May 3, 2024

Re: Cover Letter for Clinical Trials.gov NCT03689946

Study Title: Effect of Evolocumab on Coronary Artery Plaque Volume and Composition by CCTA and Microcalcification by F18-NaF PET"

This Cover Letter accompanies the approved protocol for this trial NCT03689946 which is completed.

This is to certify that the title of our study is, "**Effect of Evolocumab on Coronary Artery Plaque Volume and Composition by CCTA and Microcalcification by F18-NaF PET**" with a ClinicalTrials.gov Identifier: NCT03689946. We assure that this was a study approved by Institutional Review Board at Cedars-Sinai Medical Center. To the best of our knowledge all the information provided in this study is true and is being reported in compliance with the declaration of Helsinki for clinical trials.

Sincerely,

Daniel Berman, MD

Study Protocol

Title: Effect of Evolocumab on Coronary Artery Plaque Volume and Composition by Coronary CTA (CCTA) and Microcalcification by F18-NaF PET

BACKGROUND

Atherosclerotic coronary artery disease is the major cause of morbidity and mortality in the United States [1], and serum cholesterol levels are a strong risk factor for development and the growth of atherosclerotic plaque. The deposition of low density lipoprotein cholesterol (LDL) in the coronary artery wall is associated with the entry of macrophages and smooth muscle cells, setting the stage for atheroma formation. Atherosclerotic lesions at risk of rupture have certain histopathological characteristics that include positive remodeling, microcalcification, and a large necrotic core [2-5]. LDL cholesterol is a key mediator of atherogenesis, and inhibition of LDL synthesis with statins has been shown to be associated with both plaque regression and reduction in adverse cardiac events. LDL levels can be reduced by even a greater degree by the inhibition of PCSK9, a protease that is responsible for the degradation of LDL receptors on the cell surface, with monoclonal antibodies https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/repatha/repatha_pi_hcp_english.pdf) [6, 7].

Treatment with the PCSK9 inhibitor, evolocumab has been shown by intravascular ultrasound to be associated with a reduction of percent atheroma volume after 1.5 years of treatment; however, it is not known how evolocumab affects specific coronary plaque types and plaque inflammation [6, 7]. Although intravascular ultrasound (IVUS) can provide quantitative measurements of total atheroma volume, it is an invasive technique with associated procedural risks and therefore not practical for routine clinical monitoring of response to medical therapy. Quantitative assessment of changes in plaque burden, plaque composition and vascular inflammation in response to treatment with a PCSK9 inhibitor with noninvasive imaging (CCTA and positron emission tomography (PET) can provide a comprehensive assessment of pathophysiologic changes before and during treatment.

Our group has developed and extensively validated a semiautomatic method of comprehensive measurements of coronary plaque burden and plaque composition in the entire coronary artery tree on CCTA (Autoplaque) [8-12]. Among the many Autoplaque measurements are noncalcified plaque volume, low density non calcified plaque volume, the latter representing the necrotic core. We have shown strong correlation of noncalcified plaque volume with IVUS [10] and have documented excellent reproducibility of the various plaque measurements [12]. In 116 patients having serial studies over 3.5±1.6y, we have preliminary evidence that a 10% reduction in LDL is associated with an interval reduction in the volumes of all components of non-calcified plaque including adverse plaque characteristics associated with plaque instability and predictive of future cardiac events [13, 14].

With PET, our co-investigators have shown that microcalcification activity within coronary arteries and the aorta-reflecting the rate of deposition of calcium-can be assessed by18F sodium fluoride

(NaF) PET. This process is considered to be governed by the degree of plaque inflammation, and as such another marker of plaque vulnerability [15]. Thus, 18F NaF PET allows the assessment of the effect of therapy on a measurement related to plaque inflammation.

STUDY DESIGN

This is an early development, single-arm, prospective, open-label study of evolocumab injection in patients with calcified plaque in the coronary artery detected by CCTA. Fifty-five (55) evaluable subjects will be enrolled in the study.

OBJECTIVES

1. To test the hypothesis that PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor, evolocumab, reduces the volume of noncalcified plaque in coronary arteries as measured by coronary computed tomography angiography (CCTA)

2. To determine the components of non-calcified coronary artery plaque that are affected by treatment with evolocumab.

3. To determine if lipid lowering with evolocumab is associated with changes in microcalcification in atherosclerotic plaque as measured by F18-NaF PET

SPECIFIC AIM

To quantify changes in coronary plaque volumes and plaque composition in patients treated with evolocumab.

