Effect of Evolocumab on Coronary Plaque Characteristics:
a Multimodality Imaging Study
YELLOW III
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STUDY PROTOCOL

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BACKGROUND INFORMATION AND RATIONALE

Coronary artery disease (CAD) remains a leading cause of death in most countries despite modern therapy including intensive statin treatment, prompt coronary revascularization, and dual antiplatelet therapy. Reducing levels of low-density lipoprotein (LDL) cholesterol is a cornerstone of the prevention of cardiovascular disease (1). Statins are highly efficacious in lowering LDL cholesterol. However, many patients, especially those with very high initial LDL cholesterol levels and those who have unacceptable side effects with high-dose statins, do not reach recommended target levels of LDL cholesterol (2,3). The risk of recurrent cardiovascular events after acute coronary syndrome (ACS) or in chronic coronary heart disease remains related to LDL-C levels among statin-treated patients (4-6). These observations suggest that there is a considerable unmet medical need for additional, more effective therapeutic options with acceptable side-effect profiles.

Proprotein convertase subtilisin kexin type 9 (PCSK9) impairs LDL receptor recycling to the hepatic surface which leads to reduced removal of LDL particles from the circulation (7). Monoclonal antibodies against PCSK9 lower LDL-C levels when administered alone or in combination with statins and have shown potential as an alternative therapy for patients who experience intolerable adverse effects during statin therapy (8-10). Inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels by 59% from baseline level to 30 mg per deciliter and reduced the risk of cardiovascular events in a large randomized FOURIER trial including patients with atherosclerotic cardiovascular disease on statin therapy (11). In the GLAGOV trial,

addition of evolocumab in patients treated with moderate or high intensity statin therapy resulted in greater decrease in percent atheroma volume (PAV) assessed by intravascular ultrasound (IVUS) during 18 month of therapy (12), while there was no plaque regression observed in patients treated with statins alone. Reduction in the atherosclerotic disease burden, atheroma (PAV) was observed in 67% of the evolocumab and 47% of the placebo group regardless of baseline LDL-C levels.

One-third of the patients treated with evolocumab and almost half of statin-treated patients from the GLAGOV trial did not demonstrate plaque volume reduction despite the significant lipid reduction suggesting that different mechanisms might be responsible for lesion regression in a subgroup of patients, and these patients might require different treatment approach. Another possibility is that beneficial changes in lesion morphology were not captured in the study due to inherent limitations of IVUS. Optical coherence tomography (OCT) provides high-resolution (10-20 μm) in vivo images of plaque morphology and is the only currently available intravascular imaging modality capable of the assessment of the fibrous cap thickness in vivo (13,14). The presence of a thin fibrous cap overlying a large necrotic core is the hallmark of high-risk vulnerable plaques (14,15). While intravascular ultrasound (IVUS) lacks the spatial resolution to accurately access the changes in fibrous cap thickness (FCT), OCT's superior image resolution allows the accurate detection of thin cap fibroatheroma (TCFA) and estimate the effect of various lipid-lowering therapies on FCT (16-18). The aim of the ongoing HUYGENS study is to evaluate the effect of evolocumab combined with maximally tolerated statin therapy on

OCT defined FCT in subjects with non-ST-elevation acute coronary syndrome (NSTE-ACS).

Near-infrared spectroscopy (NIRS) detects the lipid (cholesterol) content of atherosclerotic plaques by generating lesion “chemogram” and calculating lipid core burden index (LCBI) characterizing the amount of lipid on a 0 to 1000 scale. Large lipid-core plaques (LCP) detected by NIRS have been shown to be a signature of plaques causing STEMI and are associated with a high risk of periprocedural MI (19,20).

