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Faculty of Medicine

Department of Clinical
Research (DCR)

CTU Bern

Statistical Analysis Plan

Study: Effects of the PCSK9 Antibody AliroCuMab on Coronary Atherosclerosis in PatieNts with Acute Myocardial Infarction. A Serial, Multivessel, Intravascular Ultrasound, Near-Infrared Spectroscopy And Optical Coherence Tomography Imaging Study

PACMAN-AMI

CTU project number: **430 PACMAN**

Protocol: VERSION 6 / AUGUST 10, 2019

Authored by: Dik Heg & Sylvain Losdat

Date: 14.06.2021

Version: 2.0

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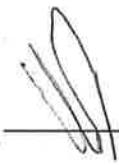
Dik Heg CTU Bern		6.12.2021
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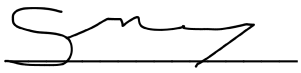
Sylvain Losdat CTU Bern		06.12.2021
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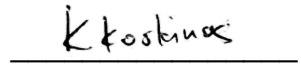
Konstantinos Koskinas Inselspital		03.12.2021

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Change history:

Version	Date	Major changes
2.0	14.06.2021	Revised power calculation based on the protocol amendment (Protocol version 6, August 10th, 2020). Updated number of patients to be enrolled (section 3.2 below).
2.0	14.06.2021	Clarification of the timing of the final study visit (section 3.5 below).
2.0	14.06.2021	Interpretation of the p-values for the primary and powered secondary endpoints will be performed based on hierarchical testing (section 6.1 below).
2.0	14.06.2021	addition of a sensitivity analysis testing the effect of delayed follow-up visits due to COVID-19 (section 6.8.8 below).
2.0	14.06.2021	Planned sub-studies (section 12 below).

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Contents

1. Study synopsis

Coronary artery disease (CAD) is the most frequent cause of mortality in the industrialized world. Hypercholesterolemia is a major risk factor for the development and progression of CAD. HMG-CoA reductase inhibitors (statins) lower plasma levels of low-density lipoprotein cholesterol (LDL-C) and reduce cardiovascular adverse events in proportion to the magnitude of LDL-C lowering. While statins currently represent the first-line, gold-standard therapy for primary and secondary prevention of cardiovascular morbidity and mortality, nearly 50% of patients in Europe and Canada treated with statins do not achieve their target levels of LDL-C or cannot tolerate effective statin doses. Subsequently, substantial LDL-associated residual risk remains. Therefore, there has been increasing interest for additional pharmacologic strategies to effectively lower cholesterol and to further reduce cardiovascular events.

Coronary atherosclerosis is characterized by substantial heterogeneity, in that atherosclerotic lesions differ distinctly in their morphological characteristics ranging from minor subintimal lipid depositions to large fibrous or fibrocalcific plaques to highly inflamed, thin-capped fibroatheromas (TCFA). Pathological studies have established that plaque composition – and not merely plaque size –determine the extent and nature of clinical manifestations. Characteristics of high-risk, so-called vulnerable plaques include a large lipid pool/necrotic core, marked infiltration with inflammatory cells, and a thin fibrous cap. Atherosclerotic lesions combining these characteristics are more prone to rupture and trigger acute coronary thrombosis. Of clinical importance, statin-mediated LDL-C reduction can halt atherosclerotic plaque progression and even achieve plaque regression when the highest doses of statins are administered, as demonstrated by landmark serial intravascular ultrasound (IVUS) analyses of changes of plaque burden in stable CAD or STEMI patients. Moreover, statins favorably affect plaque morphology and composition by reducing the lipid content and attenuating plaque inflammation, as shown consistently by preclinical and clinical investigations

A growing body of evidence indicates that **PCSK9 inhibitors** result in profound reductions in blood levels of LDL-C, with an efficacy that is more potent and incremental to the effect of high-dose statin regimens. The **present analysis, utilizing a multimodality approach of intracoronary imaging**, aims to uniquely investigate the time-dependent effect of PCSK9 inhibition on important aspects of **coronary plaque burden**, **morphology** and **composition** in humans presenting with myocardial infarction (**NSTEMI** or **STEMI**) including lipid content, inflammation, and fibrous cap thickness in the two non-infarct related arteries of patients with acute myocardial infarction. These morphological characteristics have been related to plaque vulnerability and rupture in pathological studies and, prospectively, with future cardiac events. The proposed study thereby aims to provide further insights on the effects of highly potent LDL-C reduction on atheroma progression, composition and microstructural plaque characteristics beyond the available evidence of the efficacy of PCSK9 inhibitors in reducing LDL-C levels and ongoing analyses assessing possible translation of this potent lipid-lowering potential into improved clinical outcomes. Considering the high residual risk of anatomic and clinical progression of coronary atherosclerosis in a substantial proportion of patients treated with intensive statin regimens, the proposed study aims to assess the incremental efficacy of

a novel treatment strategy in favorably affecting both plaque progression and plaque composition in a high-risk population of patients who already experienced myocardial infarction and who derive the greatest benefit from aggressive lipid-lowering and other anti-atherosclerotic medications.

2. Study objectives

2.1. Primary objective

To evaluate the effect of LDL-C lowering by means of the PCSK9 inhibitor alirocumab as compared with placebo, on the change in percent atheroma volume (**PAV**, determined by intracoronary imaging IVUS) in non-infarct-related coronary arteries of patients who present with acute myocardial infarction, undergo percutaneous coronary intervention (PCI) in the infarct-related artery, and receive guideline-recommended high-intensity statin therapy at 1 year.

2.2. Secondary objectives

- Powered secondary endpoints

To evaluate the effect of the PCSK9 inhibitor alirocumab as compared with placebo, on the change in **lipid core burden index** (determined by intracoronary imaging NIRS), **macrophage accumulation** (determined by serial intracoronary imaging OCT), and **fibrous cap thickness** of coronary plaques (determined by serial intracoronary imaging OCT) in the non-infarct-related coronary arteries at 1 year.

- Non- powered secondary endpoints

To evaluate the effect of alirocumab as compared with placebo, on change in lipid levels (cholesterol, LDL-C, HDL-C, Lp(a), triglycerides, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III), inflammatory biomarkers (hs-CRP, TNFa, IL-1b, IL-6, MPO, cystatine, SIRT1, SIRT6) and other selected biomarkers (hs-troponin T, NT-pro-BNP) and explore possible associations with changes in coronary plaque characteristics at 1 year. Lipid levels and inflammatory or selected biomarkers are determined by central laboratories using samples stored in the Inselspital BioBank.

2.3. Assessment of objectives

Three different and complementary intracoronary imaging methods are used in a serial fashion (baseline and 1 year) to assess the primary and secondary endpoints: IVUS (Intravascular Ultrasound), NIRS (Near-infrared spectroscopy), OCT (Optical Coherence Tomography). Additional secondary endpoints are measured from the BioBank samples and reported from the central laboratories located at the hospitals of Bern, Zürich and Vienna: lipid levels and inflammatory or selected biomarkers. Laboratories assess various biomarkers; key parameters by Zurich lab (A. von Eckardstein), NETs by Vienna, Proteomics by Kings College (Prof. Mayr).

2.4. Changes of the primary objective during the conduct of the study

No changes of the primary objective during the conduct of the study will be made.

3. Study design

3.1. General design and plan

This is a randomized, superiority, double-blind (assessor and patients blinded to treatment), placebo-controlled, parallel-group, multi-center trial to evaluate the effect of the PCSK9 inhibitor alirocumab on coronary atherosclerotic plaque burden and composition as assessed by multi-modality intracoronary imaging at baseline and following 52 weeks of treatment in patients presenting with acute myocardial infarction undergoing PCI. The primary endpoint will be assessed at 52 weeks post randomization.

3.2. Sample size

1) Initial sample size calculation

This is a superiority trial powered for the primary endpoint, change in PAV from baseline to 52 weeks (12 months). We assume a PAV change of -0.5% in the placebo arm and -1.8% in the alirocumab arm, with a common standard deviation of 3.4% (as a consensus from SATURN11: 3.0%, IBIS435: 3.4%, ASTEROID10: 4.0%) and an intraclass correlation coefficient of ICC=0.40 (estimated from IBIS4 data). Given that m=1.8 vessels per patients are expected to be analyzed, this gives a design effect of D=1.4 [design effect computed as D = 1+ICC(m-1)]. If dropout was ignored, a total sample size of 176 patients would be necessary to reach a statistical power of 80% at a two sided alpha level of α=5%. Anticipating a dropout rate of 25% at the 12 month imaging follow-up, a total of n=220 patients should be recruited (110 per arm).

A total of 220 patients will be randomized in a 1:1 ratio to either **Alirocumab** or **Placebo**. Patients will be screened for eligibility based on anatomic criteria (number of arteries without significant obstructive atherosclerotic disease), estimated suitability for intracoronary imaging of 2 non-infarct-related coronary arteries, clinical and LDL-C level inclusion criteria.

In case GLAGOV randomized clinical trial reports considerably lower PAV regression compared with our current assumptions (1.6% reduction or less), a protocol amendment of the present study will be submitted with a revised sample size calculation considering for the GLAGOV results.

2) Revised sample size calculation

- **primary endpoint 'change in Percent Atheroma Volume' (PAV)**

The above-mentioned condition for the revised sample size calculation has been met since the delta PAV observed in GLAGOV was 1%. We therefore revised our power calculation considering a delta PAV of 1% (instead of 1.3% initially) prior to the inclusion of the last of 220 patients. Based on data from already enrolled patients with available one year follow-up (N=54) we also revised the expected number of vessels per patient (m=2.0) and the expected drop-out rate (10%). This is a superiority trial powered on the primary endpoint: change in PAV from baseline to 52 weeks (12 months). In the revised power calculation we assume: (i) a difference of the PAV change -1.0% (alirocumab arm vs placebo arm based on the GLAGOV trial); (ii) a standard deviation of 3.4% (as a consensus from SATURN: 3.0%, IBIS4: 3.4%, ASTEROID: 4.0%); and (iii) an intraclass correlation coefficient (ICC) of approximately 0.435 (estimated from IBIS4 data). We expect m=2.0 vessels per patients to be analyzed. The design effect is calculated by D = 1+ICC(m-1). If dropout was ignored, a total sample size of 264 patients would be necessary to reach a statistical power of 80% at a significance level of α=5% using a two-sided test. Anticipating a *dropout rate of* 10% (loss of patients undergoing follow-up imaging) at the 12-month imaging follow-up, a total of n=294 patients should be recruited (147 per arm).

