospitalization for convenience and ease of scheduling only, and not because the subject's clinical situation demands that the procedure be performed prior to discharge.

Urgent: The cardiac catheterization ± PCI procedure should be performed on an inpatient basis and before discharge because of significant concerns about the risk of myocardial ischemia, MI, and/or death. For subjects who are outpatients or in the emergency department at the time that the cardiac catheterization is requested, this is a procedure that would warrant hospital admission based on clinical presentation.
3. There is no anticipation that the subject would require treatment with a glycoprotein IIb/IIIa inhibitor prior to the initiation of the cardiac catheterization ± PCI procedure if the subject were not a participant in the current research study, and no anticipation of use during the procedure.
4. The subject is willing and able to give appropriate informed consent and complete all study-related procedures, and able to adhere to dosing and visit schedules (i.e., subject signs an approved informed consent document(s) and provides HIPAA authorization).
5. The subject will undergo all of the pre-enrollment parameters according to the protocol prior to randomization and have them completed within 14 days prior to the scheduled cardiac catheterization ± PCI procedure and study drug administration.
6. Women of childbearing potential (all postmenarchal women who are <1 year menopausal or who have not had surgical sterilization or a hysterectomy are considered to be women of child-bearing potential) must agree to use a medically accepted method of contraception from the time written informed consent is given up until 90 days following the study drug administration. Injectable, implantable, patch, or oral ("the pill") hormonal contraceptives, medically prescribed intrauterine device (IUD) or partner vasectomy are medically accepted methods of contraception. Double barrier methods are acceptable although the risk of pregnancy is higher. Examples of double barrier methods are diaphragm with spermicidal gel or condoms with contraceptive foam.

Exclusion Criteria

1. Subject is pregnant, intends to become pregnant, or is breast-feeding (all women of child-bearing potential must have a negative pregnancy test result confirmed prior to randomization and it must be repeated to be within 24 hours prior to the study drug administration if necessary).
2. Any of the following allergy history(s):
 - History of an allergic reaction* or contraindication to any of the following protocol-directed drugs: aspirin, heparin, P2Y₁₂ inhibitor (clopidogrel, prasugrel, or ticagrelor), or antihistamines (diphenhydramine or famotidine); or

- History of an allergic reaction* to contrast media; or
- History of an allergic reaction* to a drug which required emergency medical treatment; or
- History of an allergic reaction* to a *Hymenoptera* sting which currently necessitates the subject to carry an EpiPen/injector or the subject has been prescribed one to treat an allergic reaction to a sting.

*An allergic (anaphylactic) reaction is characterized by an adverse local or general response from exposure to an allergen involving skin/mucosal tissue manifestations (hives, pruritus, flushing, and/or angioedema), and/or respiratory compromise (dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, and/or hypoxemia), and/or hemodynamic effects (hypo/hypertension, hypotonia, and/or syncope).

3. Participation in another research study of investigational therapy (drug or device) within the past 30 days prior to randomization or planned use of other investigational therapy(s) during this research study (until 90 days following the study drug administration).
4. Subject is part of the study staff personnel directly involved with this trial, or is a family member of the study staff (clinical site or sponsor).
5. Prior enrollment (randomization) in this research study.
6. Any condition which could interfere with, or the treatment for which might interfere with, the conduct of the research study or which would, in the opinion of the investigator, unacceptably increase the subject's risk by participating in the research study. This would include, but is not limited to alcoholism, drug dependency or abuse, psychiatric disease, epilepsy, or any unexplained blackouts.
7. Evidence of an ST-segment elevation myocardial infarction (STEMI) on presentation or during current hospitalization or a history of STEMI within the past 30 days prior to randomization.
8. Subject is scheduled to undergo PCI for known unprotected left main coronary artery (LMCA) disease (i.e., left main stenosis $\geq 50\%$ not protected by at least 1 patent bypass graft).
9. Any history of a prior stroke (hemorrhagic or ischemic) or transient ischemic attack (TIA) of any etiology.
10. Cardiogenic or any type of shock on presentation or during current hospitalization (i.e., systolic blood pressure < 90 mm Hg requiring vasopressor or hemodynamic support).
11. History of heparin-induced thrombocytopenia (HIT).
12. Any active bleeding within the past 30 days prior to randomization.
13. Any condition or personal belief (e.g., Jehovah's Witness) which would interfere with the subject's ability or willingness to undergo a blood transfusion.
14. Any of the following conditions associated with increased risk of bleeding:
 - history of intracranial, intraocular, spinal, retroperitoneal or atraumatic intra- articular bleeding;
 - gastrointestinal bleeding within the past 30 days prior to randomization;
 - gastric or duodenal ulcer disease verified by endoscopy or barium meal contrast technique within the past 6 months prior to randomization;
 - history of bleeding disorder or diathesis;
 - major surgical procedure or trauma within the past 60 days prior to randomization or a planned surgical procedure to take place within 30 days following the study drug administration;
 - history or suspicion of intracranial neoplasm, arteriovenous malformation, or aneurysm; or
 - clinical finding(s) in the judgment of the investigator that poses an increased risk of bleeding.

