Evolocumab in Acute Coronary Syndrome

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JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Despite aggressive early intervention and current secondary prevention strategies, hundreds of thousands of patients who survive hospitalization for acute coronary syndrome (ACS) experience subsequent unfavorable outcomes, including recurrent ischemic events and unfavorable cardiac remodeling associated with progressive left ventricular dysfunction and congestive heart failure. Vascular and myocardial inflammation are significantly increased in ACS patients, are closely correlated to LDL-C levels, and are associated with these adverse consequences in the post-ACS patient population. Inflammation may also play a role in platelet aggregation one of the responsible mechanisms for the index and for any recurrent coronary thrombotic events. Serum proprotein convertase subtilisin/kerin type 9 (PCSK9) levels are also increased in ACS, may raise LDL-C, and our pre-clinical studies indicate that PCSK9 is also a potent inducer of vascular inflammation. The addition of the PCSK9 antibody evolocumab, currently approved to lower LDL-C in certain patient populations, to current medical therapies would appear to be of particular benefit in an important subset of ACS patients, those with non-ST-elevation myocardial infarction (NSTEMI) by markedly reducing LCL-C, stabilizing vulnerable plaque, and limiting inflammation-associated myocardial cell loss and resultant dysfunction.

Hypothesis: In a placebo-controlled, randomized double blind trial, the addition of evolocumab to standard care in NSTEMI patients (1) decreases LDL-C during hospitalization and at 30 days, (2) decreases vascular/plaque and myocardial inflammation as assessed by PET scanning at 30 days, and improves (3) serum markers of endothelial function and of platelet function at hospital discharge and at 30 days, and (4) echocardiographic assessment of left ventricular function at 30 days and six months.

This is the first PCSK9 inhibitor trial which examines these outcomes in the ACS patient population. It will provide valuable data on the extent and time course of LDL-C reduction as well as the impact of inhibition on inflammatory markers and on imaging assessment of vascular and myocardial inflammation, all of which may significantly impact important clinical outcomes in this high risk patient cohort.[1]

2. Objectives (include all primary and secondary objectives): To conduct a placebo-controlled randomized, double blind study of the effect of the addition of evolucomab to standard care in NSTEMI patients

2.1 Primary

The primary objective is the difference in the mean % change in LDL-C from baseline to 30 days in the evolocumab and placebo groups.

2.2 Secondary

The secondary objectives are to compare in the evolocumab and placebo groups:

a. Serial serum markers of inflammation, lipids, myocardial injury, and of left ventricular function will be collected at baseline, day 1, day 3, at hospital discharge and at 30 days follow up.

   The time points of comparison are day 3, hospital discharge and 30 days.

   i. PCSK-9
   ii. Soluble LOX-1
   iii. Interleukin-6
   iv. High sensitivity C-reactive protein
   v. HDL-cholesterol
   vi. Triglyceride
   vii. Total cholesterol
   viii. Troponin
   ix. Pro-BNP

b. The change between early hospitalization or shortly following discharge and thirty day assessments of
   i. PET-FDG assessed vascular inflammation in the most diseased segment of aorta or carotid artery
   ii. Echo assessed regional wall motion in the infarct territory
   iii. Echo assessed global LV function
   iv. Echo assessed LV systolic and diastolic volumes

c. At thirty days:
   i. Comparison of PET-FDG assessment of vascular inflammation in the evolocumab versus placebo group as described in 2.2. b i
   ii. Echo assessed as described in 2.2. b ii-iv
   iii. Angina class
   iv. New York Heart Association functional class
   v. LDL-C and serum markers as described in 2.2. a
   vi. Determine the relationship if any among the extent of change in the serum makers, FDG-PET results and echocardiogram results.

d. At six months
   i. Angina class
   ii. New York Heart Association functional class
   iii. LDL-C and serum markers as described in 2.2. a
   iv. Echo assessment as described in 2.2. b ii-iv

e. At 12 months
Serum markers as described in 2.2 a

2.3 Exploratory

a. The exploratory basic science outcome is: Direct comparison of endothelial cell function in cells harvested from intravascular equipment in the evolocumab- and placebo-randomized patient groups.
b. The exploratory imaging outcome is: To assess changes in FDG-PET-guided myocardial inflammation in the evolocumab and placebo groups at thirty days. Additionally, we will compare PET assessed vascular inflammation in the evolocumab and placebo groups on the exam obtained during the early hospitalization.
c. Platelet aggregation and function studies.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