In the course of the revision of the power calculation, the study was also be powered for two key secondary endpoints derived by NIRS (change in lipid-core burden index at the 4-mm maximal segment' (maxLCBI4mm) and OCT (change in minimal cap thickness). We provide the power calculation for these two key secondary endpoints.

- **secondary endpoint 'change in lipid-core burden index at the 4-mm maximal segment' (maxLCBI4mm)**

For the change in maxLCBI4mm from baseline to 52 weeks (12 months), we assume: (i) a difference between PCSK9 arm and Placebo arm of 193.3 based on the observed difference in the YELLOW I trial (Kini AS et al. JACC 2013;62:21-29) and the expected reduction in LDL-C in PACMAN (-40% in PLACEBO and -75% in PCSK9), (ii) a standard deviation of 220 (estimated from LRP) and iii) a dropout rate of 10% at the 12-month imaging follow-up. Considering a total number of enrolled patients of n=294, a significance level of alpha=2.5% using a two-sided test, PACMAN would provide a power of more than 95% to detect the expected difference in the change in maxLCBI4mm of 193.3 between Placebo and PCSK9 if it was tested independently (see section 6.1 for achieved power in the context of the gatekeeping procedure).

- **secondary endpoint 'change in minimal cap thickness'**

For the 'change in minimal cap thickness' from baseline to 52 weeks (12 months). We assume: (i) a difference between PCSK9 arm and Placebo arm of 19.8µm for min cap thickness based on the observed difference in IBIS4 and the expected reduction in LDL-C in PACMAN (-40% in PLACEBO and -75% in PCSK9), (ii) a standard deviation of 44.8 (calculated from IBIS4);

(iii) an intracluster correlation coefficient of approximately 0.57 (estimated from IBIS4 data); (iv) m=1.59 vessels per patient (i.e. with fibroatheroma, according to PACMAN Matching Substudy), (v) 72% of the patients to show any fibroatheroma (PACMAN Matching Substudy). Considering a dropout rate of 10% at the 12-month imaging follow-up, an expected 72% of patients showing fibroatheroma, a total number of enrolled patients of n=294, a significance level of alpha=2.5% using a two-sided test, PACMAN would provide a power of 85% to detect the expected difference in the change in min. cap thickness of 19.8μm between Placebo and PCSK9 if it was tested independently (see section 6.1 for achieved power in the context of the gatekeeping procedure).

3.3. Randomization

Randomization will be performed once eligibility is confirmed (after all inclusion and exclusion criteria have been checked), written informed consent has been obtained, and after a successful baseline imaging procedure including at minimum successful IVUS of the 2 identified target vessels.

For better balance, randomization will be stratified for **study center**; use of **stable** (≥4-week) **statin treatment at presentation** vs. **no stable statin treatment**; and **STEMI** vs. **NSTEMI**. Randomization will be done in a double-blind fashion with 1:1 allocation. Allocation sequences will be based on computer-generated random numbers. These sequences were generated by an independent statistician and concealed using a central randomization system with the secuTrial EDC system. To ensure a balanced allocation of treatment and control over time, randomization lists will be generated in blocks of 2, 4, or 6 patients and to enforce concealment, block size will be generated at random. Each patient will receive one randomization number and each randomization number will be assigned to a single patient. The randomization number will be indicated on the case report form.

Each patient will be allocated to one of the following treatments in a double blind fashion:

- **Alirocumab** 150 mg Q2W SC at 1.0 ml via an autoinjector (verum PCSK9 inhibitor)
- **Placebo** Q2W SC at 1.0 ml via an autoinjector

A patient is considered randomized once randomization to IP (alirocumab or placebo) is completed. The patient has to receive the 1st IMP injection as early as possible after randomization (latest within 48 hours). Once randomized, the patient is included in the intention-to-treat (ITT) population. Study visits will occur at day 1 (randomization), Week 2, 4, 8, 12, 24, 48, 52 and 56 (section 8.1).

3.4. Blinding

All study personnel, including patients, investigators, intracoronary imaging assessors (IVUS, NIRS and OCT), study nurses, trial statistician, monitors and central data monitors will remain blinded after the assignment of the treatments. Injectors containing the drugs (**Alirocumab** or or **Placebo** injector) will only contain identifiers to allow emergency unblinding.

The trial statistician will produce blinded results (e.g. by allocating patients 1, 3, 5 etc per site as arm A and patients 2, 4, 6 etc. per site as arm B) for the initial tables. The initial tables containing the primary and secondary endpoints (see 2.1 and 2.2) are reprogrammed independently by another independent blinded statistician and a signed quality check QC documentation is filed after the results of these reprogrammed tables are compared with the tables from the trial statistician and discrepancies have been resolved.

After all queries, plausibility and validation checks have been resolved, the trial statistician will ask permission from the SC to produce all tables with the unblinded information, correctly assigning the patients to treatment **Alirocumab** or **Placebo**. The primary and secondary endpoints cannot be changed after these final tables have been produced. Note that the secuTrial EDC system will never show the real randomized arm assignments, as these are not stored within the system.

The secuTrial patient identifiers or IMP numbers will be used throughout for communication, and both identifiers do not contain the actual randomized arm assignments.

3.5. Study assessments

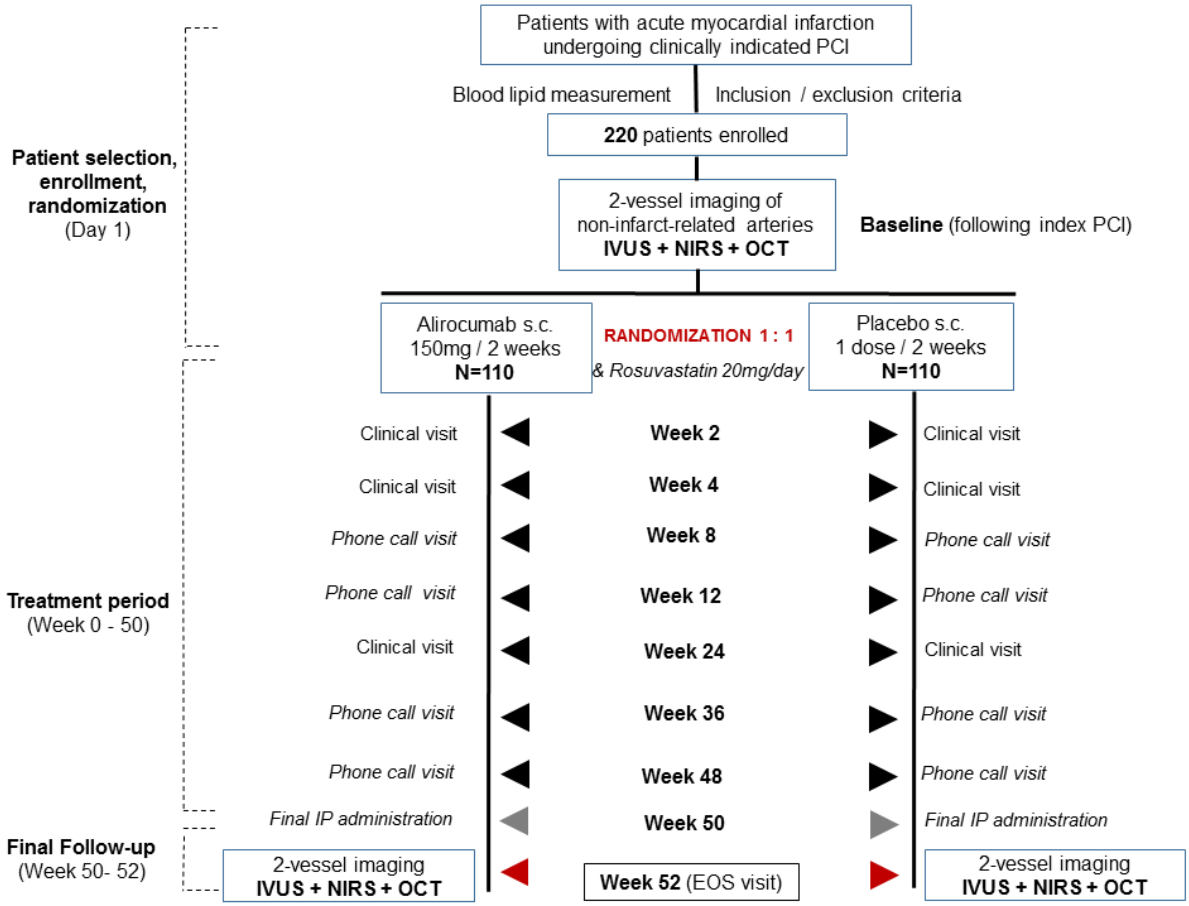
After signing the consent form, patients will be enrolled in the study. Following screening, enrollment and randomization (Day 1), the total study duration for each individual patient will amount to 52 weeks consisting of:

 A 52-week treatment period (Week 0 → Week 52) with planned follow-up and study interventions;

 The final study visit should take place at week 52 (-0/ + 14). An additional injection of the IP at week 52 shall take place to assure that the final follow-up is performed within 14 days after the last injection

The end of the study will be defined as the date when the last randomized patient completes the week 52 end-of-study (EOS) assessment.

The following figure 1 shows the visit plan for each patient:



If a patient undergoes clinically indicated repeat coronary angiography prior to the planned Week 52 visit, this will be recorded in the CRF as an intercurrent angiography. In this case, the **intracoronary imaging protocol will be allowed to be performed during the intercurrent angiography as early as 40 weeks after the baseline imaging** (Day 1) but not earlier. In case the clinically indicated coronary angiography is performed less than 40 weeks following baseline intracoronary imaging (day 1), then the patient will be asked to return for the planned follow-up imaging procedure on Week 52.

In case of intermittent revascularization of a previously imaged target segment, it will be recommended to perform IVUS and OCT of the target segment **prior to revascularization** regardless of the timing after baseline imaging, if technically and clinically feasible. The derived information will be used for the primary endpoint measures.

Patients who fulfill all inclusion criteria, meet none of the exclusion criteria, and provide signed informed consent will be enrolled in the study and undergo 2-vessel intracoronary imaging within 24 hours after completion of the clinically indicated PCI (**2-vessel imaging of non-infarct related arteries IVUS + NIRS + OCT at Baseline**). Whenever clinically reasonable, the imaging procedure shall be performed immediately after PCI. If the treating physician prefers a staged imaging procedure (e.g. due to patient discomfort), the procedure may be

performed within 24 hours after PCI. Patients with successful intracoronary imaging (defined as at minimum successful IVUS of 2 target vessels) will next undergo randomization

At the Week 50 to 52 follow-up, the primary endpoint will be assessed again by imaging (**2-vessel imaging of non-infarct related arteries IVUS + NIRS + OCT at Final Follow-up Week 50 - 52**).