Results of YELLOW I and II. In a series of YELLOW trials, we investigated the effect of statins on high-risk lipid-rich coronary plaques using intravascular imaging in patients with stable CAD. The aim of our first YELLOW (Reduction in Coronary Yellow Plaque, Lipids and Vascular Inflammation by Aggressive Lipid Lowering) trial was to explore whether these benefits are attributable to reduction in plaque lipid content in obstructive coronary lesions (21). In the study, we randomized 87 patients with multivessel CAD to intensive (rosuvastatin 40 mg daily) or standard-of-care lipid-lowering therapy. Patients underwent PCI for the culprit lesion at the baseline, while obstructive nontarget lesion (NTL) was treated at the staged procedure, follow-up. The inclusion criterion for the trial was FFR less or equal 0.8. NTLs were evaluated at baseline and after 7 weeks of therapy with NIRS and IVUS. The primary endpoint was the change in lipid-core burden index at the 4-mm maximal segment (maxLCBI4mm). Upon follow-up, median reduction in maxLCBI4mm was significantly greater in the intensive versus standard group suggesting that short-term intensive statin therapy may reduce lipid content in obstructive lesions.

In our subsequent YELLOW II study, all patients with obstructive NTL received high-dose statin therapy for 8-12 weeks (22). The aim of the study was to characterize the relationship between the changes in plaque morphology assessed by NIRS/IVUS and OCT, HDL functionality and gene expression in peripheral blood mononuclear cells (PBMC) using microarray analysis. At the follow-up, we observed a significant increase in fibrous cap thickness (FCT) in the study lesion, enhancement of cholesterol efflux capacity (CEC) and significant perturbations of PBMC transcriptome in patients with stable coronary artery disease (CAD) treated with 40 mg rosuvastatin for 8-12 weeks. As a result, the prevalence of TCFA reduced from 20 to 7% (P=0.003) and there was a significant independent association between the thickening of the fibrous cap and improved CEC independent of lipid lowering and CRP reduction. In addition, we observed significant transcriptomic perturbations in genes related to cholesterol synthesis, regulation of fatty acid unsaturation, cellular cholesterol uptake, efflux and inflammation suggesting that several independent molecular mechanisms might be responsible for the beneficial effects of statin on plaque morphology. The unique translational combination of multi-modality intravascular imaging with clinically relevant cellular biology and comprehensive transcriptomics represents a powerful approach to assessing the effects and mechanisms of the efficacy of different lipid-lowering therapies for stabilizing atherosclerotic plaques.

With OCT imaging, we observed an increase in FCT after intensive statin therapy only in a subset of the study patients. Traditionally, response to statins is measured by the changes in serum lipids, however, these changes do not predict the beneficial changes

in FCT, therefore, it is important to distinguish statin responders from non-responders using non-invasive methods. In our recent analysis, YELLOW II transcriptomic data was used to predict whether a patient's FCT increased in response to statin therapy using machine learning models (23). One of the model used 18 genes and was able identify statin responders with an accuracy of 95.7%, sensitivity of 94.3% and specificity of 97.1%.

Hypothesis. In the YELLOW III study, we hypothesize that LDL-C lowering with evolocumab 140 mg every 2 weeks will result in a significant increase in OCT-defined minimal FCT and reduction of plaque lipid content assessed by NIRS compared to baseline in patients with CAD undergoing percutaneous coronary intervention (PCI). In addition, we hypothesize that there is an association between the changes in patient's plaque characteristics and PBMC gene expression and lipid metabolites at the baseline, which would allow us to develop a predictive model for detecting subjects that demonstrate the greatest response regarding plaque morphology to PCSK9 inhibition therapy. YELLOW III will provide an additional contribution to the ongoing HYUGENS study due to its unique design combining intravascular imaging and transcriptomic based machine learning approach, which will allow to uncover molecular mechanisms responsible for the beneficial changes in atherosclerotic lesions of patients treated with evolocumab.

STUDY OBJECTIVES

The aim of the study is to assess the effect of evolocumab on coronary plaque morphology using intravascular imaging, NIRS/IVUS and OCT, and PBMC gene expression analysis in patients with stable CAD on maximally tolerated statin therapy.

Primary endpoints. The primary end-points are the changes from baseline to follow-up (follow-up value minus baseline value) in (1) the minimal FCT assessed by OCT and (2) NIRS maxLCBI4mm after 26 weeks of evolocumab.

