Design and rationale of the Evaluation of M118 IN pErcutaNeous Coronary intErvention (EMINENCE) trial

Chiara Melloni, MD, MHS,[a] Ian Fier, MBA,[b] James Roach, MD,[b] Andrzej S. Kosinski, PhD,[a] Samuel Broderick, MS,[a] Kristina Sigmon, MA, MS,[a] Shelley Myles, BSc, RN,[a] Richard C. Becker, MD,[a] and Sunil V. Rao, MD[a] on behalf of the EMINENCE Investigators ***Durham, NC; and Cambridge, MA***

Background Currently recommended anticoagulant agents used in the setting of percutaneous coronary intervention (PCI) inhibit, with varying degrees of intensity, 2 critical targets (factor Xa and/or IIa) of the coagulation cascade, yet they carry significant limitations. M118—a novel, rationally engineered heparin—provides consistent anti-Xa and anti-IIa activity with a constant anti-Xa:anti-IIa ratio over time. M118 also combines the desired anticoagulant effects of unfractionated heparin with the beneficial attributes of low-molecular-weight heparin, and may represent the next generation of heparin therapy in patients diagnosed with acute coronary syndrome.

Study Design The EMINENCE trial is a prospective, randomized, open-label, multicenter phase 2 study that will evaluate the safety and feasibility of M118 as an anticoagulant versus unfractionated heparin in subjects with stable coronary artery disease undergoing PCI. The primary end point of the study will be the combined incidence of clinical events defined as the composite of 30-day death, myocardial infarction, repeat revascularization, catheter thrombus, stroke, thrombocytopenia, bailout use of glycoprotein IIb/IIIa inhibitors, and major or minor bleeding.

Conclusion The EMINENCE trial will assess the safety and feasibility of M118 as an anticoagulant in the setting of PCI and will provide important information to determine the appropriate therapeutic range of activated clotting time for M118 and the appropriate dose or doses to be explored in a phase 3 clinical trial. (Am Heart J 2009;158:726-33.)

Percutaneous coronary intervention (PCI) is inherently thrombogenic; balloon dilation and stent implantation result in thrombin generation, platelet activation, and a profound inflammatory response. Systemic anticoagulation is needed during PCI in order to minimize the incidence and consequences of atheroemboli and to reduce the formation of thrombus on PCI equipment.[1]

Recommended strategies for anticoagulation include unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), direct thrombin inhibitors (bivalirudin and argatroban), and indirect selective factor Xa inhibitor (fondaparinux),[2,3] although not all of these agents are indicated in the setting of PCI. All have been evaluated in large phase 3 clinical trials that demonstrated efficacy and safety across a wide range of clinical indications[4-7]; however, they all have significant limitations.[4,6,8-11] Therefore, there remains an unmet need for safe and more effective agents in the cardiac catheterization laboratory.

M118 is a novel, rationally engineered heparin product that retains the desired anticoagulant effects of UFH while adding the beneficial attributes of LMWH. Preclinical studies have demonstrated that M118 has predictable pharmacokinetics and exhibits a clear dose-dependent inhibition of factor Xa and factor IIa, with an anti-Xa (aXa):anti-IIa ratio that is constant over time.[12,13] Phase 1 studies have also demonstrated that M118 is well tolerated, and its administration produces dose-dependent increases in activated clotting time (ACT).[14,15] In addition, M118's anticoagulant effects can be fully reversed with protamine sulfate.[16] M118 may be administered both intravenously (IV) and subcutaneously and appears not to exhibit clinically significant drug–drug interactions when coadministered with aspirin (325 mg) and clopidogrel (300 mg) or with glycoprotein (GP) IIb/IIIa inhibitors.[17] Due to its unique characteristics, M118 may represent the next generation of heparin therapy for patients with acute coronary syndrome at different stages of clinical management. The phase 2 EMINENCE trial was designed to explore the feasibility and safety of M118 administered intrave-

From the [a]Duke Clinical Research Institute, Durham, NC, and [b]Momenta Pharmaceuticals, Cambridge, MA.
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Reprint requests: Chiara Melloni, MD, MHS, 2400 Pratt St., Durham, NC, 27705.
E-mail: mello004@mc.duke.edu
0002-8703/$ - see front matter