See for the details of the three intracoronary imaging modalities (IVUS, NIRS and OCT) the Protocol.

4. Data management

4.1. Data export

Data are captured inside the secuTrial EDC system:

https://secutrial.insel.ch/apps/WebObjects/ST21-productive-DataCapture.woa/wa/

Data will be exported using the secuTrial data export tool:

https://secutrial.insel.ch/apps/WebObjects/ST21-productive-ExportSearchTool.woa/wa/

Data are exported as comma delimited files, and are labelled using the codebook provided by secuTrial in the same export.

The unblinded treatment assignments will be received (see 3.4. when this occurs) from the CTU Data Management. The list is password protected inside the following zipped folder:

R:\Clinical studies\430_PACMAN\10_Randomisation_Decoding_430\10_Randomisation_Decoding.zip

and the password is securely stored by CTU Data Management.

Imaging data will be received directly as text or comma delimited files or any other standardized data export, according to the specifications of the imaging software provider; and separately for each patient identifier. The imaging Core Laboratory is blinded to the patient's treatment and also to whether the images are from a Baseline or Week 50-52 follow-up visit. See for details of the Cardialysis Core Laboratory the documents provided by the CRO: Cardialysis (Westblaak 98, 3012 KM Rotterdam, The Netherlands)

Similarly, biomarker data will be received directly as text or comma delimited files or any other standardized data export, according to the specifications of the central laboratory; and separately for each patient identifier.

4.2. Data validation

The following data validation checks will be performed:

1. All tables with sample sizes per item will be checked by the Steering Committee SC for plausibility of missing data.

2. All items containing dates will be checked, particularly whether they occurred on/after the date of randomization - pre-randomization not allowed, the only exception being items from the previous medical history that can occur year(s) before the randomization.

5. Study populations

5.1. Patient flow

Only randomized patients are reported.

Whether the patient received a first and final injection (Alirocumab or Placebo) is reported in the flowchart, see for details of compliance the section **Evaluation of treatment compliance and exposure**.

Deaths are reported in the Adverse Events with date of death, confirmed in Follow-up visit as **patient died** item, and end of study.

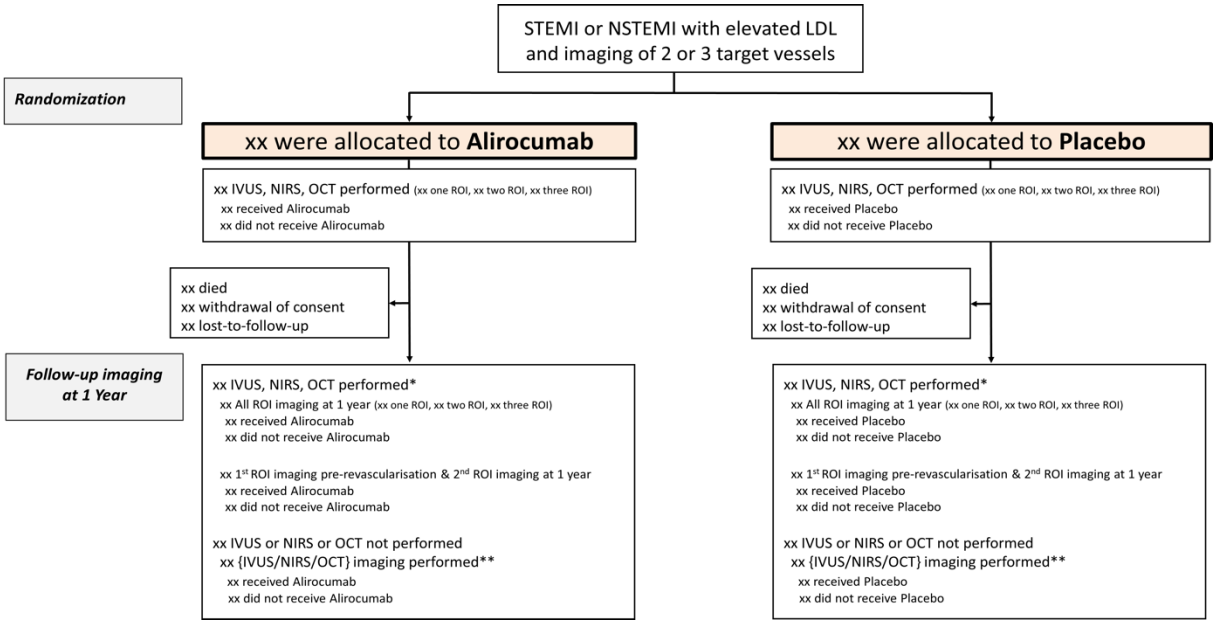
Withdrawal of consents are reported in the Follow-up visit as **patient withdrew consent/explicitly refuses follow-up**, and end of study.

Lost-to-follow up (no imaging) are reported in the Follow-up visit as **patient alive, follow-up not performed / vital status unclear**, and end of study

If applicable, **patient removed from study as determined by Study Investigator** will be reported separately in the flowchart (below patient withdrew consent).

The region of interests (ROIs) of the coronary arteries receiving the three imaging modalities are reported from the Core Labotarory, as one to three regions of interest ROI may be reported (the eCRF captures up to three ROIs but Cardialysis may discard low quality baseline or low quality follow-up 52 weeks images based on the quality assessment).

Figure 2. Flowchart



5.2. Definition of populations for analysis

All patients randomized will be analyzed for the primary and secondary endpoints by intention-to-treat.

5.3. Full analysis set (FAS)

The Full analysis set (FAS) will include all randomized patients who had a baseline and follow-up assessment of the primary endpoint (both assessments are needed to calculate percentage change in PAV). Following the intent-to-treat principle, subjects will be analyzed according to the treatment they are assigned to at the timepoint of randomization (Alirocumab vs Placebo), irrespective of whether they actually received any injection.

5.4. Per-protocol (PP)

The Per-protocol analysis set (PP) will include all randomized patients who had a baseline and follow-up assessment of the primary endpoint (both assessments are needed to calculate percentage change in PAV) and also had all the injections from randomization up to the last needed before follow-up imaging (last injection at 50 weeks, or before imaging if imaging was performed before a revascularization or if imaging was performed at an unplanned angiography between 40 and 52 weeks).

Subjects in the PP set will be analyzed according to the treatment they are assigned to at randomization (Alirocumab vs Placebo). Patients that took less than 26 injections will be excluded from the PP analysis.

5.5. Safety population

The safety population consists of all subjects in the FAS who took at least one injection of the study medication (Alirocumab or Placebo). Subjects will be analyzed according to the treatment they are assigned to at randomization unless a subject takes non-randomized study medications (i.e. the wrong injector pen containing cross-over IMP), in that case the subject will be analyzed according to the treatment actually taken.

5.6. Definition of sub-group populations in different analyses

All patients randomized who had a baseline and follow-up assessment are analysed together for all primary and secondary endpoints, no specific sub-groups are defined (except for the stratified analyses).

However, failure to conduct biomarker analyses on certain samples, e.g. because samples never arrived at the BioBank, were misplaced or otherwise not analysed due to clerical error, etc.; or failure to produce valid biomarker results (e.g. low quality of stored blood, low quality of measurement) as assessed by the Core Laboratory will reduce the sample size for certain analyses, e.g. for the **Analysis of secondary biomarker endpoints**.

6. Statistical analysis

6.1. General

All patients need IVUS performed at baseline and follow-up (52 Weeks, or earlier in case of unplanned coronary angiography between Week 40 and 52, or earlier in case of revascularization at any time between Day 1 and Week 52) to calculate the percentage change in PAV (primary endpoint), i.e. serial imaging.

Similarly all **secondary imaging endpoints** and **additional secondary imaging endpoints** need serial imaging (IVUS or NIRS or OCT as applicable), if based on a change from baseline to follow-up. If not based on a change, the follow-up imaging is sufficient.

Similarly, all secondary biomarker endpoints need serial blood analyses, i.e. comparing baseline vs Week 4, or comparing baseline vs Week 52, or comparing Week 4 (steady state) vs Week 52. If not based on a change, the follow-up blood analysis is sufficient.

Correlations are based on serial imaging or serial blood sampling (e.g. across visit comparisons), or are based on within visit comparisons (e.g. %PAV at follow-up vs secondary biomarker endpoint at follow-up).

The primary endpoint (i.e. change in PAV) and the two powered secondary endpoints (i.e. change in maxLCBI4mm and change in minimum cap thickness) will be tested separately. The resulting p-values will be interpreted using a gatekeeping procedure whereby the primary endpoint will first be tested at an alpha level=0.05. If H0 is not rejected (i.e. p-value>0.05), p-values for the two secondary endpoints will not be interpreted i.e. the two subsequent null hypotheses will be automatically accepted. If H0 of the primary endpoint is rejected, alpha will be equally split across the two secondary endpoints (alpha=0.025) using Bonferroni correction. In summary, hypothesis testing will be conducted as follows:

1) H0 for the primary endpoint ‘change in PAV’ will be rejected if significance is achieved at alpha=0.05.

2) H0 for the secondary endpoint ‘change in minimal cap thickness’ will be rejected if significance is achieved at alpha=0.025 AND if H0 for the primary endpoint was also rejected.

3) H0 for the secondary endpoint ‘change in LCBI at the 4-mm maximal segment’ will be rejected if significance is achieved at alpha=0.025 AND if H0 for the primary endpoint was also rejected.

The power to detect a difference between arms in the primary endpoint ‘change in PAV’ is 80%.

Under the condition that H0 for the primary endpoint is rejected, the power of the secondary endpoint 'change in LCBI at the 4-mm maximal segment' is 95% and the power for the secondary endpoint 'change in minimal cap thickness' is 85%.

6.2. Pooling of sites

All sites will be pooled for all analyses.

6.3. Interim analyses

Interim safety analyses will be conducted based on the reported frequency of SAE and AESI by the Data Safety Monitoring Board DSMB, not by the trial statistician.