The total burden of coronary heart disease and associated mortality have decreased over the last 10 years. Although the incidence of STEMI has decreased by 50% to 60% over the last decade [2], the proportion of patients with acute coronary syndrome who now present with NSTEMI has grown substantially and now represents approximately 70% of all acute coronary syndrome patients [3]. This shift is likely multifactorial, but relates to the aging population, an increase in diabetes mellitus, and perhaps a change in plaque characteristics with fewer of the plaque rupture events associated with STEMI [4]. Recent studies show that over the last decade the NSTEMI population is getting older with an increased prevalence of diabetes, hypertension, lung disease, chronic renal disease, and prior coronary revascularizations [5]. Acute myocardial infarction remains a major cause of morbidity and mortality in the United States, Europe and Asia [6]. Despite the majority of NSTEMI patients receiving guideline recommended dual antiplatelet, beta blocker, ACE or ARB and statin therapies in addition to coronary revascularization, in hospital mortality is 5% and six-month mortality in NSTEMI hospital survivors is 7.6% *(IBID).* Six-month mortality remains above 10% in hospital survivors with elevated baseline risk, such as advanced age and evidence of heart failure on admission *(IBID).* Long term mortality and recurrent ischemic events also remain high in NSTEMI patients [7]. Recurrent ischemic events are likely related to inflammation and the degree of residual coronary plaque burden. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study evaluated the risk for recurrent ischemic events using three vessel intracoronary ultrasound in patients receiving percutaneous coronary intervention for acute coronary syndrome [8]. During the three-year follow-up, with guideline directed risk factor modification, recurrent ischemic events were highest in patients with lesions described as thin fibrous cap atheroma, plaque burden $\geq$70%, and minimal luminal area $\leq$ 4.0 mm^2. Additionally, patients with elevated markers of inflammation (hsCRP) at six months experienced higher rates of recurrent ischemic events at follow-up. Although the number of high risk thin-cap fibroatheroma did not differ between the high-hsCRP and normal-hsCRP groups, nonculprit lesion-related ischemic events were independently predicted by an elevated hsCRP. These data indicate that inflammation increases the likelihood of vulnerable plaque rupture with result antischemic events [9]. These data suggest that despite aggressive risk factor modification in patients with acute coronary syndrome, recurrent ischemic events are frequent and are associated with non-culprit lesion plaque burden and ongoing inflammation.
In addition to recurrent ischemic events, heart failure is common post myocardial infarction and a leading cause of death in older NSTEMI patients. In a large cohort of patients 65 years of age and

older suffering a first myocardial infarction, new heart failure was diagnosed in 37% during the index hospitalization (13% mortality) with an additional 71% of hospital survivors developing heart failure during the five-year follow up period, 64% of which occurred in the first year. Short- and long- term mortality are significantly greater in those NSTEMI patients who develop heart failure [10]. Inflammatory mediators are also activated in heart failure after myocardial injury and are associated with progressive left ventricular dysfunction [11].

Evolocumab is a monoclonal antibody that inhibits PCSK9 and is FDA-approved as an adjunct to diet and maximally tolerated statins for use in certain patients who need to further significantly lower LDL-cholesterol level. In a large randomized clinical trial in patients with atherosclerotic cardiovascular disease (median of 3 years after a recent event) and LDL cholesterol levels of 70 mg per deciliter or higher who were receiving statin therapy, the addition of evolocumab significantly reduced the risk of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization during a median follow-up of 2.2 years [12]. In this study, the median LDL cholesterol on statin therapy was 92 mg / dL and the addition of evolocumab reduced LDL cholesterol by 59% to a median of 30 mg / dL. Little is known regarding other potential additional benefits of PCSK9 inhibition in the setting of ACS.

ACS is associated with a marked increase of serum PCSK9 that likely has an important pathophysiologic role in mediating vascular and myocardial inflammation, leading to plaque vulnerability of both culprit and non-culprit coronary vessels as well as adverse myocardial remodeling and resulting contractile dysfunction. Growing evidence emphasizes a potential role of PCSK9 antibodies beyond their LDL-cholesterol lowering capacity (pleiotropic effects), which are likely beneficial in managing NSTEMI [13]. The Ottawa Heart Genomics Study and the Emory Cardiovascular Biobank both demonstrated an association between elevated PCSK9 levels and adverse acute and long-term events in patients with ACS. PCSK9 levels are markedly elevated during an ACS, and in one study were related to the composite endpoint of death and recurrent ACS at 1-year follow-up.[14] Additional data indicate that elevated PCSK9 adversely affects coronary plaques through several pathways, including pro-inflammatory LDL oxidation and direct modification of plaque composition [15-17]. Additionally, chronically elevated PCSK9 levels are associated with progression of atherosclerosis [14]. Finally, a recent study suggests that increased PCSK9 levels are associated with higher platelet reactivity and are a possible predictor of ischemic events in ACS patients [18].