15. Sustained severe hypertension: systolic blood pressure >185 mm Hg or diastolic blood pressure >105 mm Hg with or without anti-hypertensive treatment (as demonstrated by repeated BP measurements >185/105 mm Hg including the final BP measurement before randomization).
16. Hypotension: systolic blood pressure <95 mm Hg (as demonstrated by repeated systolic BP measurements <95 mm Hg including the final systolic BP measurement prior to randomization).
17. Known active hepatobiliary disease, or known unexplained persistent increase in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activity to ≥ 2.5 times the upper limit of the reference range within the past 30 days prior to randomization.
18. Hemoglobin <10 g/dL or hematocrit <30%.
19. Platelet count <75,000/mm³.
20. Stage 4-5 Chronic Kidney Disease (National Kidney Foundation) or on dialysis.
21. Active sepsis or suspected sepsis.
22. Body weight <60 kg or >175 kg.
23. Current evidence of invasive cancer (persistent disease excluding basal cell carcinoma of the skin) or treatment for invasive cancer within the past 6 months prior to randomization.
24. Left ventricular ejection fraction <25% if known (any imaging technique) or New York Heart Association (NYHA) Class IV congestive heart failure.
25. Coronary interventional procedure of any kind within the past 30 days prior to randomization.
26. Anticipated subsequent staged multi-vessel PCI within 30 days following the study drug administration.
27. History of treatment with any parenteral glycoprotein IIb/IIIa inhibitor (GPI) within the past 30 days prior to randomization. (As stated in the Inclusion section, the planned treatment with a GPI prior to initiation of the cardiac catheterization \pm PCI is not allowed; however, GPI for thrombotic bailout may be used during the PCI at the investigator's discretion).
28. Concurrent or anticipated treatment with a parenteral direct thrombin inhibitor (e.g., bivalirudin) for the cardiac catheterization \pm PCI procedure.
29. History of treatment with another PARI inhibitor within the past 60 days prior to randomization or the concurrent/anticipated use after randomization up until 30 days following the study drug administration.
30. History of treatment with another IV anti-platelet drug within 30 days prior to randomization or the concurrent/anticipated use after randomization up until 30 days following the study drug administration.
31. Any of the following anticoagulant or thrombolytic/fibrinolytic treatment(s):
 - History of treatment with warfarin within 5 days prior to randomization or the concurrent/anticipated use after randomization up until 2 days following the study drug administration; or
 - History of treatment with oral Factor Xa or direct thrombin inhibitors within 2 days prior to randomization or the concurrent/anticipated use after randomization up until 2 days following the study drug administration; or
 - History of treatment with thrombolytic/fibrinolytic agents within 7 days prior to randomization or the concurrent/anticipated use of any of those agents after randomization up until 30 days following the study drug administration.

Protocol Definitions for Safety and Efficacy Assessments

Safety

Bleeding

Bleeding will be classified according to 2 separate classifications.

Thrombolysis in Myocardial Infarction (TIMI)

Primary and secondary endpoints

The following definitions apply to all settings outside of peri-CABG:

Major:

1. Any intracranial (ICH)*, or
2. Clinically significant overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ≥ 5 g/dL (or, when Hgb is not available, an absolute drop in hematocrit (Hct) of $\geq 15\%$), or
3. Fatal bleeding (bleeding that directly results in death within 7 d)

Minor: Any clinically significant overt sign of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to < 5 g/dL (or, when Hgb is not available, a fall in Hct of 9 to $< 15\%$).

Minimal: Clinically significant overt signs of hemorrhage associated with a drop in Hgb of < 3 g/dL (or, when Hgb is not available, a fall in Hct of $< 9\%$) that did not otherwise meet criteria for minor or major bleeding.

To account for transfusions, Hgb and Hct measurements will be adjusted for any packed red blood cells (PRBCs) or whole blood given between baseline (enrollment) and post-transfusion measurements by the method of Landefeld and coworkers. A transfusion of one unit of blood will be assumed to result in an increase by 1 g/dL in Hgb or by 3% in Hct. Thus, to calculate the true change in hemoglobin or hematocrit, if there has been an intervening transfusion between 2 blood measurements, the following calculations should be performed:

$$\Delta \text{ Hemoglobin (Hgb)} = [\text{Baseline Hgb} - \text{post-transfusion Hgb}] + [\text{number of transfused units}]$$

$$\Delta \text{ Hematocrit (Hct)} = [\text{Baseline Hct} - \text{post-transfusion Hct}] + [\text{number of transfused units} \times 3]$$

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

- Spontaneous: any bleeding which there is no relation to any cause or reason
- Induced: any bleeding that is precipitated by a cause or cause reason

Bleeding requiring medical attention: Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above:

- Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug), or
- Leading to or prolonging hospitalization, or
- Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Clinically significant bleeding: The presence of either TIMI major or TIMI minor bleeding, or bleeding requiring medical attention.