Hypothesis: Patients treated with evolocumab *demonstrate a reduction of coronary non-calcified plaque volume, including a preferential reduction in volume of low density non-calcified plaque components*

EXPLORATORY AIMS

To evaluate whether patients treated with evolocumab demonstrate reduced microcalcification activity in the coronary arteries as assessed by 18F NaF.

Hypothesis: Treatment with evolocumab *will be associated with reduced rate of coronary plaque inflammation which may be detected as a reduction in the rate of microcalcification activity.*

SUBJECT DESCRIPTION

Treatment Group

Inclusion Criteria

Treatment group will be comprised of 55 adult male and female patients who satisfy the following enrollment criteria:

- Evidence by CCTA of noncalcified coronary artery plaque (>440 mm^3)
- On-label indications for evolocumab treatment which includes the following criteria:

  Those who have established cardiovascular disease defined as acute coronary syndrome, history of myocardial infarction, stable angina or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.
- Non-calcified plaque (NCP) volume of 250 mm^3 or more in any single plaque in patients who do not have a total NCP >440 mm^3

Exclusion Criteria

- Creatinine > 1.5 mg/dL prior to imaging
- History of allergy to iodine contrast agents
- Allergy to evolocumab or any other ingredients contained in study drug, including latex
- Pregnancy
- Women who are breastfeeding
- Active atrial fibrillation
- History of coronary artery bypass graft
- Inability to lie flat
- Inability or unwilling to give informed consent
- Major illness or life expectancy <1 year
- Planned coronary revascularization or major non-cardiac surgery in the next 12 months
- Previously or currently on evolocumab
- Specific to beta-blocker administration: hypersensitivity or allergy to metoprolol or other beta-blockers, SBP <100mmHg, serious heart problems, such as cardiac failure (hypertension and angina), congestive heart failure, heart block, severe sick sinus syndrome, circulation problems, asthma or other breathing problems, peripheral artery circulatory disorders.

Recruitment and Enrollment

Treatment group

Investigators and/or the study coordinator will perform a weekly review of patients who have had a coronary calcium screening in the past month with coronary artery calcium (CAC), patients who have had a coronary CT angiogram with atherosclerotic plaque, and those who have plaque as documented during invasive angiography in the catherization lab at Cedars-Sinai Medical Center.

Among these patients, those who meet the inclusion criteria will be recruited to participate. Any information available in the patient's Cedars-Sinai medical records that can help determine eligibility will be viewed. The patient's cardiologist or other medical provider who ordered the CCTA or the invasive angiogram will be approached regarding appropriateness of recruiting the patient. The patient will then be contacted by an investigator or study coordinator for potential consent and participation."

All potential participants will be given enough time to consider the study. It will be explained that their participation is voluntary and will not affect their clinical care should they agree to participate or decline. We will provide a copy of the consent form to patients prior to the day of the study.

The subject's clinical status will be monitored for any adverse change prior to signing informed consent as well as prior to beginning any research procedures.

Feasibility: As of October 2017, we identified from our database 160 patients who have undergone sequential CCTA in whom total cholesterol and LDL values are also known, and who met indications for evolocumab.

DESCRIPTION OF PROCEDURES (Treatment Group)

The study protocol is comprised of a first CCTA (obtained clinically within 90 days prior to enrollment or at the first imaging visit for research purposes) and 18F-NaF PET, treatment with evolocumab for 18 months and a follow up CCTA and 18F-NaF PET.

All subjects will receive blood sampling and 18F-NaF PET scan during their initial visit. Subjects can expect to be at CSMC for approximately 5 hours.

Following the 18F-NaF PET scan, the first injection of evolocumab will be administered by a nurse at CSMC. Patients will be given instructions on how to prepare and administer evolocumab prior to use and will be provided a 6 months' supply of evolocumab for self-administration at each onsite visit.

In patients without homozygous familial hypercholesterterolemia (FH), evolocumab will be self-injected as follows: 140mg every 2 weeks or 420mg once a month subcutaneously.

Patients with homozygous FH will be instructed to administer 420mg subcutaneously once a month by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector.