6.4. Time-points for analysis

Time-points for analysis are Day 0 (at randomization, imaging and blood samples for biomarkers), Week 4 (blood samples for biomarkers only) and at Week 52 (imaging and blood samples for biomarkers). Imaging conducted between Day 0 and Week 52 is acceptable and will be used equivalent to a Week 52 imaging if: imaging obtained during unplanned coronary angiography between Week 40 and 52, or imaging obtained before revascularization at any time between Day 1 and Week 52).

6.5. Methods for handling missing data and drop-out

Missing data (incl. missing due to drop-outs) will be ignored for the primary and secondary imaging analyses. If requested, a multiple imputation of missing data will be conducted using chained equations, to impute the missing primary and secondary imaging endpoints inside one joint model, including as predictor variables: baseline risk factors (incl. age and gender), baseline and follow-up primary and secondary imaging endpoints (as available), time (in weeks) to last contact, number of ROIs. Hundred data-sets will be generated and model estimates will be combined using Rubin's rule.

Missing data in biomarkers will need separate handling, as measurements may not be available timely before the main publication. In general, missing data (incl. missing due to drop-outs) will be ignored for the secondary biomarker endpoints analyses. If requested, a multiple imputation of missing data will be conducted using chained equations, to impute the missing secondary biomarker endpoints, primary and secondary imaging endpoints inside one joint model, including as predictor variables: baseline risk factors (incl. age and gender), baseline and follow-up primary and secondary imaging endpoints and secondary biomarker endpoints (as available), time (in weeks) to last contact, number of ROIs. Hundred data-sets will be generated and model estimates will be combined using Rubin's rule.

6.6. Statistical analytical issues

6.6.1. Assessment of statistical assumptions

Primary, secondary and additional secondary imaging endpoints will be analysed using the appropriate linear mixed model (continuous and approximately normally distributed responses). The secondary imaging endpoints (macrophage AAE and $LCBI_{total}$) and (some or all) additional secondary imaging endpoints and (some or all) secondary biomarker endpoints are expected to have a skew distribution; if necessary, an adequate transformation will be used prior to deriving the change and estimating the p-values. Residual model fits will be explored to assess the model fit.

If no change is reported, but the follow-up Week 52 measurements in itself are reported: linear mixed model (continuous and approximately normally distributed responses) or generalized linear mixed model (for binary responses with logit-link, or counts with log-link - other links explored in case of over/under-dispersion) will be used. Residual model fits will be explored to assess the model fit.

6.6.2. Adjustments for covariates

No adjustment for covariates are intended for the primary, secondary and additional secondary imaging endpoints.

Sensitivity analyses of secondary biomarker endpoints may include as covariates the baseline biomarker endpoint, and the risk factor(s) known to increase or decrease the specific biomarker endpoint, including parameters assessed up to Week 4 for a Week 4 to Week 52 comparison.

6.6.3. Multicenter studies

The study will be conducted at 7 centers: in Switzerland (4), Austria (1), Danmark (1), the Netherlands (1), and possibly another two additional centers.

6.6.4. Multiple comparisons

No multiple comparisons are intended.

Multiple endpoint assessments are not corrected for, as formal conclusions concerning the Alirocumab vs Placebo comparison will only be made using the primary endpoint (mean difference in %PAVC change).

6.6.5. Use of efficacy subset

No separate subset is defined.

6.6.6. Active-control studies intended to show equivalence

Not applicable.

6.6.7. Examination of subgroups

Prespecified stratified analyses of the primary endpoint will be performed according to the following characteristics: age, gender, diabetes mellitus, vessel localization, statin use at baseline, LDL reduction throughout study period, baseline plaque burden, maxLCBI$_{4mm}$ at baseline, hsCRP on treatment levels.

6.6.8 Sensitivity analysis due to COVID-19

Due to the COVID-19 several patients had (or will have) a delay of several weeks before their week 52 follow-up visit. To cope with this situation, these patients will be taking additional IMPs (one IMP injection every two weeks as before). To identify a potential effect of this delay on the primary endpoint, we will perform a sensitivity analysis. To do so, we have implemented a new field in the SecuTrial database to capture whether or not a patient had a delay in its follow-up visit at 1 year specifically due to the COVID-19 (yes/no variable). We will explicitely test whether this delay had an influence on the primary endpoint as follows; we will run the same mixed-effect model as for the main analysis (see 6.6.1) but in addition to the arm as independent variable, we will also add the delay (yes/no) and the interaction between arm and delay due to COVID-19. Should this interaction be significant, we will discuss the results of the main analysis.

7. Evaluation of demographics and baseline characteristics

7.1. Baseline characteristics, Angiography and Procedure

Baseline and angiographic characterisics are shown in Tables 1 and 2. Randomization will occur after the angiography, after the quality of the IVUS, NIRS and OCT baseline assessments during the angiography has been confirmed. Consequently, no p-values will be shown for the Baseline. Medication at both baseline and follow-up are summarized in Table 3.

7.1.1. Table 1: Baseline Clinical Characteristics

	Alirocumab (N=)	**Placebo (N=)**
Age — years (±SD)	x.x ± x.x	x.x ± x.x
Male gender — no. (%)	x (x.x%)	x (x.x%)
Body mass index — kg/m^2 (±SD)	x.x ± x.x	x.x ± x.x
Family history of CAD or vascular disease — no. (%)	x (x.x%)	x (x.x%)
Peripheral arterial disease — no. (%)	x (x.x%)	x (x.x%)
Diabetes mellitus — no. (%)	x (x.x%)	x (x.x%)
Oral-treated	x (x.x%)	x (x.x%)
Insulin-treated	x (x.x%)	x (x.x%)
Arterial hypertension — no. (%)	x (x.x%)	x (x.x%)
Hypercholesterolemia — no. (%)	x (x.x%)	x (x.x%)
Active smoker — no. (%)	x (x.x%)	x (x.x%)
History of smoking — no. (%)	x (x.x%)	x (x.x%)
Previous MI — no. (%)	x (x.x%)	x (x.x%)
Previous PCI — no. (%)	x (x.x%)	x (x.x%)
Previous CABG — no. (%)	x (x.x%)	x (x.x%)
Premature CAD, cerebral or PVD — no. (%)	x (x.x%)	x (x.x%)
History of congestive heart failure— no. (%)	x (x.x%)	x (x.x%)
History of stroke — no. (%)	x (x.x%)	x (x.x%)
History of TIA — no. (%)	x (x.x%)	x (x.x%)
History of malignancy — no. (%)	x (x.x%)	x (x.x%)
Thyroid disease — no. (%)	x (x.x%)	x (x.x%)
Hyperthyroidism — no. (%)	x (x.x%)	x (x.x%)
Hypothyroidism — no. (%)	x (x.x%)	x (x.x%)
Renal Failure (GFR<60 ml/min) — no. (%)	x (x.x%)	x (x.x%)

LDL-C — mmol/L (±SD)*	x.x ± x.x	x.x ± x.x
Baseline Medications — no. (%)	x (x.x%)	x (x.x%)
Statins	x (x.x%)	x (x.x%)
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)
Ezetimibe	x (x.x%)	x (x.x%)
Fibrates	x (x.x%)	x (x.x%)
Niacin	x (x.x%)	x (x.x%)
Resins	x (x.x%)	x (x.x%)

Data expressed as n (%) or means±standard deviations.

CAD: coronary artery disease; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; PVD: peripheral vascular disease; TIA: transient ischemic attack.

*Measured on-site before randomization.

7.1.2. Table 2: Angiographic and Procedural Characteristics

	Alirocumab (N=)	**Placebo (N=)**
Total contrast administered — cc (±SD)	x.x ± x.x	x.x ± x.x
Procedure time — minutes (±SD)	x.x ± x.x	x.x ± x.x
Access site		
Radial — no. (%)	x (x.x%)	x (x.x%)
Femoral— no. (%)	x (x.x%)	x (x.x%)
Acute coronary syndrome — no. (%)	x (x.x%)	x (x.x%)
Non ST-elevation MI	x (x.x%)	x (x.x%)
ST-elevation MI	x (x.x%)	x (x.x%)
Time of symptom onset <24h — no. (%)	x (x.x%)	x (x.x%)
Left ventricular ejection fraction — % (±SD)	x.x ± x.x	x.x ± x.x
Nr of lesions	(N=)	(N=)
No. of treated lesions per patient — no (±SD)	x.x ± x.x	x.x ± x.x
Vessel location per lesion — no. (%)		
Left anterior descending artery	x (x.x%)	x (x.x%)
Left circumflex artery	x (x.x%)	x (x.x%)
Right coronary artery	x (x.x%)	x (x.x%)

Restenotic lesion — no. (%)	x (x.x%)	x (x.x%)
Total occlusion — no. (%)	x (x.x%)	x (x.x%)
Chronic total occlusion — no. (%)	x (x.x%)	x (x.x%)
Type of treatment per lesion — no. (%)		
Stent implantation	x (x.x%)	x (x.x%)
Balloon angioplasty only	x (x.x%)	x (x.x%)
Failed intervention	x (x.x%)	x (x.x%)
Conservative treatment	x (x.x%)	x (x.x%)
Number of stents per lesion – no (±SD)	x.x ± x.x	x.x ± x.x
Type of stent per lesion – (%)		
Drug-eluting stent	x (x.x%)	x (x.x%)
Bare-metal stent	x (x.x%)	x (x.x%)
Bioresorbable scaffold	x (x.x%)	x (x.x%)
Direct stenting per lesion — no. (%)	x (x.x%)	x (x.x%)
Total stent length per lesion — mm (±SD)	x.x ± x.x	x.x ± x.x
Maximum stent diameter per lesion — mm (±SD)	x.x ± x.x	x.x ± x.x
Bifurcation treatment per lesion — no. (%)	x (x.x%)	x (x.x%)
Overlapping stents or scaffolds per lesion — no. (%)	x (x.x%)	x (x.x%)
Post-dilatation per lesion — no. (%)	x (x.x%)	x (x.x%)
Residual stenosis per lesion — % (±SD)	x.x ± x.x	x.x ± x.x
Baseline TIMI flow per lesion — no. (%)		
0 or 1	x (x.x%)	x (x.x%)
2	x (x.x%)	x (x.x%)
3	x (x.x%)	x (x.x%)
TIMI Flow post intervention per lesion — no. (%)		
0 or 1	x (x.x%)	x (x.x%)
2	x (x.x%)	x (x.x%)
3	x (x.x%)	x (x.x%)

Data expressed as n (%) or means±standard deviations.