For subjects experiencing a hemorrhage that occurs as a result of CABG, the following criteria will be used:

Major: Any hemorrhage that meets any of the following criteria:

- a. Fatal bleeding (i.e., bleeding that directly results in death), or
- b. Perioperative intracranial bleeding*, or

- c. Reoperation following closure of the sternotomy incision for the purpose of controlling bleeding, or
- d. Transfusion** of ≥ 5 U of whole blood or PRBCs within a 48 hour period, or
- e. Chest tube output > 2 L within a 24-hour period

None: Not qualifying as a major bleed in setting of CABG.

*In light of the increased sensitivity of brain imaging for microhemorrhages of uncertain clinical significance, brain imaging with an incidental finding of microhemorrhage (< 10 mm evident only on gradient-echo MRI) in the absence of associated clinical symptoms/findings will not be considered to meet the protocol definition of intracranial hemorrhage.

**Cell saver transfusion will not be counted in calculations of blood products.

Non-bleeding

Adverse event

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

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

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

Serious adverse event

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

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

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

Efficacy

Major Adverse Cardiac Event (MACE)

Defined as the composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, recurrent ischemia with hospitalization, or urgent coronary revascularization.

Death

Cardiovascular death is the endpoint defined in this trial (as opposed to all-cause death) and only suspected CV death cases will be submitted for adjudication to the CEC. Death will be classified as cardiovascular, non-cardiovascular, or unknown/undetermined. All deaths will be assumed to be cardiovascular in nature unless a non-cardiovascular cause can be clearly shown, with the exception of death without any additional information, which will be classified as unknown/undetermined.

The primary cause of death is determined by the principal condition that caused the death, not the immediate mode of death, as per the following:

Cardiovascular death:

Acute MI

Death by any cardiovascular mechanism (arrhythmia, sudden death, HF, stroke, pulmonary embolus, PAD) within 30 days after an acute MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable (attributable) mechanisms of cardiovascular death during this time period, but for simplicity, if the cardiovascular death occurs within 30 d of an acute MI, it will be considered a death due to MI.

Note: Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat an MI (PCI or CABG), or to treat a complication resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to an MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to a cardiovascular procedure.

Sudden cardiac death

Death that occurs unexpectedly and not within 30 d of an acute MI.

Note: Sudden cardiac death includes the following scenarios:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 min of the onset of new or worsening cardiac symptoms unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on ICD review)
- Death after unsuccessful resuscitation from cardiac arrest (e.g., ICD unresponsive sudden cardiac death, pulseless electrical activity arrest)
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or noncardiac etiology
- Unwitnessed death in a subject seen alive and clinically stable ≤ 24 h before being found dead without any evidence supporting a specific non-cardiovascular cause of death (information about the subject's clinical status preceding death should be provided if available)

Unless additional information suggests an alternate specific cause of death (e.g., death due to Other cardiovascular causes), if a subject is seen alive ≤ 24 h before being found dead, sudden cardiac death should be recorded (e.g., subject found dead in bed but who had not been seen by a family member for >24 h).

Death due to heart failure

Death associated with clinically worsening symptoms and/or signs of HF, regardless of etiology.

Note: Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or nonischemic cardiomyopathy, hypertension, or valvular disease.

Death due to stroke

Death after stroke that is either a direct consequence of the stroke or a complication of the stroke.

Note: Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

Death due to cardiovascular procedures

Death caused by the immediate complication(s) of a cardiovascular procedure.

Death due to cardiovascular hemorrhage

Death related to hemorrhage such as a nonstroke intracranial hemorrhage (e.g., subdural hematoma), nonprocedural or nontraumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

Death due to other cardiovascular causes

Cardiovascular death not included in the above categories but with specific, known cause (e.g., PE, PAD).

Non-cardiovascular death: defined as any death with a specific cause that is not thought to be cardiovascular in nature:

- Pulmonary
- Renal
- GI
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Inflammatory/immune (includes SIRS, immunological, autoimmune diseases and disorders, anaphylaxis from environmental allergies)
- Hemorrhage that is neither cardiovascular bleeding nor a stroke
- Non-cardiovascular procedure or surgery
- Trauma (includes homicide)
- Suicide
- Prescription drug reaction or overdose (includes anaphylaxis)
- Nonprescription drug reaction or overdose
- Neurological (excludes cardiovascular death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke, or cardiovascular hemorrhage of central nervous system)
- Malignancy
- Other non-cardiovascular cause of death

Unknown/Undetermined cause of death: refers to death not attributable to either cardiovascular or noncardiovascular cause

Myocardial Infarction (MI)

Third Universal Definition of Myocardial Infarction

Note: cTnI or cTnT is the preferred biomarker. If a cTnI or cTnT assay is not available, the best alternative is CK-MB (measured by mass assay). In this study, the centralized cTnI results (conventional, non-high sensitivity) will be used to reduce intermarker and interassay variability. An increased cTn concentration is defined as a value exceeding the 99th percentile of a normal reference population (upper reference limit (URL)). The locally available results (conventional, non-high sensitivity) will be submitted by the clinical sites and may be used in the adjudication process as a secondary source.