Over the past few decades, our understanding of the vascular biology of atherogenesis and its clinical presentations has advanced significantly. It is now apparent that inflammatory processes play a key role not only in the initiation and progression of ASCVD but also in the clinical events associated with instability of already established atherosclerotic plaques [19-21]. Traditional and novel cardiovascular risk factors trigger a chronic inflammatory process, which is accompanied by loss of vasodilatory and antithrombotic properties of the vascular endothelium [22-24]. Clinical studies show that this emerging biology of inflammation in atherosclerosis applies directly to human pathology [25]. Elevated inflammatory markers predict outcomes of ACS patients independently of the extent of myocardial damage [25]. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker hsCRP, prospectively independently defines risk of atherosclerotic complications, thus adding to the prognostic information provided by traditional risk factors [26, 27]. Moreover, certain treatments that reduce coronary risk also limit inflammation [28, 29].

Identifying reliable endothelial cell (EC) function markers for *in vivo* testing remains a challenge. In this clinical trial, we propose to utilize the emerging EC function marker sLOX1. The LOX1 receptor is an endothelial receptor for atherogenic oxidized-LDL and is implicated in the

pathogenesis of atherosclerosis [30]. In addition, nuclear imaging studies detecting radiolabeled LOX1 report significantly higher accumulation of LOX1 in grade IV atheroma than in more stable lesions [31]. It was recently reported that LOX1 is converted to soluble molecules by proteolytic cleavage at the membrane proximal site of the extracellular domain. In the same study, EC activation by pro-inflammatory stimuli, e.g. TNF-a, led to cell-surface expression of LOX-1 which precedes soluble LOX-1 production [32]. sLOX1 is also proposed as a marker of plaque instability in ACS patients [33]. Finally, persistently elevated sLOX1 levels in ACS patients are linked to adverse clinical outcomes [34]. Based on the scientific evidence, we believe that sLOX1 is a suitable marker for endothelial dysfunction and possibly plaque instability in the setting of ACS and NSTEMI.

In this pilot study, we will utilize non-invasive PET imaging to assess vascular/plaque and myocardial inflammation. A recent review article nicely summarizes the utility of PET in the setting of ACS [35]. The strength of PET-guided imaging in this setting is the identification of activated inflammatory cells in the atherosclerotic plaque, providing important information regarding the mechanism of vascular instability. Furthermore, longitudinal PET studies can assess the effectiveness of novel anti-inflammatory therapies, such as evolocumab. Initial validation of FDG-PET imaging in the setting of ACS was performed in mice [36], but other reports also provide proof of feasibility in large animals and humans [37, 38]. Ripschler et al. subsequently demonstrated that the extent of FDG-derived myocardial inflammation early after myocardial infarction correlated with infarct size and systemic inflammatory markers at that time and with LVEF and cardiac volumes at 6-9 month follow-up [39].

The multimodality dal-PLAQUE imaging study successfully utilized FDG-PET to assess plaque inflammation and burden in patients with high risk of coronary heart disease [40]. A subsequent study reported a functional alteration of the plaque, characterized by activation of resident inflammatory cells, which can cause plaque instability and occlusive thrombus formation [41]. Since persistent activation of adaptive immunity in patients with unstable angina is linked to coronary instability [42], we propose to evaluate the impact of evolocumab on the extent and degree of vascular inflammation in our study cohort.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

This is a phase 2, double-blind, randomized, placebo controlled clinical trial of 420 mg evolocumab administered subcutaneously using an autoinjector/pen in NSTEMI patients during early hospitalization at the Johns Hopkins Hospital or the Johns Hopkins Bayview Medical Center.. The placebo and evolocumab will be given exactly the same way with the same Amgen provided device. All participants will receive standard care for NSTEMI, including high dose statin, aspirin, beta blocker, and, as appropriate, ACE-I or ARB and early intervention. High dose statin therapy consists of atorvastatin 40mg or 80mg or rosuvastatin 20mg or 40mg per the most recent ACC/AHA guidelines. [43] After signing informed consent, subjects will be randomized to receive one dose of evolocumab or matching placebo subcutaneously. Research blood samples for LDL-C and inflammatory markers, and PET imaging assessment of vascular inflammation as well as echocardiographic studies for left ventricular function will be obtained. An independent Data and Safety Monitoring Committee will review all potential side effects and clinical outcomes during the twelve months of follow-up.