7.2. Table 3: Medications and General IMP compliance

	Alirocumab (N=)	Placebo (N=)	p-value
During primary intervention — no. (%)			
Aspirin*	x (x.x%)	x (x.x%)	x.xx
Clopidogrel*	x (x.x%)	x (x.x%)	x.xx
Prasugrel*	x (x.x%)	x (x.x%)	x.xx
Ticagrelor*	x (x.x%)	x (x.x%)	x.xx
Unfractionated Heparin	x (x.x%)	x (x.x%)	x.xx
Low-molecular-weight heparin (LMWH)	x (x.x%)	x (x.x%)	x.xx
Glycoprotein IIb/IIIa inhibitors	x (x.x%)	x (x.x%)	x.xx
Thrombolytic therapy	x (x.x%)	x (x.x%)	x.xx
Injected with IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
At discharge — no. (%)			
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx

Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx
At 2 weeks of follow-up — no. (%)			
Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx

Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx
At 4 weeks of follow-up — no. (%)			
Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx

40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx
At 8 weeks of follow-up — no. (%)			
Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx

Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx
At 12 weeks of follow-up — no. (%)			
Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx

10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx

At 24 weeks of follow-up — no. (%)

Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx

Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx
At 36 weeks of follow-up — no. (%)			
Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx

Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx
At 48 weeks of follow-up — no. (%)			
Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx
Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx

ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx
At 50 weeks of follow-up — no. (%)			
Injected with all doses of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Injected with final dose of IMP — no. (%)	x (x.x%)	x (x.x%)	x.xx
Statins	x (x.x%)	x (x.x%)	x.xx
Rosuvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Atorvastatin	x (x.x%)	x (x.x%)	x.xx
10mg/day	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
Fluvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Pravastatin	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
80mg/day	x (x.x%)	x (x.x%)	x.xx
Simvastatin	x (x.x%)	x (x.x%)	x.xx
20mg/day	x (x.x%)	x (x.x%)	x.xx
40mg/day	x (x.x%)	x (x.x%)	x.xx
Other lipid lowering drugs (any)	x (x.x%)	x (x.x%)	x.xx
Ezetimibe	x (x.x%)	x (x.x%)	x.xx
Fibrates	x (x.x%)	x (x.x%)	x.xx
Niacin	x (x.x%)	x (x.x%)	x.xx
Resins	x (x.x%)	x (x.x%)	x.xx
Aspirin	x (x.x%)	x (x.x%)	x.xx
Clopidogrel	x (x.x%)	x (x.x%)	x.xx

Ticagrelor	x (x.x%)	x (x.x%)	x.xx
Prasugrel	x (x.x%)	x (x.x%)	x.xx
Dipyridamole	x (x.x%)	x (x.x%)	x.xx
Non-Vit-K oral anticoagulants (NOAC)	x (x.x%)	x (x.x%)	x.xx
Vitamin K antagonists	x (x.x%)	x (x.x%)	x.xx
ACE inhibitor	x (x.x%)	x (x.x%)	x.xx
ATII antagonist	x (x.x%)	x (x.x%)	x.xx
Betablocker	x (x.x%)	x (x.x%)	x.xx
Amiodarone	x (x.x%)	x (x.x%)	x.xx
Antiarrhythmic**	x (x.x%)	x (x.x%)	x.xx
Ca-antagonist	x (x.x%)	x (x.x%)	x.xx
Digoxin	x (x.x%)	x (x.x%)	x.xx
Oral antidiabetics	x (x.x%)	x (x.x%)	x.xx
Insulin	x (x.x%)	x (x.x%)	x.xx
NSAID	x (x.x%)	x (x.x%)	x.xx
PPI	x (x.x%)	x (x.x%)	x.xx
Immunosuppressive	x (x.x%)	x (x.x%)	x.xx
Antiretroviral therapy	x (x.x%)	x (x.x%)	x.xx
Hormonotherapy	x (x.x%)	x (x.x%)	x.xx
Antidepressant	x (x.x%)	x (x.x%)	x.xx

Data expressed as n (%) and p-values are from Fisher's tests.

*Loading or already on daily dosage.

**Other than betablocker and amiodarone.

NSAID: non-steroidal antiinflammatory drugs; PPI: proton-pum inhibitor

See for details injections with IMP: Supplementary Material

8. Evaluation of treatment compliance and exposure

8.1. Compliance to study drug and treatment

8.1.1. Compliance to study drug

Compliance is reported in the medication Table (Table 3, see above). Whether and when the patient received the randomized injection (containing either Alirocumab or Placebo) is captured for each visit with the item:

Double blind injection of study drug at study site (baseline, recorded in Discharge Medication eCRF, as injection is also allowed after the PCI)

Has patient taken all doses of study drug as planned up to current visit (at each follow-up by either telephone call or during clinical visit, recorded in Follow-up Medication eCRF):

- Compliant are considered patients who answered **yes**, or answered **no** with **One or more injections delayed by less than or equal to 7 days and scheduled dose administered**. Considering the wash-out time, the latter patient are regarded as sufficiently compliant.
- Not compliant are considered patients who answered **no** with: **One or more injections delayed by more than 7 days and scheduled dose not administered** or **Completely stopped taking the study drug**.
- **Completely stopped taking the study drug** answer is attributed to the visit and all visits beyond until alive at end of study (restarts are not expected).

8.1.2. Measurement of treatment compliance

Table 4 shows the percentage of injections taken per patient with respect to the total number of injections needed per visit (number of 2-week periods including one injection at randomization). If the patient died, the total number of injections needed per visit will be established before the date of death.

Table 4: Details of IMP injection compliance

	Alirocumab (N=xx)	Placebo (N=xx)	Mean difference (95% CI)	p-value
Injected with all doses of IMP until follow-up IVUS* — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Total percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
Injected with all doses of IMP up to and including 50 weeks — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	
At week 2				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 4				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 8				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 12				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 24				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 36				

Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 40				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 48				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
At week 50				
Percentage of injections IMP per patient — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x% - x.x%)	x.xx
One or more injections delayed ≤7 days — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
One or more injections delayed >7 days or skipped — no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx
Cumulative IMP discontinuation— no. (%)	x (x.x%)	x (x.x%)	x (x.x% - x.x%)	x.xx

*Until primary endpoint assessment: which is up to 50 weeks, or up to early IVUS follow-up imaging at revascularisation or coronary angiography.

On schedule or One or more injections delayed by less than or equal to 7 days with a scheduled dose administered are considered both as compliant.

Two-sided p-values are Fischer's exact, Mann-Whitney or t-tests, as appropriate.

Reported are compliance during the period since the last visit, except discontinuation which is cumulative.

8.2. Exposure to study drug

8.2.1. Extent of exposure

Treatment with the investigational product (IP) (Alirocumab or Placebo) will start on Day 1 (Week 0) and finish on Week 50.

Patient get an injection with the IP every second week, starting at Week 0 (Day 1 at randomization).

This treatment will be on top of evidence-based optimal medical treatment, including rosuvastatin 20mg/day throughout the entire study period of 52 weeks for all patients.

8.2.2. Duration of exposure

From Day 1 Week 0 (first injection) to Week 50 (last injection).

 A 50-week treatment period (Week 0 → Week 50) with planned follow-up and study interventions;

 A 2-week period (Week 50 → Week 52 (+0 days/ -7 days) between completion of the treatment period and final follow-up.

From Day 1 Week 0 (first injection) to Week 52 (extra injection), in case:

 it is not possible to schedule the final visit on week 52(+0 days/-7 days), a maximal delay of 14 days may be acceptable (i.e. 52 weeks +14 days). In this case, an additional injection of the IP at week 52 shall take place to assure that the final follow-up is performed within 14 days after the last injection.

8.2.3. Dose of exposure

Patients will receive a single dose of 150mg alirocumab every second week, starting at Week 0 (Day 1) until and including Week 50 (last injection).

8.2.4. Drug concentrations

Alirocumab (PCKS9 inhibitor) will be administered as a sterile solution in a single-use, disposable, prefilled autoinjector pen for fixed-dose subcutaneous injection. The prefilled pen contains 1.0 ml volume of 150mg alirocumab in histidine, pH 6.0, polysorbate 20, and sucrose.

Placebo will be prepared in the same formulation as alirocumab without the addition of protein and will be administered in an identical prefilled pen containing 1.0 ml of deliverable volume. Both preparations will be manufactured and packaged by Sanofi / Regeneron, and will be stored refrigerated and protected from light.

8.2.5. Drug injection

A prefilled pen training guide (auto-injector training guide) will be provided to the sites and instructions for use (auto-injector for use) will be provided to the patient. The Investigational Product IP (boxes with autoinjector pens containing either Alirocumab or Placebo) will be kept outside the refrigerator at room temperature for about 30 to 40 minutes immediately prior to administration. Each administration will consist of 1.0 mL SC injection in the abdomen, thigh, or outer area of upper arm (deltoid region). If another concomitant drug is being injected the patient should be advised to use different injection sites. The used prefilled pens will be discarded in a sharp container which will be provided to patients.

8.2.6. Drug dose adjustment and withdrawal

There will be no dose adjustment of the IP in this study. If in the judgment of the investigator a patient cannot tolerate the IP, administration will be discontinued but the patient will be asked to return for all protocol-required visits and study procedures until completion of the study. The steering committee should be contacted prior to discontinuation of the IP. Reports from the central laboratory after planned blood sampling at Week 4 will be reviewed. A decision to withdraw the IP may be made on the basis of laboratory results (elevated levels of liver enzymes or CK levels).

9. Imaging procedures

9.1. Imaging of coronary arteries

Following completion of coronary angiography and of the qualifying PCI procedure on Day 1, patients will undergo intracoronary imaging with IVUS, NIRS and OCT for determination of detailed baseline plaque characteristics preferably immediately after PCI and latest within 24 hours after PCI (baseline imaging).

Patients will be readmitted at 52 weeks for catheterization and repeat intracoronary imaging using IVUS, NIRS and OCT of the same regions of interest (ROIs or “target segments”) of the two proximal non-infarct-related arteries (“target vessels”) imaged at baseline (follow-up at 1 year imaging).

In case the patient needs revascularization of two imaging target ROIs between Day 1 and 52 weeks: IVUS, NIRS and OCT will be performed on these lesions, and these images will be used to assess the primary and secondary imaging endpoints.