Acute MI

The term *acute* myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction:

Type 1: Spontaneous

Spontaneous clinical syndrome related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection, with resulting intraluminal thrombus, and leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis.

This classification requires:

- a) Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least 1 value >99th percentile of the URL and
- b) At least one of the following:
 - i. Symptoms of myocardial ischemia
 - ii. New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB) on the ECG
 - iii. Development of pathological Q waves on the ECG
 - iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
 - v. Identification of an intracoronary thrombus by angiography or autopsy.

Notes: One or more coronary arteries may be involved. The subject may have underlying severe CAD but on occasion may have non-obstructive CAD.

Type 2: Ischemic imbalance

Spontaneous clinical syndrome where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand (e.g., coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/bradyarrhythmias, anemia, respiratory failure, hypotension, and hypertension with or without LVH).

This classification requires:

- a) Detection of a rise and/or fall of cardiac biomarker values (preferably cTn) with at least 1 value >99th percentile of the URL and
- b) At least one of the following:
 - i. Symptoms of myocardial ischemia
 - ii. New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB) on the ECG
 - iii. Development of pathological Q waves on the ECG
 - iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Type 3: Death, no markers

Death where symptoms suggestive of myocardial ischemia are present, and with (presumed) new ischemic changes or new LBBB on ECG, but where death occurs before cardiac biomarkers can be obtained or could rise or (in rare cases) were not collected.

Type 4a: Percutaneous coronary intervention (PCI)-related

MI associated with and occurring within 48 h of PCI, with elevation of cardiac biomarker values to >5 × 99th percentile of the URL in subjects with normal baseline values (≤99th percentile URL), or a rise of biomarker values >20% if the baseline values are elevated and are stable or falling. This classification also requires at least one of the following:

- i. Symptoms suggestive of myocardial ischemia (i.e., prolonged ischemia ≥20 minutes)
- ii. New ischemic changes on ECG or new LBBB

- iii. Angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or no flow or embolization
- iv. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

When a cTn value is $<5 \times 99^{\text{th}}$ percentile of the URL after PCI and the cTn value was normal before the PCI- or when the cTn value is $>5 \times 99^{\text{th}}$ percentile in the absence of ischemic, angiographic or imaging findings- the term **‘myocardial injury’** should be used. If the baseline cTnI values are elevated and are stable or falling, then a rise of $>20\%$ is required for the diagnosis of a type 4a MI, as with ‘reinfarction’.

Type 4b: Stent thrombosis

MI associated with stent thrombosis as detected by coronary angiography or at autopsy, where symptoms suggestive of myocardial ischemia are present, and with a rise and/or fall of cardiac biomarker values, with at least 1 value $>99^{\text{th}}$ percentile of the URL.

Type 4c: Stent restenosis

MI associated with stent restenosis as detected by coronary angiography or at autopsy, occurring >48 h after PCI, without evidence of stent thrombosis but with symptoms suggestive of myocardial ischemia, and with elevation of cardiac biomarker values to $>99^{\text{th}}$ percentile of the URL. This classification also requires the following:

- i. Does not meet criteria for any other classification of MI
- ii. Presence of a $\geq 50\%$ stenosis at the site of previous successful stent PCI or a complex lesion and no other significant obstructive CAD of greater severity following 1) Initially successful stent deployment, or 2) Dilation of a coronary artery stenosis with balloon angioplasty to $<50\%$ stenosis

Type 5: Coronary artery bypass grafting (CABG)-related

MI associated with and occurring within 48 h of CABG surgery, with elevation of cardiac biomarker values to $>10 \times 99^{\text{th}}$ percentile of the URL in subjects with normal baseline cardiac biomarker values ($\leq 99^{\text{th}}$ percentile URL). This classification also requires at least 1 of the following:

- i. New pathological Q waves, new LBBB on ECG
- ii. Angiographic new graft or new native coronary artery occlusion
- iii. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Acute MI- Symptoms

Presence of acute symptoms of myocardial ischemia (angina or equivalent symptoms that need to be treated medically or lasting ≥ 20 min). Ischemic symptoms as determined by the treating physician include but are not limited to weakness, shortness of breath, wheezing, tiredness, fainting, sweating, nausea/vomiting, abdominal pain, back pain, jaw pain, palpitations, fast heartbeat, drug use for chest pain (e.g., nitroglycerin, morphine, beta blocker, etc.). This is one of the noncardiac marker criteria supporting the diagnosis of acute MI Types 1, 2, 3, 4a, 4b, and 4c.