Patients will undergo monitoring for adverse effects and for adherence with treatment every 3 months (phone calls at 1,3, 9, and 15 months of treatment and on-site visit with a nurse practitioner (NP) or MD at 6, 12 and 18 months of treatment. Patients will also receive a sharps container to safely discard all used syringes immediately after administration of the dose. The filled container will be returned during each on-site follow-up visits for drug accountability and proper disposal. After 18 months of treatment with evolocumab, patients will undergo a CCTA and 18F-NaF PETCT. Acquisition protocols will be identical to their baseline study.

Blood testing (estimated procedure time = 15 minutes)

Prior to beginning any imaging, patients will have blood drawn from a peripheral vein (<30 cc) to check creatinine (I-STAT® (Abbott Laboratories). Plasma and serum samples will be drawn for assessment of plasma and serum biomarkers including inflammatory, cardiac, and lipid markers, which may include C-reactive protein, IgM, interleukin-12 p70, tumor necrosis factor α, erythrocyte sedimentation rate, lipoprotein-associated phospholipase (Lp-PLA2), brain natriuretic peptide, oxidized low-density lipoprotein (LDL), high-sensitivity troponin as well as novel biomarkers being developed in the laboratory of co-investigator Dr. Jennifer Van Eyk, PhD.

18F-NaF PET Scan (estimated procedure time = 4 hours from time of 18F NaF injection)

1) Study subjects will be administered a dose of 250 MBq 18F-NaF intravenously.
2) All subjects will undergo dual cardiac and respiratory-gated PET-CT imaging of the thoracic aorta with a GE Discovery PET/CT 710 (GE Medical Systems) 180 minutes after injection. Scanning will utilize an attenuation correction CT scan (non-enhanced 120 kV and 50 mA), followed by PET imaging of the thorax in list-mode for 30 minutes.

CCTA (estimated procedure time = 0.5 hours)

The protocol used is the standard clinical protocol for CCTA that was employed in the baseline CCTA. The typical protocol is as follows:

1) CCTA will be performed using a SOMATOM Definition scanner (Force, Siemens Medical) as previously described [16]. When needed, oral and/or intravenous beta blockers (metoprolol) is administered to achieve a target heart ≤70 beats/min (bpm). Immediately before CTA scanning, 0.4 or 0.8 mg of sublingual nitroglycerin (ScielePharma, Alpharetta, Georgia) is administered. Images are acquired after a bolus injection of 80-100 ml contrast (Omnipaque or Visipaque, GE Healthcare, Princeton, New Jersey) at a rate of 5-6 ml/s, using either axial or helical scanning with dose modulation. Scanning parameters will include: tube voltage of 120 or 100 kVp, tube current 600 to 800 mA, depending on patient size; table feed/scan 3.8 mm; and pitch factor 0.2-0.4 (Heart rate dependent). Real-time bolus-tracking technique is used to trigger scan initiation. Axial images will be reconstructed at 0.6-mm slice thickness, 0.3-mm slice increment, 250-mm field-of-view, and 512 × 512 matrix.

Follow-up calls and visits

Phone Calls: At the beginning of the 3rd, 9th, and 15th month of treatment with evolocumab, patients will be contacted by phone to determine if they have had any adverse effects from evolocumab and to assess their adherence to monthly injections. A final phone call will also be made 3-7 days after the last dose and scan to determine adverse events and concomitant medications.

Visits to Cedars-Sinai: At the beginning of the 6th, and 12th months of treatment with evolocumab, patients will be seen by a NP at Cedars Sinai for on-site follow-up safety visits. Adherence to treatment and adverse effects will be assessed at these visits. Blood will be drawn at these visits to measure serum total cholesterol, LDL, HDL and TG as well as to confirm that patient is not pregnant. Patient will return the sharps container with the used syringes to CSMC research staff and new container will be dispensed. An additional 6 months' supply of evolocumab will also be dispensed at the follow-up visits (months 6 and 12), and re-training of injection technique/disposal will be provided as needed.

There will also be a final visit at the end of 18 months of treatment at which time adverse events and adherence will also be assessed and blood will be collected for a lipid panel and to confirm pregnancy status; samples will be stored for biomarker assessment. Patients will undergo a CCTA and PET-CT at that time as described above.