Secondary endpoints. The secondary endpoints are the changes in (1) the maximal lipid arc, lipid length, lipid volume index, macrophage accumulation and calcification by OCT; (2) PAV and TAV defined by IVUS and (3) PBMC gene expression. In recognition of the role of lipids in CAD and atherosclerosis, we will perform lipidomics to analyze lipid metabolites and lipid derivatives in blood plasma and serum in order to identify CAD biomarkers. Measuring lipid metabolites (and their effectors) might directly lead to the identification pathways of lipid action or lipid metabolism in patients receiving treatment. We will also perform Mass Cytometry (CyTOF) of PBMC to characterize the immune profile and responses in patients receiving a combination of evolocumab plus statin with an eye on identifying biomarkers for detecting and/or predicting favorable changes in plaque morphology as a result of PCSK9 inhibition therapy. Other parameters including the levels of CRP, resistin, adiponectin, perilipin and Lp(a) will also be measured for the same purpose.

Exploratory endpoints. Major Adverse Cardiac Events (MACE) will be defined as a combined clinical endpoint of death, MI (Q wave or non Q-wave with CK-MB >3 times above the upper normal limit (48 U/L), urgent revascularization or stroke at 30 days and 1 year.

STUDY PROCEDURES

This is a single center single arm study, which will be performed in the Cardiac Catheterization laboratory of the Mount Sinai Hospital, New York, NY. After informed consent, patients undergoing clinically indicated elective PCI with a non-obstructive lesion and optimal background statin therapy will be eligible for screening (Figure 1). Non-obstructive lesions (30-50% stenosis) identified by angiography in a non-culprit vessel with lipid-rich plaque will be studied. Subjects will receive evolocumab 140 mg subcutaneously every 2 weeks for 26 weeks. Serial NIRS/IVUS and OCT imaging will be performed in the non- obstructive lesions, first during PCI and subsequently after 26 weeks.

1. **Screening.** Written informed consent must be obtained from all subjects before any study-specific procedures are performed. We will screen patients scheduled for elective coronary angiography and/or coronary artery stenting, who are receiving statin therapy for at least 4 weeks or with history of statin intolerance (should not exceed 20% of the total cohort) with acceptable LDL-C levels. Patients with non-obstructive lesion (30-50% stenosis) by angiography and lipid-rich plaque with lipid arc >90° and minimal fibrous cap thickness ≤ 120 μm detected by OCT will comprise

the final study population. Women of childbearing potential will undergo urine pregnancy testing. If necessary, we may request serum pregnancy testing to confirm equivocal urine-based results.

2. **PCI and baseline imaging.** Culprit vessel PCI will be performed according to best current practice. During the same angiographic procedure baseline OCT and NIRS/IVUS imaging of the non-obstructive study lesion will be performed after administration of intra-coronary NTG. A total of 25ml of blood will be drawn from the sheath during angiography for transcriptomic profiling of PBMC (mRNA and miRNA), lipidomics and cytokine analyses. Patients will undergo assessment of lipid levels, CK-MB, Troponin I, liver function, CBC, and hsCRP.
3. **Study drug allocation.** All patients will receive subcutaneously administered evolocumab 140 mg every 2 weeks for 26 weeks in addition to statins. Evolocumab will be administered on day 1 (the day of the first treatment) and through week 26 with a personal injector or prefilled auto injector/pens.
4. **Clinical visits.** Study visits will occur during screening (day 1), weeks 12 and 26 (time of follow-up procedure). Subjects must fast overnight when fasting lipid samples are to be obtained.
5. **Follow up Procedure.** The follow-up procedure will be scheduled 26 weeks after the baseline PCI and should occur within ±2 weeks of their specified date. First, routine angiography to check the previous stent will be performed, then, repeat NIRS/IVUS and OCT of the non-obstructive study lesion will be performed after administration of intra-coronary nitroglycerin. A total of 25ml of blood will be drawn

from the sheath during angiography for transcriptomic profiling of PBMC (mRNA and miRNA), lipidomics and cytokine analyses.. All study patients will undergo repeat assessment of lipid levels, CK-MB, Troponin I, liver function, CBC, and hsCRP. Bivalirudin or Heparin will be used as anticoagulation as per standard PCI protocol. All patients will have repeat CK-MB and TnI levels measured at 6-8 hours and if in hospital, 16-24 hours post PCI, and thereafter if levels continue to rise