Acute MI- Acute Ischemic Changes on ECG

Presence of new or presumed new significant ST-segment-T wave (ST-T) changes or new LBBB consistent with acute myocardial ischemia. This is one of the noncardiac marker criteria supporting the diagnosis of acute MI Types 1, 2, 3, and 4.

- Ischemic changes on ECG
 - In the absence of LVH and LBBB pattern (or other confounder such as a paced rhythm) on ECG, either:
 - a) ST elevation
 - New (or presumed new) ST elevation at the J point in 2 contiguous leads with the following cut points: ≥ 0.1 mV in all leads other than leads V_2 to V_3 where the following cut points apply: ≥ 0.2 mV in men ≥ 40 y of age; ≥ 0.25 mV in men <40 y of age, or ≥ 0.15 mV in women; or

- b) ST depression and T-wave changes
New (or presumed new) horizontal or downsloping ST-segment depression ≥ 0.05 mV in 2 contiguous leads and/or T inversion ≥ 0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio > 1 .

- LBBB
New (or presumed new) LBBB pattern on ECG.

Acute MI- New Q Waves on ECG

Presence of new or presumed new pathological Q waves consistent with MI. This is one of the noncardiac marker criteria supporting the diagnosis of acute MI Types 1, 2, 4, and 5.

New (or presumed new):

- a) Any Q wave in leads V_2 to V_3 ≥ 0.02 s or QS complex in leads V_2 and V_3
- b) Q wave ≥ 0.03 s and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V_4 to V_6 in any 2 leads of a contiguous lead grouping (I, aVL; V_1 to V_6 ; II, III, aVF)
The same criteria are used for supplemental leads V_7 to V_9 .

Acute MI- Coronary Thrombus Present

Presence of thrombus in a major epicardial vessel consistent with an acute MI. This is one of the noncardiac marker criteria supporting the diagnosis of acute MI Type 1.

- Thrombus on angiography
In the patient with a presumed acute STEMI, the angiographic appearance of thrombus (typically a filling defect) on angiography. This includes the aspiration of thrombus from the infarct vessel before coronary intervention during primary PCI for acute STEMI.
- Thrombus at autopsy
Identification of thrombus in a major epicardial vessel at autopsy.

Acute MI- Change in Noninvasive Imaging

Demonstration of a new change in myocardial viability or function consistent with MI. This is one of the noncardiac marker criteria supporting the diagnosis of acute MI Types 1, 2, 4a, and 5.

- New loss of viable myocardium
Noninvasive imaging evidence of a loss of viable myocardium when compared with the most recent previous noninvasive imaging study.
- New regional wall motion abnormality
Noninvasive imaging evidence of a decrease in regional wall motion contractility compared with the most recent previous noninvasive imaging study.

Acute MI- PCI Angiographic Complication

Occurrence of an adverse angiographic finding during PCI consistent with acute myocardial ischemia. This is one of the noncardiac marker criteria supporting the diagnosis of acute MI Type 4a.

- Loss of major coronary
Angiographic loss of patency of a major epicardial vessel.
- Loss of side branch
Angiographic loss of patency of a side branch.
- Slow flow/no flow/embolization
Angiographic reduction of flow into the coronary microcirculation.

Acute MI- Acute Vessel Occlusion After CABG

Angiographic documentation of a new CABG or new native coronary artery occlusion within 48 h of CABG surgery. This is one of the noncardiac marker criteria supporting the diagnosis of acute MI Type 5.

Prior MI

Presence of any 1 of the following criteria meets the diagnosis for prior MI (before study initiation):

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes
 - a) Any Q wave in leads V_2 to $V_3 \geq 0.02$ s or QS complex in leads V_2 and V_3
 - b) Q wave ≥ 0.03 s and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V_4 to V_6 in any 2 leads of a contiguous lead grouping (I, aVL; V_1 to V_6 ; II, III, aVF)
 - c) The same criteria are used for supplemental leads V_7 to V_9
 - d) R wave ≥ 0.04 s in V_1 to V_2 and $R/S \geq 1$ with a concordant positive T wave in the absence of a conduction defect
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a prior MI

Silent MI

Asymptomatic patients who develop new pathologic Q wave criteria for MI detected during routine ECG follow-up, or reveal evidence of MI by cardiac imaging, that cannot be directly attributed to a coronary revascularization procedure, should be termed 'silent MI'. The diagnosis of a new silent Q wave MI should be confirmed by a repeat ECG with correct lead placement, or by an imaging study, and by focused questioning about potential interim ischemic symptoms.

Recurrent MI

'Incident MI' is defined as the individual's first MI. When features of MI occur in the first 28 days after an incident event, this is not counted as a new event. If characteristics of MI occur after 28 days following an incident MI, it is considered to be a recurrent MI.