In case the patient needs revascularization of one imaging ROI between Day 1 and 52 weeks: IVUS, NIRS and OCT will be performed on this ROI, and these images will be used to assess the primary and secondary imaging endpoints for the first lesion. The second ROI will receive imaging at 52 weeks, and the analyses at this time-point will be used to assess the primary and secondary imaging endpoints for the second lesion.

In case the patient undergoes clinically indicated repeat coronary angiography between Week 40 and 52 weeks: IVUS, NIRS and OCT will be performed on these ROIs, and these images will be used to assess the primary and secondary imaging endpoints.

In case the clinically indicated coronary angiography is performed less than 40 weeks following baseline intracoronary imaging (day 1), then the patient will be asked to return for the planned follow-up imaging procedure on Week 52.

9.2. IVUS imaging

The imaging procedure should always start with the IVUS investigation (primary endpoint). IVUS of the proximal segments of two non-infarct related coronary arteries will be performed. The aim is to acquire a segment between two landmarks that exceeds 50mm. The regions of interest (ROIs) will be selected between two anatomical landmarks (distal: side-branch; proximal: left main bifurcation and ostium of the RCA). The combined NIRS-IVUS catheter will be advanced beyond the distal landmark and a motorized pullback at a speed of 0.5mm/second will be performed after the administration of 100-200 µg intracoronary nitroglycerine. Images will be acquired and recorded on a DVD. Recordings will be sent to an independent Core Laboratory (Cardialysis, Rotterdam, NL) for quality control; only if pre-specified criteria are met will the runs be considered for analysis. The investigator will be

provided with a feedback with regards to the pullback quality. IVUS analysis will be performed by Cardialysis (Rotterdam, NL).

9.3. NIRS imaging

Using the same protocol as for IVUS imaging, NIRS will be performed at baseline and at follow-up 52 weeks, using a 3.2-F NIRS catheter (InfraReDx, Inc.).

Spectroscopic information obtained from raw spectra will be transformed into a probability of lipid core that will be mapped to a red-to-yellow color scale, with the low probability of lipid shown as red and the high probability of lipid shown as yellow. The measurement of the probability of lipid core is displayed as an NIRS 'chemogram', a color-coded map of the location and intensity of lipid core, with the X-axis indicating the pullback position in millimeters (every 0.1 mm) and the Y-axis indicating the circumferential position. Analyses will be performed offline using the Matlab-based software. Presence of lipid core burden will be assessed and quantified by the lipid core burden index (LCBI), a quantitative summary metric of lipid core presence in a given longitudinal region. All NIRS endpoints are summarized in the table below (Table 5). NIRS analysis will be performed by Cardialysis (Rotterdam, NL).

9.4. OCT imaging

OCT imaging will be performed using a frequency-domain OCT system. ILUMIEN OPTIS (St. Jude Medical, St. Paul, MN, USA) system is recommended for co-registration of angiography and OCT, but its use is not mandatory.

Lipid will be defined as a diffusely bordered signal-poor region with signal attenuation by the overlying signal-rich layer, and lipid-rich plaque as a plaque with lipid >90° of the circumference. For lipid-rich plaque, we will determine lipid arc and lipid-core length. Lipid arc will be measured every 1 mm within a lipid-rich plaque, and mean and maximum values will be recorded. Lipid-core length will be defined as the length of plaque with >90° of lipid and measured on the longitudinal view. Macrophage related data from two matched regions of interest (ROI) per patient will be acquired at baseline and at follow-up. The Angular Extension of macrophages is measured in degrees for each OCT frame. Its value is 0 for frames that do not contain any macrophages detectable by OCT. If disjoint regions of the frame contour contain macrophages, the sum of the corresponding angles is taken. A single quantitative summary metric per ROI for the accumulation of macrophages, the Average Angular Extension of macrophages (AAE), is obtained by taking the average over Angular Extension value from all frames of a ROI, including those where Angular Extension = 0. All OCT endpoints are summarized in the table 5 below. OCT analysis will be performed by the Inselspital Core Lab (Bern, CH). OCT pullbacks will be blinded (patient ID, timepoint and all identifying information will be blinded) by the CTU Bern.

Table 5: IVUS, NIRS and OCT endpoints

	Alirocumab (N=)	Placebo (N=)	Mean difference (95% CI)	p-value
IVUS performed at baseline and follow-up	n =	n =		
Total number of ROIs — no.	n =	n =		
%PAV at baseline — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	
%PAV at follow-up — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
%PAV change — % (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Total atheroma volume at baseline — mm^3 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Total atheroma volume at follow-up — mm^3 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Total atheroma volume change — mm^3 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Normalized total atheroma volume at baseline — mm^3 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Normalized total atheroma volume (mm^3) at follow-up — mm^3 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Normalized total atheroma volume change — mm^3 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average atheroma area at baseline — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average atheroma area at follow-up — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average atheroma area change — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average lumen area at baseline — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average lumen area at follow-up — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average lumen area change — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average vesse area at baseline — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average vessel area at follow-up — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average vessel area change — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
NIRS performed at baseline and follow-up	n =	n =		
Total number of ROIs — no.	n =	n =		
LCBI total at baseline — n (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	
LCBI total at follow-up — n (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
LCBI total change — n (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
$MaxLCBI_{4mm}$ at baseline — index (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
$MaxLCBI_{4mm}$ at follow-up — index (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
$MaxLCBI_{4mm}$ change	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
OCT performed at baseline and follow-up	n =	n =		
Total number of ROIs — no.	n =	n =		
Macrophage at baseline — % of frames (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	
Macrophage at follow-up — % of frames (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Macrophage change — % of frames (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Macrophage angleat baseline — max over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Macrophage angle at follow-up — max over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Macrophage angle change — max over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Macrophage angle at baseline — mean over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Macrophage angle at follow-up — mean over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Macrophage angle change — mean over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx

Minimum cap thickness at baseline — µm (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Minimum cap thickness at follow-up — µm (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Minimum cap thickness change — µm (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Mean cap thickness at baseline — µm (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Mean cap thickness at follow-up — µm (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Mean cap thickness change — µm (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Lipidic arc at baseline — max over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Lipidic arc at follow-up — max over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Lipidic arc change — max over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Lipidic arc at baseline — mean over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Lipidic arc at follow-up — mean over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Lipidic arc change — mean over frames ° (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average lumen area at baseline — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average lumen area at follow-up — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Average lumen area change — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Minimum lumen area at baseline — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Minimum lumen area at follow-up — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx
Minimum lumen area change — mm^2 (±SD)	x.x ± x.x	x.x ± x.x	x.x (x.x - x.x)	x.xx

LCBI total ranges from 0 to 1000
Two-sided p-values are from linear mixed models (patient as random intercept).

10. Evaluation of efficacy parameters

Primary analyses will be based on the intention to treat principle (ITT). This is a superiority trial and two-sided p-value will be reported. Only vessels with baseline and follow-up measurement available will be analyzed for the primary and secondary imaging endpoints and biomarker endpoints.

10.1. Analysis of primary, secondary, and other efficacy endpoints

10.1.1. Analysis of primary imaging endpoint

IVUS intracoronary imaging analyses will be performed in accordance with current recommended standards.

The arterial lumen and external elastic membrane (EEM) borders will be segmented from digitized end-diastolic IVUS images. The primary IVUS-derived parameter will be **percent atheroma volume** (**PAV**) according to the following equation:

$PAV = [\Sigma(EEM_{CSA} – Lumen_{CSA}) / \Sigma EEM_{CSA}]x100$

where EEM_{CSA} is the external elastic membrane cross-sectional area and $Lumen_{CSA}$ is the luminal cross sectional area. For each region of interest (ROI), the change in PAV between baseline and follow-up will be computed. Matching the same segments between baseline and follow-up pullbacks will be based on the anatomical location of readily visible IVUS-derived landmarks (side branches.

10.1.2. Analysis of secondary imaging endpoints

NIRS spectroscopic information will be transformed into a probability of lipid core, see for more details the Protocol:

Presence of **lipid core burden** will be assessed and quantified by the lipid core burden index (**LCBI**), a quantitative summary metric of lipid core presence in a given longitudinal region obtained during NIRS intracoronary imaging analyses.

LCBI is computed as the fraction of valid pixels within the study region that exceed a lipid-core plaque (LCP) probability of 0.6, multiplied by 1000.Thus, LCBI is measured on a scale from 0 to 1000. For each vessel, we will calculate the LCBI over the total length of the ROI ($LCBI_{total}$) and also for the 4-mm region with maximum LCBI from any 4-mm segment within the ROI ($maxLCBI_{4mm}$). The secondary endpoint for the present study will be the change in $LCBI_{total}$ between baseline and follow-up investigation.

OCT intracoronary imaging analyses will be performed using a frequency-domain OCT system.

Macrophages will be defined as signal-rich, distinct or confluent structures causing strong attenuation and shadowing of underlying structures. Shadows are sharply delineated laterally, following the direction of emitted light.

Fibrous cap thickness will be assessed using a dedicated cap measurement program. Fibrous cap thickness will be measured using a previously validated, highly reproducible, semi-automated method as described in Radu et al. (*Variability in the measurement of minimum fibrous cap thickness and reproducibility of fibroatheroma classification by optical coherence tomography using manual versus semi-automatic assessment*, Eurointervention 12 e987-997, 2016).

10.1.3. Analysis of additional secondary imaging endpoints

 Change in maximum LCBI in any 4-mm segment (maxLCBI4mm) as determined by NIRS.

See the LCBI assessment described above: it is the maximum of LCBI.

 Change in minimal and fibrous mean cap thickness as determined by OCT

See the fibrous cap thickness assessment described above: it is the minimum of fibrous cap thickness, and respectively, the mean of fibrous cap thickness.

 Change in Average Angular Extension (AAE) of macrophages as determined by OCT, between baseline and 12-month follow-up from matched ROI.

 Change in normalized total atheroma volume (NTAV) between baseline and follow-up as determined by IVUS and calculated as average atheroma area*median(ROI length), where the median was taken over baseline and follow-up vessels.

 Plaque classification was performed according to international consensus statement (Tearney GJ, Regar E, Akasaka T, Adriaenssens T, Barlis P, Bezerra HG. *Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: a report from the International Working Group for Intravascular Optical Coherence Tomography Standardization and Validation*. *J Am Coll Cardiol* 2012;**59**:1058-1072, 2016).