At the 30-day follow-up visit we will perform a physical exam and obtain a history of any clinical events including adverse events. We will perform a second FDG-PET study to assess vascular and myocardial; inflammation. Additionally, we will assess LDL-C and serum markers of inflammation and endothelial function as outlined in 2.2 a.

At the 6-month follow-up visit will perform a physical exam and obtain a history of any clinical events including adverse events. Additionally, we will assess LDL-C and serum markers of inflammation and endothelial function as outlined in 2.2 a.

At the 9-month follow-up visit, we will contact the participant by phone to learn of any adverse events. If the participant was admitted to the Emergency Department or Hospital we will obtain permission to obtain medical records.

At 12-month follow-up visit we will assess lipid profile and serum markers of inflammation and endothelial function as outlined in 2.2 a.

All above are research studies with the exception of the clinical echocardiogram during the initial hospitalization.

b. Study duration and number of study visits required of research participants.

The study duration for each participant is twelve-months and there are three study visits required.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

The investigators and participants are blinded. Blinding is necessary to avoid potential bias in data gathering and analysis. The Hopkins Investigational Pharmacy will have access to study drug assignment if there is a clinical need for the subjects' treating physician to be aware of assignment.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

All participants will receive routine care and will not have current therapy stopped. Evolocumab is not standard of care for ACS or NSTEMI patients.

e. Justification for inclusion of a placebo or non-treatment group.

Inclusion of a placebo, comparator group is necessary to best determine the safety and efficacy of evolocumab in NSTEMI patients. As noted above, evolocumab is not considered "treatment" for this patient population and hence we do not believe there is a "non-treatment" group, or ethical concern by inclusion of a placebo group.

f. Definition of treatment failure or participant removal criteria.

<u>Early stopping rules:</u>

Only participants who go to CABG (unanticipated) will be removed, because procedures utilizing the heart and lung machine itself are associated with markedly increased inflammation.

a. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants will only receive one dose of the study drug and will not receive any additional study related therapy.

5. Inclusion/Exclusion Criteria

5.1 Inclusion Criteria

a. Age 25 to 90 years.
b. NSTEMI with troponin I $\geq$ 5.0 ng/dL, with compatible symptoms and ECG changes.
c. Permission of attending physician.
d. Ability to understand the risk, benefits, and alternatives of participation.

5.2 Exclusion Criteria

a. STEMI
b. Patients requiring invasive support because of compromised hemodynamics.
d. Scheduled for cardiac surgery.
e. Current or prior treatment with a PCSK9 antibody.
f. Current participation in an intervention clinical trial.
g. Female of childbearing potential. This is a female subject who has not used acceptable method(s) of birth control (see below) for at least one month prior to screening, unless the subject is sterilized or postmenopausal. Menopause is defined as: 12 months of spontaneous and continuous amenorrhea in a female $\geq$ 55 year of age.

- Acceptable method(s) of birth control definition: One highly effective method (methods that can achieve a failure rate of less than 1% per year when used consistently and correctly)
  - Combined hormonal (estrogen and progestogen) contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
  - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Sexual abstinence

h. Contraindication to statin therapy.
i. Subject likely not to be available to complete all protocol-related study visits or procedures.
j. Latex allergy
k. History of severe hypersensitivity to any monoclonal antibody.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

The drug evolocumab was chosen because of studies indicating that it reduces inflammation and improves lipid profile in patients already on statin therapy. [12] The dose was chosen based on

that approved by the FDA for clinical use in patients with stable coronary disease, available in the United States and reduces LDL cholesterol. [44]

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Evolocumab is an FDA approved medication that will be administered for a non-FDA approved indication, hospitalized patients with NSTEMI. This is justified based on clinical and pre-clinical data indicating that vascular and myocardial inflammation is increased in NSTEMI patients, that inflammation is associated with adverse outcomes in this patient group, that in stable CAD patients, anti-inflammatory interventions improve outcomes, and that evolocumab has anti-inflammatory properties. The dose and route of administration are the same as that administered for FDA approved indications.