Reinfarction

The term 'reinfarction' is used for an acute MI that occurs within 28 days of an incident or recurrent MI. Reinfarction should be considered when ST elevation >0.1 mV recurs, or new pathognomonic Q waves appear, in at least two contiguous leads, particularly when associated with ischemic symptoms for 20 min or longer. ST depression or LBBB alone are non-specific findings and should not be used to diagnose reinfarction.

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction of sudden onset,

- a) with persistence of symptoms for ≥ 24 hours or results in death (in <24 hours) and is not due to an identifiable non-vascular cause (i.e., brain tumor, trauma), or
- b) with symptoms of short duration (<24 hours) but evidence of infarction on cerebral imaging.

Stroke will be subclassified into 1 of 3 mutually exclusive categories:

1. Ischemic

An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

Note: Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

2. Hemorrhagic

An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular or subarachnoid hemorrhage.

Note: Subdural hematomas are intracranial hemorrhagic events and not strokes.

3. Undetermined

An acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information (brain image via CT/MRI or autopsy) to allow categorization as either ischemic or hemorrhagic (without documentation or if tests are inconclusive).

As a matter of differentiation, transient ischemic attack (**TIA**) is a transient episode (resolves spontaneously without any evidence of residual deficit <24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction. TIAs will not be reported as endpoints but will be reported as an AE.

Recurrent Ischemia with Hospitalization

Recurrent ischemia with hospitalization is defined as ischemic discomfort or equivalent meeting the following criteria:

- a) lasting ≥ 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration, and precipitated by minimal exertion), considered to be myocardial ischemia upon final diagnosis, and
- b) prompting hospitalization (including an overnight stay on an inpatient unit) within 48 hours of the most recent symptoms, and
- c) at least 1 of the following additional criteria for coronary artery disease and/or ischemia:
 - new and/or dynamic ST depression ≥ 0.05 mV, ST elevation ≥ 0.1 mV, or symmetric T-wave inversion ≥ 0.2 mV on a resting ECG; or
 - definite evidence of ischemia on stress echocardiography, myocardial scintigraphy (e.g., an area of clear reversible ischemia), or ECG-only stress test (e.g., significant dynamic ST shift, horizontal or downsloping); or
 - angiographic evidence of epicardial coronary artery stenosis of $\geq 70\%$ diameter reduction and/or evidence for intraluminal arterial thrombus.

If subjects are admitted with suspected myocardial ischemia, and subsequent testing reveals a noncardiac or non-ischemic etiology, this will not be recorded as meeting this end point. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as ischemia requiring hospitalization.

Urgent Coronary Revascularization

Urgent coronary revascularization is defined as ischemic discomfort or equivalent meeting the following criteria:

- a) lasting ≥ 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, considered to be myocardial ischemia upon final diagnosis, and
- b) prompting coronary revascularization during an unscheduled visit to health care facility or during an unplanned (or prolonged) hospitalization for these symptoms or revascularization, which was either done emergently or not previously planned during the course of hospitalization.

Attempted revascularization procedures, even if not successful, will be counted. Potential ischemic events meeting the criteria for myocardial infarction will not be adjudicated as urgent coronary revascularization.

Coronary Stent Thrombosis

All cases of reported death, MI, recurrent ischemia with hospitalization and urgent coronary revascularization will be reviewed and adjudicated with respect to stent thrombosis according to the Academic Research Consortium definition below:

Timing:

Acute stent thrombosis*	0 to 24 hours after stent implantation
Subacute stent thrombosis*	>24 hours to 30 days after stent implantation
Late stent thrombosis†	>30 days to 1 year after stent implantation
Very late stent thrombosis†	>1 year after stent implantation

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the subject has left the catheter laboratory.

*Acute or subacute can also be replaced by the term early stent thrombosis. Early stent thrombosis (0-30 days)

†Includes primary as well as secondary late stent thrombosis; secondary late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Grading:

Three categories of evidence define the probability that coronary artery stent thrombosis has occurred:

1. Definite stent thrombosis*
 - a) Angiographic confirmation of stent thrombosis†

The presence of a thrombus‡ that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:

 - Acute onset of ischemic symptoms at rest
 - New ischemic ECG changes that suggest acute ischemia
 - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)
 - Nonocclusive thrombus
Intracoronary thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
 - Occlusive thrombus
TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).
 - b) Pathological confirmation of stent thrombosis
Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.
2. Probable stent thrombosis
Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:
 - Any unexplained death within the first 30 days§
 - Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.
3. Possible stent thrombosis
Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death >30 days after intracoronary stenting.

*Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

†The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).

‡Intracoronary thrombus.

§For studies with ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

When available data support >1 classification, the highest level of certainty should be reported.