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Table I. Primary end point

Death	Defined as all-cause mortality
Myocardial infarction	Assessed inhospital and at the 30-day visit. ECGs will be obtained at those visits. MI within 2 d of PCI: New Q-wave ≥0.04 s duration in ≥2 contiguous leads or Elevated CK-MB ≥3 times ULN in 1 sample MI occurring >2 d after PCI: New Q-wave >0.04 s duration in ≥2 contiguous leads or; Elevated CK-MB >ULN for the site in 1 sample or; Elevated troponin I or T >ULN for the site in 1 sample MI occurring after surgical coronary vessel revascularization: New Q wave >0.04 s duration in ≥2 contiguous leads or; Elevated CK-MB ≥5 times ULN for the site in 1 sample
Bleeding	Bleeding complications will be defined as those occurring within 24 h after PCI and will be assessed using the REPLACE-2 scale.[4] Major bleeding is defined as: Transfusion of >2 units whole blood or packed red blood cells, or Intracranial hemorrhage, or Retroperitoneal hemorrhage, or A fall in Hgb >4 g/dL (or 12% of HCT) with no bleeding site identified despite attempts to do so, or Spontaneous or non-spontaneous blood loss associated with a Hgb drop >3g/dL (or 10% of HCT) Minor hemorrhage is defined as any observed bleeding event that does not meet the criteria for a major hemorrhage.
Stroke	Defined as a new, sudden, focal neurological deficit resulting from presumed cerebrovascular cause that is not reversible within 24 h and not due to a readily identifiable cause such as a tumor or seizure. Stroke is also defined if symptoms last <24 h but brain image shows a new or suspect new lesion that anatomically is consistent with symptoms.
Repeat revascularization	Any revascularization will be assessed at the 30-day time point. Target vessel revascularization is defined as a procedure (PCI or CABG) involving any target vessel that was treated during the index procedure. Urgent revascularization is defined as ≥1 episodes of rest pain, presumed to be ischemic in origin and lasting ≥5 min, which result in either urgent repeat PCI or urgent CABG. In the absence of pain, new ischemic ST-segment or T wave changes, acute pulmonary edema, ventricular arrhythmias presumed to be ischemic in origin or hemodynamic instability presumed to be ischemic in origin will constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG will generally be initiated within 24 h of the last episode of ischemia. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guidewire removal. CABG initiated within 24 h of PCI (index or repeat) due to an unsatisfactory or unstable result, even in the absence of documented ischemia, will also be considered an urgent revascularization.
Catheter thrombus	Defined as any evidence of clot or thrombus on coronary guide catheter, guide wire, or coronary device in the target vessel not felt to be associated with first coronary lesion or coronary dissection.
Thrombocytopenia (HIT)	Defined as a platelet count <100,000/mm3 or a ≥50% decrease in platelet count from the preprocedure value occurring within 24 h of index procedure. If HIT is suspected, a sample containing 3 mL of serum will be sent to Quest Diagnostics for assessment of HIT.
Bailout use of GP IIb/IIIa inhibitors	Bailout use of GP IIb/IIIa inhibitors is permitted for complications during PCI. Possible indications for bailout use are decreased TIMI flow (0–2) or slow reflow, dissection with decreased flow, new thrombus or suspected thrombus, persistent residual stenosis, distal embolization, unplanned stent, side branch closure, abrupt closure, and prolonged ischemia.

Adjustments to Hgb concentration and HCT will be made for any transfusion of packed red blood cells or whole blood given between enrollment and the post-transfusion measurements by the method of Landefeld et al, as follows:
ΔHgb = [baseline Hgb – post transfusion Hgb] + [number of transfused units].
ΔHCT = [baseline HCT – post transfusion HCT] + [number of transfused units × 3].
ECG, Electrocardiogram; *CK–MB*, Creatinine Kinase MB isoenzyme; *ULN*, upper limit of normal; *HCT*, hematocrit; *Hgb*, hemoglobin; *CABG*, coronary artery bypass graft.

nously in patients with stable coronary artery disease (CAD) undergoing PCI.

Study objectives

This prospective, randomized, open-label, multicenter trial will evaluate the safety and feasibility of M118 as an anticoagulant versus UFH in subjects with stable CAD undergoing PCI. The secondary objectives of the study are: (1) to evaluate the effect of M118 on procedural indices including procedure success, abrupt closure, post-procedure TIMI flow, and catheter thrombus and (2) to define the appropriate therapeutic range of ACT for M118 as measured by clinical outcomes and indices of procedural success.

Primary end point

The primary end point of the study will be the combined incidence of clinical events defined as the composite of 30-day death, myocardial infarction (MI), repeat revascularization, catheter thrombus, stroke, thrombocytopenia, bailout use of GP IIb/IIIa inhibitors, and major or minor bleeding (Table I).

A central adjudication committee of clinicians blinded to treatment allocation will adjudicate stroke, MI, and bleeding events.