We are applying for an exemption from the FDA such that an IND is not needed for the proposed mechanistic study in NSTEMI patients. Safety information on the use of these drugs is detailed above.

An IND exemption request will be submitted to the FDA.

7. Study Statistics

a. Primary outcome variable.

The primary outcome will assess the difference of LDL-C serum concentration between the placebo and evolocumab groups at 30 days. To assess the primary endpoint of the mean percent change from baseline in LDL-C at day 30, a repeated measures linear effects model will be used in comparing the efficacy of evolocumab vs placebo.

b. Secondary outcome variables.

For the secondary outcome of comparing the changes in target to background ratio (TBR) over time (30-day FDG PET scan minus early hospitalization or shortly following discharge FDG PET scan) between the groups, the following statistical approach will be used consistent with the prior literature.[45] Specifically, difference in the percent change in TBR at 30 days from early hospitalization (30 day – early hospitalization TBR) between the two randomized groups will be compared with ANCOVA using the baseline TBR as a covariate. The percent difference between the index vessel MDS TBR in the placebo and evolocumab groups at 30 days will be analyzed using Kruskal Walis testing.
The non-parametric biomarkers of the secondary endpoint will be log transformed, and the results interpreted as the difference in geometric means between the groups. The analysis will be performed in the primary evaluable population, defined as data from subjects that provided imaging/laboratory data at the indicated time points.
A one-sided p-value ≤ 0.05 will be considered significant, based on the assumption that evolocumab will reduce, and not increase, inflammation.

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c. Statistical plan including sample size justification and interim data analysis.

We are providing power calculations for the primary as well as key secondary endpoints (see Tables 1-4).

Primary endpoint:
For calculation of power for the primary endpoint, we anticipate median baseline presentation LDL-C of 110 (90 – 130) mg/dL in our patient population. This number is informed by prior ACS trials (i.e. TIMI-22) as well as local experience with the ACS population at the Johns Hopkins Hospital (with approximately 25%-35% of the population already on baseline statin therapy). We expect this LDL-C value to be reduced by approximately 50% by high intensity statin therapy in the standard treatment arm (i.e. LDL-C of 55 (40- 70) mg/dL at 30 days). We anticipate a further 50% lowering of LDL-C at 30 days after the administration of evolocumab (i.e. LDL-C of 28 (14 – 42) mg/dL. As is shown below (Table 1), using a one-sided p-value of 0.05, the study has nearly 100% power to detect this difference, and will have 80% power to detect an absolute LDL-C reduction of 9.5 mg/dL (17% reduction in LDL-C at 30 days). Additionally, Table 2 presents the expected mean ± SD baseline and 30-day LDL-C levels and the expected percent LDL-C change in the placebo and evolocumab arms.

Table 1

N in each group	Median (IQR) LDL-C in ACS Population at baseline	Anticipated Percent LDL-C Reduction in the Standard of Care Arm	Estimated Power to Detect a 50% Additional LDL Lowering	Detectable Point Estimate at 80% Power
N = 30	110 (90-130)	50% (40 – 60%)	99+%	-9.5 mg/dL

Table 2: Expected mean ± SD LDL-C levels at baseline and thirty days and the percent change from baseline to 30 days in the placebo and evolocumab groups.

Groups:		LDL-C, mg/dl		% change from baseline, mean (SD)
		Baseline, mean (SD)	30 day, mean (SD)	
Atorvastatin 80mg	+Placebo	110 (±14)	55 (±11)	-50 (±12)
	+Evolocumab		28 (±10)	-75 (±14)

Secondary Endpoint:
Previously published clinically relevant, drug-induced TBR changes are reported in the range of 5%-15%. [46] The power calculations for a 10% and 15% TBR difference based on a sample size of 30 patients per study arm are outlined in Table 3 & 4 below. The primary outcome for this calculation of sample is the % difference in TBR between the groups at 30 days in the most diseased segment of aorta or carotid artery. Table 1 uses a 1-sided p-value of 0.05, under the hypothesis that evolocumab will lower inflammation and will not raise it, consistent with the approach used in the Dal-PLAQUE study. For completeness, we replicated the analysis in Table 4 using a 2-sided p-value of 0.05. Calculations are performed using non-parametric statistics accounting for the possibility of non-normally distributed TBR data; calculations using parametric statistics and the following anticipated means and standard deviations yield similar results, as shown in Table 5 below:

Table 3: Power calculations using a 1-sided p-value, i.e. only assumes that PCSK9 inhibition will lower TBR in the most diseased segment (MDS) and will not raise TBR.