Patients who discontinue the study after 12 months of treatment with evolocumab will be encouraged to undergo CCTA and 18F-NaF PET, which will be the EOS (end-of-study) imaging for this group.

Study Schedule

Study Schedule: Effect of PCSK9 inhibitor, Repatha on coronary artery plaque composition and microcalcification by Coronary CTA and F18-NaF PET

Study Procedure	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
	Screening/ Enrollment	F/U Call	F/U Call	Safety F/U	F/U Call	Safety F/U	F/U Call	Final On-site Visit	EOS [h]
	Initial visit (1 or 2 days)	1 month ± 7 days	3 months ± 30 days	6 months ± 30 days	9 months ± 30 days	12 months ± 30 days	15 months ± 30 days	18 months ± 30 days	3-7 days after Visit 8 ± 30 days
Informed consent	x			x		x		x	
Eligibility Criteria	x								
Demographhics	x								
Medical History	x								
Concomitant medication	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x
Labs	x			x		x		x	
Pregnancy Test [a]	x			x		x		x	
CCTA [b]	x [b]							x	
18F-NaF PET	x							x	
Adminster IP [c]	x			x		x		x	
IP site monitoring	x			x		x		x	
IP re/training [d]	x			x		x			
Monitor drug adherence	x	x	x	x	x	x	x	x	
Dispense IP [e]	x			x		x			
Dispense sharps container [f]	x			x		x			
Provide drug diary [i]	x			x		x			
Collect drug diary				x		x		x	
Return IP [g]				x		x		x	

[a] If female subject is of child bearing age, and the first day of their last menstrual cycle is not within the past 30 days, a one-step HCG urine test will be done

[b] Patients who have already undergone a CCTA as part of screening within the past 90 days, will not need to udnergo a CCTA at the time of their initial 18F-NaF PET scan

[c] IP will be administered subcutaneously by a nurse and then self- administered for the rest of the study. At Visits 4, 6, and 8 subject will administer the IP in the presence of a medical professional to ensure proper technique/compliance

[d] Nurse will train subjecta t Visit 1. At Visits 4,6,and 8 subject will administer IP in the presence of medical professional and re-training will be provided as needed.

[e] Six months supply of IP will be dispensed to subject at Visits 1,4, and 6

[f] New sharps container will be provided for subject to discard used IP autoinjectors

[g] Subject will discard autoinjector after each administration of IP in provided sharps container, and return the filled container to the next on-stie visit (safety f/u)

[h] End of Study (EOS) safety phone call will be made 3-7 days after dose and scan (± 30 days)

[i] Subject will be provided a drug diary to document date, time, and location of each self-administration and return the completeted diary to the next on-site visit (safety f/u)

COLLECTION OF CLINICAL INFORMATION

Clinical information including age, sex, BMI, ASCVD risk factors, medications and dose of statin and antiplatelet therapy and laboratory data will be collected.

DATA PROCESSING AND ANALYSIS

I. Data anonymization/blinding

a. Anonymization

i. DICOM files of each CCTA and PET for each subject who completed the follow-up scan were anonymized of all identifiers except for the Series Description, using “diconymize”. A randomization generator randomized all baseline and follow-up scans and provided new subject IDs (prefix “EVO”) and procedure IDs (prefix CT or PET, depending on the procedure).

ii. CTs and PETs related to the same visit have the same 4 alpha-numeric ID with the CT or PET prefix to signify which studies were evaluated together. A linking file was accessible only to the study manager who were unblinded to which scans are baseline and follow-up.

iii. Once all scans are anonymized, the folder was zipped and uploaded to a BOX folder, accessible to the PIs and readers.

b. Blinding

i. In order to blind readers to the order of the scans, a linking file was created to randomize the subject’s ID, order of enrolment and order of scan

II. CCTA image analysis

i. The CCTA imaging core lab (Cedars-Sinai Medical Center, Los Angeles, CA, USA) performed qualitative and quantitative measurements of CCTA using AI enabled plaque quantification research software (Autoplaque, Cedars-Sinai Medical Center, Los Angeles, CA, USA). All qualitative and quantitative analyses were reported as per-patient and per-lesion level.