Power Calculations

This NIH-sponsored TRIP-PCI study had sufficient resources to enroll patients at 3 clinical sites over a 2 year period which accrued a total of 100 patients as a proof-of-concept study, however power calculations were used to evaluate the size of non-inferiority margins that could potentially be detected from a larger study of 600 participants, 400 of whom were to be randomized to PZ-128 and 200 to placebo, using the assumption that the incidence of major plus minor bleeding among placebo-treated subjects would range from 2% to 6%. Furthermore, this assumed that the true difference in the incidence of the participants on the PZ-128 arms and those in the placebo arms were likely to be in the range of 0% to 2%. Based on these assumptions, the minimum non-inferiority margin that could have been demonstrated with at least 80% power, where that non-inferiority margin is based on the upper limit of a one-sided 95% confidence interval for the difference in bleeding event rates for (PZ-128 – placebo) is identified below. This sample size was adequate to demonstrate acceptable upper safety bounds if placebo bleeding rates were $\geq 2\%$. Given a sample size of 600 and estimated range of incidences associated with placebo, the study would have been able to demonstrate that the bleeding risk of PZ-128 is non-inferior to the risk associated with placebo with non-inferiority margins in the range of 2.6 to 6.6, depending on the underlying bleeding risk of placebo.

Anticipated Bleeding Rates and Associated Non-Inferiority Margins

True Incidence or Risk of Bleeding for placebo	Minimum Demonstrable Non-inferiority margin	
	True Incidence Difference of 0%	True Incidence Difference of 2%
2%	2.6%	5.0%
3%	3.2%	5.5%
4%	3.7%	5.9 %
5%	4.1%	6.3%
6%	4.4%	6.6%

Table I. Clinical efficacy outcomes up to 90 days

	Placebo (n=34)	PZ-128 0.3 mg/kg (n=33)	PZ-128 0.5 mg/kg (n=31)	PZ-128 Pooled 0.3/0.5 mg/kg (n=64)
Key secondary endpoints				
Composite of 5-point MACE at 30 days	2 (6)	0	0	0
Composite of 5-point MACE at 90 days	2 (6)‡	0	1 (3)	1 (2)§
Other secondary endpoints				
Components of the key secondary endpoint at 30 days				
Cardiovascular death	0	0	0	0
Myocardial infarction (non-fatal)*	1 (3)	0	0	0
Stroke (non-fatal)	1 (3)	0	0	0
Recurrent ischemia requiring hospitalization	0	0	0	0
Urgent coronary revascularization (PCI/CABG)	0	0	0	0
Components of the key secondary endpoint at 90 days				
Cardiovascular death	0	0	0	0
Myocardial infarction (non-fatal)*	1 (3)‡	0	1 (3)	1 (2)§
Stroke (non-fatal)	1 (3)‡	0	0	0
Recurrent ischemia requiring hospitalization	0	0	0	0
Urgent coronary revascularization (PCI/CABG)	0	0	0	0
Stent thrombosis at 30 days†	0	0	0	0
Stent thrombosis at 90 days†	0	0	0	0
Exploratory endpoint				
Myocardial injury* (myonecrosis) through 48 hours				
ACS (n=42)	6 (43)	3 (23)	6 (40)	9 (32)
High-risk CAD + ACS (n=83)	7 (26)	6 (21)	8 (30)	14 (25)
All patients (n=95)	7 (21)	6 (19)	9 (30)	15 (25)

Data shown as n (%). Secondary endpoints based on adjudicated data in the intention-to-treat population (n=98). Exploratory endpoint based on non-adjudicated data in a modified intention-to-treat population which comprised randomized patients who underwent cardiac catheterization ± PCI and received any amount of investigational product and had adequate research-based cardiac troponin I data for evaluation (n=95).

*Determined based on the Third Universal Definition of Myocardial Infarction. Two subjects (out 97 total) cTnI values were censored due to rising baseline cTnI prior to the procedure. ‡Data available for 97% of placebo study sample (n=33). §Data available for 97% of study combined PZ-128 sample (n=62). †Academic Research Consortium definition.

ACS = acute coronary syndromes (unstable angina + non-ST-segment elevation myocardial infarction); CABG = coronary artery bypass grafting; MACE = major adverse cardiac events – cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, recurrent ischemia requiring hospitalization, or urgent coronary revascularization; PCI = percutaneous coronary intervention.