			Estimated Power	Detectable

	N in each group	Median (IQR) TBR in ACS Population at 30 days	at 10% & 15% TBR Difference	Point Estimate at 70% & 80% Power
Aorta MDS	N = 30	3.2 (2.7 – 4.0)	66% 93%	-10.6% -12.0%
Carotid MDS	N = 30	2.5 (2.1 – 3.0)	78% 98%	-9.0% -10.2%

Table 4: Power calculations using a standard 2-sided p-value of 0.05

	N in each group	Median (IQR) TBR in ACS Population at 30 days	Estimated Power at 10% & 15% TBR Difference	Detectable Point Estimate at 70% & 80% Power
Aorta MDS	N = 30	3.2 (2.7 – 4.0)	54% 87%	-12.0% -13.6%
Carotid MDS	N = 30	2.5 (2.1 – 3.0)	68% 95%	-10.4% -11.6%

The tables above show fair to good power to demonstrate a difference of 10%, and an excellent power to show a difference of 15% in the primary outcome.

Mean and standard deviations of anticipated TBR in ACS population at 30 days:

- Aorta MDS: 3.3 ± 0.6
- Carotid artery MDS: 2.6 ± 0.4

Table 5: Power calculations using a 1-sided p-value of 0.05 and assuming a normal distribution.

	N in each group	Mean (SD) TBR in ACS Population at 30 days	Estimated Power at 10% & 15% TBR Difference	Detectable Point Estimate at 70% & 80% Power
Aorta MDS	N = 30	3.3 (0.6)	69% 94%	-10.3% -11.8%
Carotid MDS	N = 30	2.6 (0.4)	81% 98%	-8.7% -10.0%

d. Early stopping rules.

The Johns Hopkins DSMB will perform any interim analysis they require to monitor patient safety and provide reports advising continuation of the study.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Study drug:

Evolocumab is supplied as a sterile, single-use, preservative free solution for subcutaneous injection in a disposable, spring-based prefilled autoinjector/pen (AI/pen). The AI/pen contains a 1.0 mL deliverable volume of 140 mg/mL evolocumab or placebo and three 140mg/ml AI/pens will be dispensed by the Johns Hopkins Investigational Drug Service and will be administered by one of the investigators to each study participant. Evolocumab is well tolerated with few side effects. A prior clinical trial reported no significant differences in adverse events (AEs) and serious adverse events (SAEs) between those participants receiving evolocumab and

those receiving placebo in a randomized, placebo- controlled trial over three months of administration (Rutherford 2) [47]. Other trials reported no SAEs and no differences in AEs between treatment with the PCSK9 inhibitor and placebo[48]. The most common reasons for withdrawal were unrelated to the study drug. The GAUSS-3 randomized trial comparing evolocumab and ezetimibe reported no difference in AEs between the study arms and no SAEs reported over 24 weeks [49]. A recent large metanalysis of PCSK9 inhibitor trials showed no difference in treatment-emergent AEs or SAEs in evolocumab-treated and placebo-administered patients[50]. Overall, injection site reactions are manageable and rarely lead to discontinuation of the PCSK9 antibody. Other side effects are all comparable to those reported in the placebo groups. Importantly, very few musculoskeletal side effects are reported in major clinical trials, and are comparable to those seen in placebo-treated patients, and there is no difference in laboratory abnormalities reflective of liver or kidney damage over 12 weeks of treatment in the evolocumab vs. placebo groups. [50]

Table 6: The most common adverse effects of evolocumab are listed below and do not differ from those which occurred in patients who received placebo. [50]

Most Common Safety Endpoints	**Evolocumab (12 week)**	**Placebo (12 week)**	**P value**
	Pooled event rate (95% CI)		
Musculoskeletal disorders	9.8 (4.1-15.4)	7.1 (1.6-12.6)	0.74
Nasopharyngitis	6.2 (3.6-8.8)	4.2 (2.1-6.3)	0.11
Gastrointestinal disorders	5.6 (2.7-8.4)	5.3 (1.9-8.7)	0.73
Upper respiratory tract infection	4.2 (2.5-5.9)	2.9 (0.3-5.6)	0.96
Headache	3.4 (2.2-4.6)	2.6 (1.5-3.7)	0.33
Injection site reactions	2.2 (1.3-3.1)	1.7 (0.9-2.5)	0.82

PET studies:

Intravenous Line during PET study: can cause some slight discomfort when the needle is inserted into the arm vein. The potential side effects of taking blood samples may include dizziness, soreness and/or bruising of the skin for several days. In very rare circumstances, bleeding or infection can develop at the needle puncture site. However, because the procedure is performed by a trained specialist using sterile and standard medical practices, that is very unlikely.