6. **Post Follow-up.** After the follow up procedure patients will be referred back to their primary care physician as is our usual practice. All further adjustment of lipid lowering and other medications will be at the discretion of the primary care physician. The treatment received after 26 weeks of evolocumab will be documented, and clinical telephone follow up will be performed at 30 days, 6 months and 1 year after the follow-up procedure
7. **Data analysis**. Off-line image analysis will be performed by the Mount Sinai Intravascular Imaging core laboratory, which will have no knowledge of patient clinical presentation and treatment.. Statistical and bioinformatics analyses will be performed by an independent biostatistician unaware of clinical data.

   For predictive model construction, each patient will be identified as an evolocumab responder or non-responder depending on whether FCT increased or decreased after the treatment. Similar to our YELLOW II transcriptomic sub study (23), an elastic net regularized generalized linear model and K top scoring pair (KTSP) classifier model will be built using clinical variables and PBMC transcriptomic, lipidomics and cytokine analyses data to predict changes in FCT to ascertain whether a patient's FCT will increase in response to treatment. The transcriptomic data will be pre-processed to identify the

mechanism of missing data, and data imputations will be performed for non-ignorable missing data. The accuracy, sensitivity and specificity of both algorithms will be evaluated in order to select the highest performing model. We believe that the predictive model might allow patients to have their FCT response approximated without undergoing intravascular imaging.

8. **Safety reporting**. Subjects will be carefully monitored during the study for possible Adverse Events (AEs) from the time of enrollment to the completion of their participation in the study. All adverse events will be fully investigated by the Principal Investigator, classified according to the current definitions of the International Organization for Standardization (ISO) and reported to the Mount Sinai Hospital IRB and Amgen Safety. Timeframes for submission of safety data and aggregate reports to Amgen are described in Tables 1 and 2.

   In addition, an independent data and safety monitoring board (DSMB), comprising 3 cardiologists with extensive clinical research experience will oversee this study. The DSMB will be informed within 24 hours of all major adverse events (MACE) defined as a combined clinical endpoint of death, MI (Q wave or non Q-wave with CK-MB >3 times above the upper normal limit (48 U/L), urgent revascularization or stroke at 30 days and 1 year. All minor adverse events will be reported to the DSMB within 5 working days of knowledge of the event. The DSMB will convene after 30, 70 and 110 patients have completed the final procedure and at study closure. The DSMB will have complete discretion to adjudicate all events (major and minor), and, after fair deliberation and at any stage of the trial, to recommend the termination of the study, for whatever reason as they see fit insofar as it may pertain to adverse event occurrence(s). If the DSMB is to recommend termination of the study, the investigators will be given a single opportunity to respond to any concerns the DSMB may raise. After final consideration, if the DSMB again recommends termination of the study, then the study will be terminated. The DSMB may only terminate the study on the basis of MACE and adverse events.

9. **Institutional Review Board (IRB).** Prior to study initiation and when amended, the study protocol and will be submitted for review and approval to the Icahn School of Medicine at Mount Sinai IRB. Site personnel must provide reports of the progress, or completion, termination or discontinuation of the study to the institutional IRB at appropriate intervals. The primary 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

Inclusion criteria:

- Men or women aged 18 years or older at screening who signed written Informed Consent
- Patients with coronary artery disease undergoing cardiac catheterization and PCI for a culprit lesion, who also have a non-obstructive study lesion (30-50% stenosis) identified by angiography in a non-culprit vessel.
- Patients with non-obstructive coronary artery disease and a 30-50% lesion identified by angiography
- Patients who are not candidates for PCI or CABG over the next 12 months, in the opinion of the investigator
- Patients treated with statins for at least 4 weeks with LDL-C level ≥ 80 mg/dL for low- or moderate -intensity statin use and ≥ 60 mg/dL for high-dose statin at screening (Table 3). Patients with history of statin intolerance and LDL-C ≥ 100 mg/dL.