ii. All coronary segments ≥2 mm according to the 18-segment SCCT model were evaluated by level III-experienced readers blinded to clinical and PET data. Two serial scans (date blinded) were assessed at the same time. Overall study quality was recorded using a 5-point image quality assessment tool (excellent/good/fair/poor/non-diagnostic). The presence of coronary

plaque was defined as any tissue structure <1mmm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericoronary tissue or the vessel lumen itself. Between two serial scans, lesions were matched between two serial CCTAs using lesion location (involved coronary segment) and branch points as landmarks.

iii. **Qualitative APC measurements**

1. Stenosis severity was visually graded according to the CAD-RADS (Coronary Artery Disease – Reporting and Data System). All plaques were qualitatively assessed for the presence of adverse plaque characteristics: positive remodeling, low attenuation plaque, spotty calcification, and napkin-ring sign. Positive remodeling was defined by a vessel remodeling index >1.1. Low attenuation plaque was defined by the presence of any voxel <30 Hounsfield units (HU). Spotty calcification was defined as visually detectable calcification <3 mm in any direction within a plaque. Napkin-ring sign was defined as noncalcified plaque with a central area of hypoattenuation surrounded by a peripheral rim of hyperattenuation. High risk plaque was defined as presence of two or more APCs.

iv. **Quantitative measurements**

1. In axial and multiplanar views, the expert level III reader placed a region of interest in the ascending aorta to define normal blood pool and control points in the coronary lumen to define the centerline. The proximal and distal limits of lesions was manually defined, following which adaptive scan-specific Hounsfield Unit (HU) thresholds for plaque components were automatically generated. Automatic segmentation of the vessel wall and lumen were performed with manual adjustment as required. Plaque volume (mm3) was calculated on a per-lesion level for the following components: total plaque, calcified plaque, noncalcified plaque, and low-attenuation plaque (defined by a fixed attenuation threshold <30 HU). Quantitative diameter stenosis (%) was calculated as the ratio of minimal lumen

diameter to the mean of 2 (proximal and distal) non-diseased reference points. The contrast density difference is defined as the maximum percent difference in contrast density (the luminal attenuation per unit area over 1-mm cross-sections) within the plaque, with respect to the proximal normal reference cross-section.

III. PET image analysis

i. PET reconstruction

1. PET images was reconstructed into 4 cardiac phases using a vendor provided software (JS-Recon12, Siemens, Knoxville, TN, USA). All PET image reconstructions were performed with corrections for time-of-flight and point-spread function. Using 4 cardiac gates, we reconstructed the data on a 256×256 matrix (109 slices, slice thickness 2.027 mm) using 2 iterations, 21 subsets and 5-mm Gausian filter.

ii. Cardiac Motion correction

1. Cardiac motion corrected images were obtained from the gated PET reconstructions through PET-PET image co-registration using a diffeomorphic registration and dedicated software (FusionQuant version 1.19.2.7, Cedars-Sinai Medical center).

iii. Image registration

1. Prior to image analysis, the PET reconstructions were registered to the CCTA images, using a rigid translation of the PET images. The PET to CCTA registration was ensured using five key points of reference; sternum, vertebrae, blood pool in the left and right ventricle (based upon high ^{18}F-NaF activity in the blood pool in comparison to the surrounding myocardium), and the great vessels.

iv. Blood clearance correction

1. To minimize the impact of variations in background blood pool activity introduced by the injection-to-scan delays, we standardized the background blood pool activity to an injection-to-scan delay of 180 minutes using a previously described correction factor:

*SUVBackground corrected = SUVBackground*e(−0.004*(60−t))*

where t represents the injection-to-scan delay in minutes.

v. CMA quantification

1. To obtain the CMA values, two distinct steps were performed. First, we selected the proximal and distal end of the vessel (>2 mm) and applied a vessel tracking algorithm to extract whole-vessel tubular 3D volumes of interest from CCTA using dedicated Autoplaque software (version 3, Cedars-Sinai Medical Center, Los Angeles, CA). These encompassed all the main epicardial coronary vessels and their immediate surroundings (4-mm radius) facilitating per-vessel and per-patient uptake quantification. In a tubular VOI, along the extracted centerlines, with 4-mm radius, we measured the CMA on the PET/CCTA co-registered images. For this study, we evaluated ^{18}F-NaF activity along the entire course of coronary arteries regardless of the presence of coronary stents, and we included the left main in the left anterior descending artery VOI. CMA was defined as the average SUV within the activity volume above threshold of background SUV mean +2 standard deviations. The background activity was measured in the right atrium.