Table II. Inhibition of Platelet Aggregation (% IPA) to Select Agonists

		5 μ M SFLLRN	12 μ M SFLLRN	20 μ M SFLLRN	5 μ M ADP	20 μ M ADP	160 μ M AYPGKF	4 μ g/mL Collagen	20 μ g/mL Collagen
Placebo	Predose	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
n=20	30 min	5 (2)	4 (2)	3 (1)	5 (2)	5 (2)	22 (8)	27 (9)	27 (8)
	1 h	14 (4)	7 (2)	8 (2)	7 (3)	11 (4)	18 (6)	35 (8)	28 (8)
	2 h	9 (3)	10 (3)	7 (2)	31 (10)	20 (7)	27 (9)	45 (9)	29 (8)
	4–6 h	20 (8)	23 (10)	10 (6)	52 (13)	33 (11)	29 (11)	64 (13)	31 (10)
	24 h/discharge	21 (9)	19 (11)	14 (7)	57 (20)	60 (15)	33 (14)	72 (16)	46 (15)
	14 days	15 (5)	10 (4)	8 (3)	35 (11)	30 (9)	18 (8)	40 (9)	17 (7)
PZ-128	Predose	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.3 mg/kg	30 min	15 (7)	10 (5)	8 (2)	18 (8)	5 (2)	16 (7)	24 (7)	10 (3)
n=19	1 h	8 (3)	9 (2)	10 (2)	19 (8)	9 (3)	7 (2)	31 (9)	16 (4)
	2 h	10 (3)	9 (2)	7 (2)	35 (10)	20 (6)	8 (2)	29 (7)	17 (4)
	4–6 h	33 (8)	20 (5)	22 (4)	65 (11)	45 (13)	18 (5)	50 (10)	41 (9)
	24 h/discharge	23 (12)	13 (8)	11 (7)	70 (16)	49 (17)	8 (4)	49 (14)	24 (12)
	14 days	15 (5)	12 (3)	12 (3)	46 (11)	31 (9)	15 (7)	15 (6)	14 (5)
PZ-128	Predose	0 (0)	9 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.5 mg/kg	30 min	10 (5)	4 (2)	5 (2)	5 (2)	4 (1)	11 (6)	25 (7)	8 (3)
n=17	1 h	19 (7)	14 (5)	15 (5)	21 (7)	13 (5)	22 (8)	46 (9)	25 (7)
	2 h	34 (8)**	19 (4)	17 (3)	32 (8)	27 (7)	35 (10)	56 (9)	39 (8)
	4–6 h	40 (11)	20 (7)	21 (4)	67 (16)	63 (13)	34 (10)	54 (13)	47 (11)
	24 h/discharge	61 (7)**	30 (7)	36 (6)***	95 (3)	85 (9)	37 (9)	53 (14)	36 (12)
	14 days	32 (8)	22 (7)	14 (3)	44 (11)	38 (10)	26 (6)	29 (9)	16 (5)
Global p value		0.007	-	0.0006	-	-	-	-	-

Data are mean (SEM) final (7 min) aggregation levels and are presented for a pharmacodynamics sub-study of patients (n=56), as treated. Extent of agonist-mediated platelet inhibition (IPA) was normalized to each patient's own baseline. Statistical analysis using repeated measures, two-way analysis of variance mixed effects models, with dose of PZ-128 and time (global p value) and between group comparisons with placebo (p value vs. placebo) were conducted.

** p value versus placebo was <0.01. *** p value versus placebo was <0.001. - not significant.

Table III. Pharmacokinetic Parameters of PZ-128 Administered over 2 Hours

	PZ-128 Phase 2 Doses		PZ-128 Phase 1 Dose
	0.3 mg/kg (n=10)	0.5 mg/kg (n=8)	0.5 mg/kg (n=6)
AUC _{inf} (ng·h/mL)*	3526 (802)	7436 (1868)	7690 (1230)
C _{max} (ng/mL)	1426 (412)	2598 (1007)	2670 (423)
Range	1050–2320	1260–4150	1910–3010
t _{1/2} (hours)	1.20 (0.07)	1.31 (0.03)	1.57 (0.22)
Range	1.05–1.24	1.29–1.34	1.38–1.95
Cl (mL/min)	130 (21)	77 (26)	90 (18)
Range	96–159	53–105	71–118
V _{ss} (L/kg)	0.14 (0.03)	0.10 (0.03)	0.12 (0.01)
Range	0.10–0.17	0.07–0.12	0.10–0.14

Data are mean (SD) unless otherwise indicated. The PZ-128 Phase 2 doses were administered to coronary artery disease (CAD) and acute coronary syndrome patients undergoing cardiac catheterization ± percutaneous coronary intervention and were compared to the Phase 1 dose previously administered to subjects with CAD/risk factors.

AUC_{inf} indicates area under the plasma concentration-time curve from time of dosing to 2 weeks; Cl, clearance; C_{max}, maximum observed plasma concentration; kel, fraction of drug eliminated per unit of time; LLOQ, lower limit of quantification (=50 ng/mL); t_{1/2}, terminal elimination half-life; V_{ss}, volume of distribution at steady state.

*AUC was calculated based on C_{max}, Cl, kel and V_{ss} parameters.

Major Resources Table

Animals (in vivo studies)

Species	Vendor or Source	Background Strain	Sex	Persistent ID / URL
NA	NA	NA	NA	NA