- Angiographic criteria: 30-50% reduction of lumen diameter in addition to the target study lesion. The study segment should not have a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and may not be a bypass graft.
- OCT criteria: study lesion should have a lipid-rich plaque with lipid arc >90° and fibrous cap thickness ≤120 μm.
- Women of childbearing potential must agree to be on an acceptable method of birth control/contraceptive

Exclusion criteria:

- Patients who have acute myocardial infarction (Q wave or non-Q wave with CK-MB > 5 times above the upper normal (31.5 ng/ml) within 72 hours)
- Patients who are in cardiogenic shock
- Patients with left main disease or patients requiring coronary artery bypass graft surgery
- Patients with elevated CK-MB (>6.3 ng/ml) or TnI (>0.5 ng/ml)
- Patients with platelet count < 100,000 cell/mm^3
- Patients who have co-morbidity which reduces life expectancy to one year
- Patients who are currently participating in another investigational drug/device study
- Patients with liver disease
- Patient with creatinine > 2.0 mg/dL
- Pregnant women and women of childbearing potential who intend to have children during the duration of the trial
- Patients having undergone heart transplantation, or those that may undergo heart transplantation during the study period
- Patients with active autoimmune disease

Table 1. Timeframes for submission of safety data and aggregate reports to Amgen

Safety Data	Timeframe for submission to Amgen	Send to
Suspected Unexpected Serious Adverse Reaction (SUSARs)	At time of regulatory submission	Amgen Safety
Pregnancy/Lactation exposure and any associated reports/outcomes (i.e. unexpected pregnancy, pregnancy of partner, spontaneous abortion, congenital anomaly etc.)	Within 1 business day of Sponsor awareness, for reports meeting serious criteria Not to exceed 15 calendar days of Sponsor awareness, for non-serious reports	Amgen Safety
Listing for Safety data reconciliationa[a]	Once per year and at the end of the study	NASCR Manager
Annual Safety Report (US IND Annual Report)	Annually	NASCR Manager
Other aggregate analyses (any report containing Safety data generated during the course of the study)	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.)	NASCR Manager
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.) but no later than 1 calendar year of study completion	NASCR Manager

[a] Listing for reconciliation should include all ICSRs submitted to Amgen Safety per contract

Table 2. Timeframes for submission of safety data and aggregate reports to Amgen - Device related adverse events for studies using Amgen devices[a] and Product complaints

Safety Data	Timeframe for submission to Amgen	Send to
Serious Adverse Device Effect[b] (SADE)	Within 1 business day of Sponsor awareness	Amgen Safety
Adverse Device Effect (ADE)	Not to exceed 15 calendar days of Sponsor awareness	Amgen Safety
Product Complaint[c]	Immediately, not to exceed 1 business day of Sponsor awareness	Amgen Quality

[a] Refer to local Safety representative (LSO) to clarify reporting requirements for the Amgen device per regulations in the country where the study is being conducted.

[b] Adverse device effect is: any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

[c] Product Complaint is: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug, combination product, or device after it is released for distribution to market or clinic by either: (1) Amgen or (2) distributors or partners for whom Amgen manufactures the material. This includes all components distributed with the drug, such as packaging, drug containers, delivery system, labelling, and inserts. Examples include:

- Device that is damaged or broken
- Bent or blunt needles
- Missing or illegible labeling
- Inability of customer to administer the product
- Product with an unexpected color, appearance, or particles
- User error (i.e, an act or omission of an act that results in a different combination product or medical device response than intended by the manufacturer or expected by the user, where the user attempted to use the combination product or medical device in good faith and experienced difficulty or deficiency administering the product).

Reports of misuse of a combination product or medical device (i.e, the intentional and improper use of a combination product or medical device not in accordance with the authorized product information) are not considered Product Complaints.