vi. TBR_{MAX} quantification

1. On the co-registered PET and CTA images, ^{18}F-NaF PET uptake was measured in all coronary segments with a vessel diameter ≥2 mm as defined by CTA. The ^{18}F-NaF uptake in these lesions were evaluated in a 3D spherical volume of interest (VOI) (radius 5 mm). In all plaques meeting these criteria, the maximum standardized uptake values (SUV_{MAX}) were measured within manually drawn regions of interest. TBR_{MAX} values were calculated by dividing the coronary SUV_{MAX} by the blood pool activity measured in the right atrium (cylindrical volume of interest radius 10 mm and thickness 5 mm) at the level of the right coronary artery ostium.

vii. Diagnostic Evaluation of CMA and TBR_{MAX}

1. Using CMA, the individual coronary arteries were marked as high ^{18}F-NaF if CMA>1.56. We assessed the burden of activity on a per-vessel and per-patient level. To allow a per-patient analysis, we added the CMA activity of all major epicardial vessels (CMA_{total}). For TBR, PET uptake was quantified based on the CCTA lesion position, with lesions categorized as ^{18}F-NaF-positive (TBR_{MAX} ≥1.3) or ^{18}F-NaF-negative (TBR_{MAX} <1.3).

BENEFITS

Evolocumab is clinically indicated for patients with ASCVD as defined in the inclusion criteria. We are not aware of any direct benefit for subjects from quantification of plaque volumes or microcalcification.

OFF-LABEL USE OF SODIUM FLUORIDE F-18-NaF

Sodium Fluoride F-18 Injection is a radioactive diagnostic agent for PET approved to use in imaging of bone to define areas of altered osteogenic activity. Sodium Fluoride F-18 Injection is not, however, approved for the indication of cardiac imaging.

The prescribed dose for an adult bone study is 300-450 MBq (approved dose for bone scanning). This study will employ a lower dose of 250 MBq. This follows the recommendation that the dose be minimized consistent with the objectives of the procedure and the nature of the radiation detection devices employed. The use of this lower dose has been shown to be effective in previous studies conducted at CSMC.

The 18F-NaF for this study will be manufactured by PetNet (Culver City, CA) and will be received by our radiopharmacy in the S. Mark Taper Imaging Center, Nuclear Medicine division. Our radiopharmacist will prepare the doses for administration for the cardiac imaging procedures.

Use of 18F-NaF in this study does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of 18F-NaF for the approved use in bone scanning.

The investigators have no intention of reporting data from this study to the FDA for change in indications or labeling.

RISKS

18F-NaF PET: According to the package insert, there are no contraindications and no adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. As with any injectable drug product, allergic reactions and anaphylaxis may occur. This research procedure is being conducted in a clinical setting and emergency resuscitation equipment and personnel are immediately available.

As with other radiopharmaceuticals, this injection has the potential to cause harm to an unborn child. Pregnant women will not be enrolled. Department policy states that all females of child bearing age (10-60yo) are screened to determine pregnancy status. If the female volunteer is of child bearing age and the first day of their last menstrual cycle is not within the past 30 days, we will administer a one-step HCG urine test (QuickVue®, Quidel Corp) in the department to determine their pregnancy status. To minimize the risks to a nursing infant, it is recommended that mothers interrupt nursing for at least 24 hours.

CCTA: The physical procedure of CCTA and administration of intravenous contrast are generally considered low-risk in patients without significant renal dysfunction and other contraindications to intravenous contrast. We will be performing the CCTA at least 48 hours after the initial dye load in the cath lab (if they have been enrolled from the cath lab), the risk of renal dysfunction is minimal.

Beta-Blocker and Nitroglycerin: Administration of metoprolol and sublingual nitroglycerin is associated with minimal risk since patients with clinical contraindications will be excluded.

Radiation: Estimated total radiation exposure from 18F-NaF is approximately 0.81 Rem from the combined 18F-NaF and associated attenuation scans. This calculation is based on 0.0027 Rem/MBq dose equivalent for ^{18}F-NaF and 0.138 Rem average radiation for cine-CT attenuation scan [22], and approximately 0.8 rem from the coronary CTA.