Isotope (F-18 fluorodeoxyglucose (FDG) Injections (PET-scans):
This research study includes exposure to radiation from x-rays or gamma rays. This radiation exposure is for research purposes only and is not part of medical care. X-rays and gamma rays from natural or medical sources can damage the genetic material (DNA) in cells. At low doses, the body is usually able to repair the damage.

The radiation exposure that a study participant will get in this research study is 3.1 rem. This is more than the 0.3 rem that the average person in the United States gets each year from natural sources like the sun, outer space, air, food and soil. It is less than the 5 rems of radiation that is allowed each year for people who are exposed to radiation in their jobs.

The radiation exposure described here is what the study participant will get from this research study only. It does not include any exposure the patient may have received or will receive from other tests outside of this study that are a part of medical care. Radiation risk builds up with each exposure. The study participant should think about his history of radiation exposure from

tests (like x-rays or CT scans) in deciding about the radiation in this study. We encourage all study participants to ask questions about the total amount of radiation he/she will be receiving.

b. Steps taken to minimize the risks.

To protect against and minimize the potential risks of evolocumab treatment, study participants will undergo a careful history as well as physical examinations at baseline to identify any condition which might increase their risk from the medication but not known to the patients or documented in their medical records. The subcutaneous injections of the study drug (evolocumab or placebo) will be administered by one of the physician investigators. In addition, patients will be evaluated closely at regular intervals following the injection for side-effects. Patients who experience significant symptoms will be evaluated.

Trained personnel will perform the blood collection procedure and will make every effort to minimize any risks or discomfort.

c. Plan for reporting unanticipated problems or study deviations.

All clinically significant unanticipated problems or study deviations will be reported to the DSMB and the IRB according to The Johns Hopkins Medicine Institutional Review Boards published guidelines. The DSMB will include a cardiologist familiar with the management of patients with acute coronary symptoms, a statistician and an individual with a background in medical ethics. The DSMB will have access to study drug assignment and will make recommendations to Dr. Leucker regarding any safety concerns and continuation of the study.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Once the data are acquired, they will be assigned a code for each subject with identification secured and accessible only to the principal and other investigators, and the research coordinator. Patient clinical information such as copies of clinical studies and imaging reports will be filed in a locked filing cabinet with access under control of Dr. Leucker or one of the other investigators and study coordinators. Patient information summarized and/or converted into electronic form (tables, images, etc.) will be identified by the assigned code. We will abide by the Johns Hopkins Institutional policy that all identifiers in images and data acquired under IRB-approved research protocols must be removed if they leave the institution, for example in presentations.

e. Financial risks to the participants.

All study related costs will be paid from research sources, as stated in the consent form.

9. Benefits

a. Description of the probable benefits for the participant and for society.

Results from this study may benefit patients with an ACS in the future by providing information on the role of lipid lowering and anti-inflammatory medications in patients with an ACS. This would support the use of PCSK9 inhibitors to complement existing ACS treatment strategies in this population. However, we do not currently know whether subjects

will have an immediate benefit. It could be that this agent (evolocumab) reduces inflammation and LDL cholesterol and improves vascular and/or myocardial inflammation and this would, at least in the short term, benefit the patients receiving that drug. In prior non-ACS studies, the risks of receiving evolocumab were not different from placebo. In addition, the risks would be relatively short term since study participants will be only receiving a one-time dose of evolocumab. The low risk is reasonable in relation to the potential knowledge gained that may guide future therapeutic studies.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

For every outpatient visit study participants will receive $75. For study participants who have to travel $\geq$ 75 miles, or have an early morning heart scan, a hotel room for one night may be provided. Additionally, study participants will be reimbursed for transportation and parking expenses and given a $10 meal voucher following procedures requiring prior fasting.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There is no cost to the participants related to the study procedures or drugs.

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