 Fibroatheroma (FA) was defined as plaque with evidence of lipid-pool >90° and no lateral delineation. OCT-defined TCFA was a FA with minimum FCT (FCTmin) ≤ 65μm, whereas a thin-cap FA (ThCFA) was a FA with FCTmin >65μm. Fibrocalcific plaque was defined by evidence of calcification >90°. Fibrous plaque was defined by high backscattering and homogeneous OCT signal and was any plaque not meeting either FA or fibrocalcific plaque definitions

Change in plaque type will be described in table 6.

Table 6: plaque type change between baseline and follow-up

		Alirocumab					
	Baseline		**Follow-up**				
		Total	TCFA	ThCFA	Fibrous plaque	Fibrocalcific plaque	Resolved
Total		x lesions	xx	xx	xx	xx	xx

TCFA	xx (x.x %)	xx	xx	xx	xx	xx
ThCFA	xx (x.x %)	xx	xx	xx	xx	xx
Fibrous plaque	xx (x.x %)	xx	xx	xx	xx	xx
Fibrocalcific plaque	xx (x.x %)	xx	xx	xx	xx	xx
No lesion	xx (x.x %)	xx	xx	xx	xx	xx

Placebo

Baseline		**Follow-up**				
	Total	TCFA	ThCFA	Fibrous plaque	Fibrocalcific plaque	Resolved
Total	X lesions	xx	xx	xx	xx	xx
TCFA	xx (x.x %)	xx	xx	xx	xx	xx
ThCFA	xx (x.x %)	xx	xx	xx	xx	xx
Fibrous plaque	xx (x.x %)	xx	xx	xx	xx	xx
Fibrocalcific plaque	xx (x.x %)	xx	xx	xx	xx	xx
No lesion	xx (x.x %)	xx	xx	xx	xx	xx

Values are number of lesions (%). TCFA, thin cap fibro-atheroma; ThCFA, thick cap fibro-atheroma

10.1.4. Analysis of secondary biomarker endpoints

Levels of change in measured biomarkers will be compared Alirocumab vs Placebo. Levels of measured biomarkers will be correlated with coronary percent atheroma volume progression/regression by IVUS, changes in lipid content by NIRS, and changes in macrophage accumulations by OCT between baseline (Day 1) and follow-up (Week 52):

 Change in LDL-cholesterol, hs-CRP, hs-TnT and NT-pro-BNP, total-C, LDL-C (Friedewald equation), HDL-C, triglycerides, non-HDL-C, measured LDL-C (beta quantification), Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, Lp(a), TNFa, IL1b, IL-6, MPO, cystatine, SIRT1, SIRT6, PCSK9 levels, DNAase activity using (Neutrophil extracellular trap [NET]) between baseline (Week 0) and **Week 52**.

As substantial noise in many biomarkers is expected at baseline due to the qualifying diagnosis of myocardial infarction (unlikely to reflect baseline properties of non-culprit coronary arteries), analysis will also focus on biomarker levels at Week 4 (steady-state condition). This will allow us to collect biomarker data in a quiescent baseline status after the qualifying event. Therefore,

levels of change in measured biomarkers will be compared Alirocumab vs Placebo. Levels of measured biomarkers will be correlated with coronary percent atheroma volume progression/regression by IVUS, changes in lipid content by NIRS, and changes in macrophage accumulations by OCT between baseline (Day 1) and follow-up (Week 4):

 Change in LDL-cholesterol, hs-CRP, hs-TnT and NT-pro-BNP, total-C, LDL-C (Friedewald equation), HDL-C, triglycerides, non-HDL-C, measured LDL-C (beta quantification), Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, Lp(a), TNFa, IL1b, IL-6, MPO, cystatine, SIRT1, SIRT6, PCSK9 levels, DNAase activity using (Neutrophil extracellular trap [NET]) between baseline (Week 0) and **Week 4**.

Additionally, levels of biomarkers assessed will be correlated with imaging parameters (IVUS, NIRS or OCT):

 Association between levels of biomarkers, including NETs, and changes in plaque characteristics as described in the primary and secondary imaging endpoints.

10.1.5. Analysis of secondary clinical endpoints

The following clinical endpoints will be adjudicated by a Clinical Event Committee CEC, and reported based on the CEC decision (Table 7):

 Death

 Cardiac death

The definition of cardiac death includes any death due to immediate cardiac cause, procedure-related deaths, and death of unknown cause.

 Myocardial infarction

 Any coronary revascularization

 Stroke, transient ischemic attack

Table 7: Secondary clinical endpoints at 52 weeks after randomization

	Alirocumab (N=xx)	Placebo (N=xx)	Rate Ratio [Alirocumab/Placebo] (95% CI)	p-value
All-cause Death	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Cardiac death	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Myocardial infarction	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Coronary revascularisation	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx

Cerebrovascular Event	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Transient ischemic attack	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Stroke	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx

Number of events and percentages are reported. Rate ratios are estimated using the Mantel-Cox method with two-sided p-values from log-rank test. All events were censored beyond 365 days.

10.2. Method for analysis of efficacy endpoints

10.2.1. Binary data

Binary data will be analysed with logistic regression with the treatment arm as fixed effect. Binary data of imaging endpoints will be analyzed with generalized linear mixed models with a logit link, where the treatment arm represents the fixed effect and patient identifier is included as random intercept to account for the non-independence of endpoints measured on the same patient. Other link functions will be explored in case of over- or underdispersion (e.g. zero-inflation).

10.2.2. Count data

Count data will be analysed with poisson regression with the treatment arm as fixed effect. Count data of imaging endpoints will be analyzed with generalized linear mixed models with a log-link where the treatment arm represents the fixed effect and patient identifier is included as random intercept to account for the non-independence of endpoints measured on the same patient. Other link functions will be explored in case of over- or underdispersion (e.g. zero-inflation).

10.2.3. Continuous scale data

The primary endpoint is defined at vessel level (matched ROI within vessels) and will be analyzed with linear mixed models where the treatment arm represents the fixed effect and patient identifier is included as random intercept to account for the non-independence of endpoints measured on the same patient. Subgroups will be analysed separately (see **Examination of subgroups**), the interaction p-value will be derived from a full-factorial linear mixed model and reported if the estimate converges (i.e. depending on the sample size per subgroup, as zero or low sample sizes may lead to non-convergence).

The primary endpoint, change in PAV, is expected to be close to normally distributed, hence transformation would not be necessary. Superiority of the active treatment will be declared if

the mean change in PAV is larger than the mean of the placebo arm and if the corresponding p-value is ≤0.05.

The secondary endpoints (macrophage AAE and $LCBI_{total}$) are expected to have a skew distribution; if necessary, an adequate transformation will be used prior to deriving the change and estimating the p-values.

Other continuous endpoints will be analyzed with linear models where the treatment arm represents the fixed effect. Other continuous endpoints of imaging endpoints will be analyzed with linear mixed models where the treatment arm represents the fixed effect and patient identifier is included as random intercept to account for the non-independence of endpoints measured on the same patient.

A sensitivity analysis for patients with missing data will be conducted and baseline characteristics will be compared with those of patients with complete data.

10.2.4. Time-to-event data

Secondary clinical endpoints will be reported as counts of first event of each event type and percentage of all patients randomized. Event rates will compared using Mantel-Cox's log-rank test with rate ratios (95% confidence intervals) reported.

10.2.5. Ordinal scales and non-ordered scales data

Ordinal scale data will be analysed with ordinal regression with the treatment arm as fixed effect. The residuals of the model will be inspected and if they appear not well balanced, a multinomial regression will be conducted instead.

Count data of imaging endpoints will be analyzed with generalized linear mixed models with a log-link where the treatment arm represents the fixed effect and patient identifier is included as random intercept to account for the non-independence of endpoints measured on the same patient. The residuals of the model will be inspected and if they appear not well balanced, a multinomial regression will be conducted instead.

11. Evaluation of safety parameters

The primary objective is to evaluate adverse events in patients treated with the PCSK9 inhibitor alirocumab. Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), product complaints, laboratory data.

11.1. Adverse events

11.1.1. Brief summary of adverse events

Adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) are collected.

The following AESI are defined:

Increase in ALT

ALT >3 x ULN.

Allergic events

Allergic drug reactions and/or local injection site reactions deemed to be allergic by the Investigator (or have an allergic component), that require consultation with another physician for further evaluation of hypersensitivity/allergy as per the Investigator's medical judgment should be reported as an AESI.

Pregnancy

Pregnancy occurring in a female patient during the study or within 70 days following the last dose of study drug. - Pregnancy will be recorded as AESI in all cases. Pregnancy will be qualified as an SAE only if it fulfils one or more SAE criteria. - In the event of pregnancy of a female patient included in the study, study product should be discontinued. - The follow-up of the pregnancy will be mandatory until the outcome has been determined.

Symptomatic overdose

An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least twice of the intended dose within the intended therapeutic interval (i.e., 2 or more injections are administered in <7 calendar days), to be reported using the Term "symptomatic OVERDOSE (accidental or intentional), indicating the circumstance in parentheses (e.g., "symptomatic overdose [accidental]" or "symptomatic overdose [intentional]"). The patient should be monitored and appropriate symptomatic treatment instituted. - The circumstances of the overdose should be clearly specified in the verbatim and symptoms, if any, entered on separate AE/SAE forms. - Of note, asymptomatic overdose should be reported as a standard AE.

Neurologic events

Neurologic events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI. If the event does not require additional examinations/procedures and/or referral to a specialist, it should be reported as a standard AE.

Neurocognitive events

All neurocognitive events will be considered as AESI.

11.1.2. Display of adverse events

The number of adverse events per treatment arm will be reported in Table 8 and Alirucomab vs Placebo with be compared using rate ratios (95% confidence interval) from Poisson regression with the time to end of study as the offset.

Table 8: Adverse events of special interest at 52 weeks after randomization

	Alirocumab (N=xx)	Placebo (N=xx)	Rate Ratio [Alirocumab/Placebo] (95% CI)	p-value
Neurocognitive events	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
SAE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
AE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
ALT increase	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
SAE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
AE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Symptomatic overdose	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
SAE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
AE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
General allergic reaction	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
SAE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
AE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Local injection site reaction	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
SAE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
AE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
Pregnancy	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
(Serious) Adverse event other than any of the above	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
SAE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx
AE only	x (xx%)	x (xx%)	x.x (x.x - x.x)	x.xx

Number of events and percentages are reported. Rate ratios are estimated using Poisson regression with time to study end as offset (censored at 365 days), with two-sided p-values. All events were censored beyond 365 days.

SAE: serious adverse event; AE: adverse event.