The study includes a baseline and a final 18F-NaF as well as a baseline and a final CCTA. The baseline CTA may be eligible if done clinically within 60 days prior to enrollment.

Evolocumab:
Hypersensitivity reactions (e.g., rash, urticaria) have been reported in patients treated with evolocumab, including some that led to discontinuation of therapy. If signs or symptoms of serious allergic reactions occur, discontinue treatment with evolocumab, treat according to the standard of care, and monitor until signs and symptoms resolve. Please see section 6 of the appendix Repatha prescribing information.pdf.

PRIMARY ENDPOINT

1. Change in noncalcified coronary artery plaque volume from baseline to month 18 of treatment with Evolocumab.
2. Change in plaque composition (low density non-calcified and calcified) from baseline to month 18 of treatment with Evolocumab.

STATISTICAL ANALYSIS PLAN

For all statistical analyses, two-sided tests will be conducted and p-values < 0.05 will be considered significant. Continuous variables will be presented as mean ± standard deviation (SD) or median (interquartile range) as appropriate. Annualized rate of change in total plaque volume, and the volume of non-calcified plaque, specifically, low density non calcified plaque components will be analyzed. . Mean values will be compared using a paired Student's t-test median values will be compared using the Wilcoxon rank-sum (Mann-Whitney) test. The relationship between decrease in LDL and changes in plaque volume and individual plaque components per year will be evaluated after adjusting for the effects of confounding variables including age, diabetes, hypertension, smoking, family history of premature coronary artery disease, statin use, baseline LDL and baseline plaque volume. Reproducibility of measurements of, volume of plaque components and total plaque volume will be assessed using intra-class correlations and coefficients of variation.

SAMPLE SIZE POWER CALCULATIONS

In a study of 116 patients who underwent sequential CTA, we observed a reduction in total plaque volume and NCPV among patients who experienced a reduction in LDL of >10% of their baseline LDL level under the influence of statins alone. Based on this preliminary work, we expect to detect a difference of at least 50mm^3/year in non-calcified plaque volume (ΔNCPV = $NCPV_{pre\text{-}treatment} - NCPV_{post\text{-}treatment}$) among patients who were treated with evolocumab. From our data, we estimate the population standard deviation for measurement of (ΔNCPV/year) to be 115mm^3. Using a paired t-test with a power of 80% and an alpha value of 0.05, we would need 44 patients in our treatment group.

After accounting for approximately 10 patients who might withdraw from the study, we propose to enroll 55 patients in our treatment group.

INSTITUTIONAL REVIEW BOARD (IRB)

Prior to study initiation and when amended, the protocol and any applicable advertisement for patient recruitment will be submitted for review and approval to the IRB charged with this responsibility. Site personnel must provide reports of the progress, or completion, termination or discontinuation of the study to the IRB at appropriate intervals. The investigator will verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

DATA COLLECTION AND MANAGEMENT

All information from the 18F-NaF PET scan and CCTA scan performed while the subject is at CSMC may be used for research analysis including the actual images, acquisition parameters of the imaging protocol, any information collected at the time of the test, and information from the patient's medical record.

DATA AND SAFETY MONITORING

All suspected unexpected serious adverse reactions (SUSARs) related or possibly related to evolocumab and their follow-up reports will be reported to Amgen within 24 hours of submission to the regulatory agency, IRB or IEC. A copy of any safety report involving an Amgen drug (e.g. evolocumab) submitted to the regulatory agency, IRB or IEC, will be faxed to Amgen, within 24 hours of such submission.

The sponsor will report all pregnancies and pregnancies occurring in the partner of a patient participating in the study or potential infant exposure through lactation within 10 calendar days of sponsor's awareness to Amgen.

DATA REPORTING

Routine reporting of recruitment, protocol compliance and data collection is planned annually to the IRB once recruitment begins. Occurrence of safety incidences including adverse events are reported according to CSMC compliance requirements. The investigators will provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. The investigators have no intention of reporting data from this study to the FDA for change in indications or labeling.

PATIENT CONFIDENTIALITY

The data source files will be kept in a locked room in the office of the cardiovascular imaging research team in the Mark Taper Imaging Institute building at Cedars Sinai Medical Center. The data will be stored in a de-identified manner. The identifiable information will not be reused or disclosed except as consistent with this protocol and signed HIPAA Authorization for Research.

References

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