Table 3. High-, Moderate-, and Low-Intensity Statin Therapy*

High-Intensity Statin Therapy	Moderate- and low- intensity statin therapy
Atorvastatin ≥40 mg Rosuvastatin ≥20 mg	Atorvastatin <40 mg Rosuvastatin <20 mg Simvastatin < 80 mg Pravastatin ≤ 80 mg Lovastatin ≤ 40 mg Fluvastatin ≤ 80 mg Pitavastatin ≤ 4 mg

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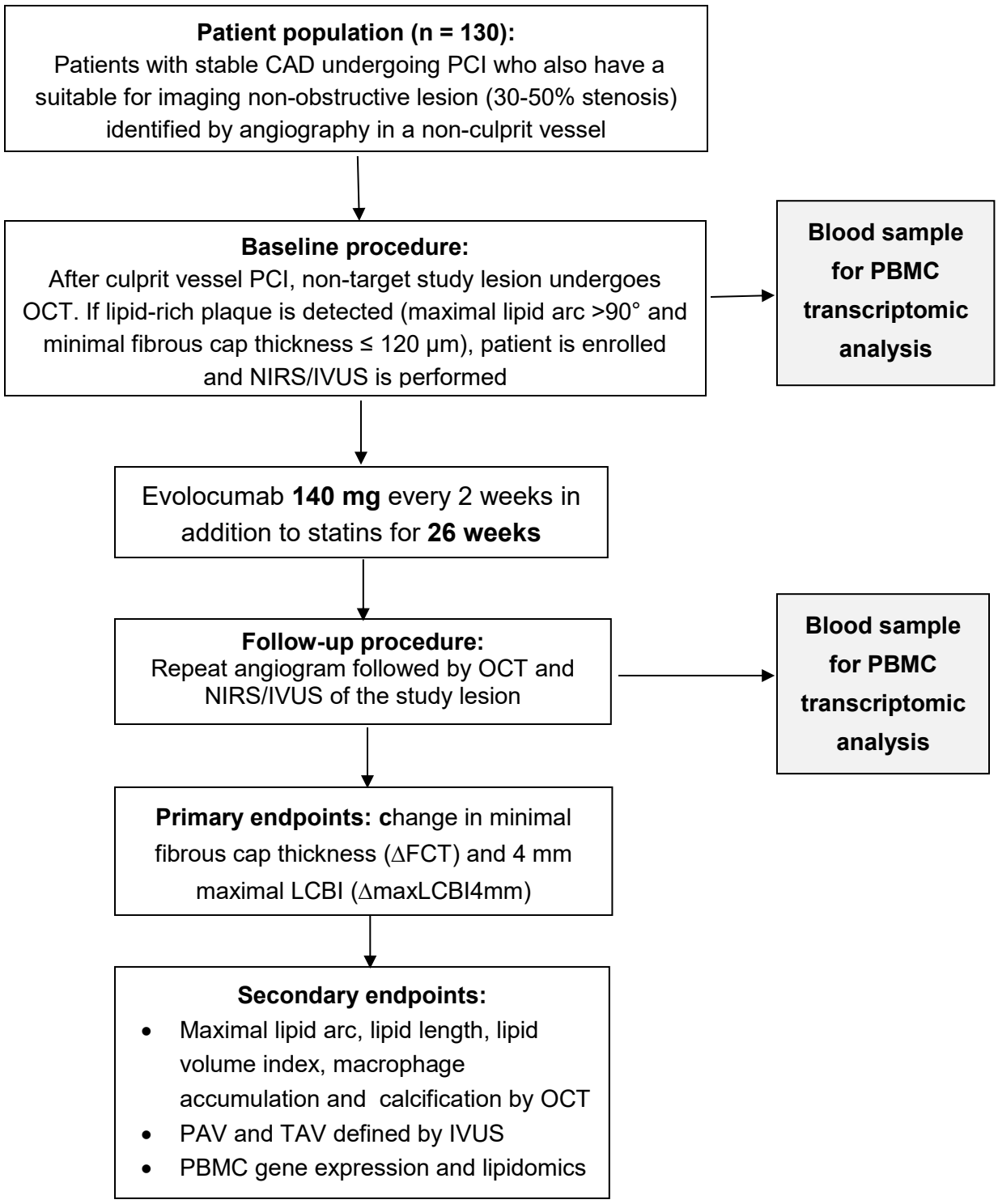
Figure 1. YELLOW III study flow chart



ACS – acute coronary syndrome; LCBI – lipid core burden index; OCT – optical coherence tomography; PAV=percent atheroma volume; SC – subcutaneously; TAV=total atheroma volume; FCT – fibrous cap thickness; PBMC - peripheral blood mononuclear cell

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