11.1.3. Analysis of adverse events

The number of adverse events per treatment arm will be reported in the Supplementary Material and compared Alirucomab vs Placebo with rate ratios (95% confidence interval) from Poisson regression with the time to end of study as the offset.

11.1.4. Listing of adverse events by patient

Listing of adverse events by patient or case histories will be provided from the eCRF on request.

11.1.5. Deaths, serious adverse events, and significant other adverse events

See **Analysis of secondary clinical endpoints**.

11.1.6. Analysis of deaths, serious adverse events, and significant other adverse events

See **Analysis of secondary clinical endpoints**.

11.2. Clinical laboratory evaluations

Baseline laboratory values will be measured in local labs at each participating center and will include **hematocrit**, **hemoglobin**, lipid values (**total cholesterol**, **LDL-C**, **HDL-C**, **triglycerides**), **glucose**, liver panel (**ALT**, **AST ALP**, **total bilirubin**) and **CK** levels. A blood sample for rapid determination of **LDL-C** levels (study inclusion criterion) will be drawn among potential study candidates ("baseline blood draw #1"). If eligibility with respect to LDL-C levels is confirmed and the patient is enrolled in the study (section 4.1), a subsequent blood draw ("baseline blood draw #2") will be made for measurement for all other variables listed above at the local lab of the participating center. During the same blood draw, samples will be obtained that will be transferred to a dedicated biobank for specific subsequent measurements (see **Analysis of secondary biomarker endpoints**). To avoid patient discomfort related to consecutive blood draws, blood samples for "blood draw #1 and #2" will be drawn from venous catheters that are placed in patients with acute myocardial infarction as per standard clinical practice; no consecutive puncture will be required for the purpose of serial blood draws.

11.3. Concomitant medications

11.3.1. Concomitant therapy

Consistent with current guidelines, all patients will receive effective statin therapy consisting of rosuvastatin 20mg/day throughout the 52-week study period, starting on Day 1

(randomization). If patients were on previous statin treatment other than rosuvastatin 20mg prior to screening, this will be stopped and replaced by rosuvastatin 20mg.

Between randomization and end of study, the background statin therapy should not be changed. At hospital discharge after the qualifying event, treating physicians (general practitioners and/or treating cardiologists) will be informed about the patient's participation in the study and the study requirements. If during the study follow-up period treating physicians strongly wish to discontinue treatment with rosuvastatin (e.g. due to higher treatment cost compared with other stains, as the statin will be prescribed and not provided free-of-charge to patients), physicians will be strongly advised to switch to atorvastatin 40mg (a regimen equipotent to rosuvastatin with regard to LDL-C lowering as well as effect on coronary atheroma burden by IVUS). The medical monitor will need to be informed about these changes.

In the event of adverse events deemed to represent statin intolerance (e.g. muscle-related symptoms with or without CK elevation), treating physicians will be advised to contact the local study representative. In these patients, in accordance with current consensus documents, it will be advised to reduce the dose of rosuvastatin to 10mg/day or 5mg/day as judged clinically indicated. Depending on the clinical course of the symptoms and/or CK levels, patients will either remain on reduced rosuvastatin dose or rosuvastatin will be discontinued and treatment with ezetimibe 10mg / day will be initiated. All effort will be made that the steering committee is informed prior to such changes.

In addition to statin treatment, optimal medical therapies including antiplatelet therapy, beta-blockers, ACE inhibitors if indicated, will start at the time of the index event and will be continued throughout the study period according to current guidelines for management of patients with acute myocardial infarction, and according to clinical judgment of treating physicians.

11.3.2. Prohibited and Non-recommended Concomitant therapies

Throughout the study duration, prescription of concomitant medications deemed by the Investigators or treating physician to be clinically indicated is allowed, expect for medications listed below as prohibited:

- Other PCSK9 inhibitors
- Bile acid sequestrants
- Fibrates
- Niacin
- Over the counter products/nutraceuticals known to impact lipids (e.g., plant stanols, flax seed oil, psyllium) except for omega-3 fatty acids which may be used as part of the usual care
- Amphetamines or amphetamine derivatives, weight loss medications

 Red yeast rice products

In addition, the following treatments or dietary habits are not recommended (albeit not prohibited) during the study period due to possible effect on rosuvastatin metabolism:

 Potent inhibitors of the CYP3A4 isoenzyme (antifungal azoles, macrolide antibiotics, HIV protease inhibitors)

 Grapefruit juice consumed in large quantities (>1 L/day)

11.4. Vital signs and physical examination

Patients will be advised to adhere to ATP III TLC diet or equivalent. Dietary recommendations will be communicated to patients at baseline, and at scheduled clinical visits. Lifestyle and dietary habits as well as level of physical exercise should be maintained stable if possible.

12. Planned substudies

Table 9: Overview of PACMAN-AMI substudies

	Day 1: In-hospital					End of study	Extended follow-up		
Time / Point Substudy	Before PCI	Baseline IVUS/NIRS+OCT	Before first IMP injection	12-24 hours after first IMP injection	Week 4 clinical visit	Week 52 clinical visit IVUS/NIRS + OCT	2 year phone call	5 year phone call	10 year phone call
1) Biobank	x				x	x			
2) Therapeutic drug monitoring	x				x	x			
3) Platelet function			x	x	x	x			
4) Endothelial function					x	x			
5) Lipidomics			x			x			
6) Matching		x							
7) Shear stress		x				x			
8) Neoatherosclerosis						x			
9) Neutrophilic extracellular trap	x					x			
10) PET/CT				x		x			
11) Quantitative flow ratio		x				x			
12) Legacy effect							x	x	x

Supplemental Online Content: Nonauthor Collaborators

*First name, last name, and suffix (if applicable) are required and will appear in PubMed.

***Group Name(s): PACMAN AMI investigators**							
***First Name and Middle Initial(s)**	***Last Name**	***Suffix (eg, Jr, III)**	Academic Degrees	Institution	Location (city, state/province, country)	Role or Contribution, eg, chair, principal investigator	Group (if more than 1 Group listed in the byline) and/or Subgroup (eg, Steering Committee)
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André	Frenk		PhD	Department of Cardiology, Bern University Hospital	Bern, Switzerland	study coordinator	
Laura U.	Morf		PhD	Department of Cardiology, Bern University Hospital	Bern, Switzerland	study coordinator	
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Supplemental Online Content: Nonauthor Collaborators

*First name, last name, and suffix (if applicable) are required and will appear in PubMed.

***First Name and Middle Initial(s)**	***Last Name**	***Suffix (eg, Jr, III)**	Academic Degrees	Institution	Location (city, state/province, country)	Role or Contribution, eg, chair, principal investigator	Group (if more than 1 Group listed in the byline) and/or Subgroup (eg, Steering Committee)
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Tim	Ten Cate		MD	Department of Cardiology, Radboud UMC	Nijmegen, The Netherlands	Investigator	

Supplemental Online Content

Räber L, Ueki Y, Otsuka T, et al; for the PACMAN-AMI collaborators. Effect of Alirocumab Added to High-Intensity Statin on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction. *JAMA.* Published online April 3, 2022. doi:10.1001/jama.2022.5218

Supplement 4. eMethods and eResults

This supplemental material has been provided by the authors to give readers additional information about their work.

Statistical Methods

Initial sample size calculation

For the primary endpoint, we assumed a change in percent atheroma volume (PAV) of -0.5% in the placebo arm and -1.8% in the alirocumab arm, with a common standard deviation of 3.4% (as a consensus from SATURN11:3.0%[1], IBIS-4[2]: 3.4%, ASTEROID[3]: 4.0%) and an intraclass correlation coefficient of ICC=0.40 (estimated from IBIS4 data[2]). Given that m=1.8 vessels per patients are expected to be analyzed, this gives a design effect of D=1.4 [design effect computed as D = 1+ICC(m-1)]. If dropout was ignored, a total sample size of 176 patients would be necessary to reach a statistical power of 80% at a two sided alpha level of α=5%. Anticipating a dropout rate of 25% at the 12 month imaging follow-up, a total of n=220 patients should be recruited (110 per arm).

In case the GLAGOV randomized clinical trial reported considerably lower PAV regression compared with our current assumptions ($\leq$ 1.6% difference in the change in PAV with evolocumab vs palcebo), a protocol amendment of the present study would be submitted with a revised sample size calculation accounting for the GLAGOV results.

Revised sample size calculation

i. Primary Endpoint

The above-mentioned condition for the revised sample size calculation was met, since the between-group difference in change in PAV observed in GLAGOV was 1%.[4] We therefore revised our sample size calculation, considering a change in PAV of 1% (instead of 1.3% initially). Based on data from already enrolled patients with available one year follow-up at the time point of the revised sample size calculation (N=54), we also revised the expected number of vessels per patient (m=2.0 instead of 1.8 initially) and the expected dropout rate (10% instead of 25% initially). This was a superiority trial powered on the primary endpoint, change in PAV from baseline to 52 weeks. In the revised power calculation we assumed: (i) a difference in change in PAV of -1.0% (alirocumab vs placebo, based on the findings of the

GLAGOV trial[4]); (ii) a standard deviation of 3.4% (as a consensus from SATURN[1]: 3.0%, IBIS-4[2]: 3.4%, ASTEROID[3]: 4.0%); and (iii) an intraclass correlation coefficient (ICC) of approximately 0.435 (estimated from IBIS-4 data[2]). We expected m=2.0 vessels per patients to be analyzed. The design effect was calculated by D = 1+ICC(m-1). If dropout was ignored, a total sample size of 264 patients would be required to reach a statistical power of 80% at a significance level of α=5% using a two-sided test. Anticipating a dropout rate of 10% (loss of patients undergoing follow-up imaging) at the week 52 imaging follow-up, a total of n=294 patients should be recruited (147 per arm).

ii. Powered Secondary Endpoints

- Change in lipid-core burden index at the 4-mm maximal segment ($maxLCBI_{4mm}$)

For the change in $maxLCBI_{4mm}$ from baseline to 52 weeks, we assumed: (i) a difference between PCSK9 arm and Placebo arm of 193.3 based on the observed difference in the YELLOW I trial[5] and the expected reduction in LDL-C levels in PACMAN-AMI (-40% with placebo and -75% with alirocumab), (ii) a standard deviation of 220 (estimated from the LRP trial[6]) and iii) a dropout rate of 10% at the week 52 imaging follow-up. Considering a total number of enrolled patients of n=294, a significance level of alpha=2.5% using a two-sided test, the trial would provide a power of more than 95% to detect the expected difference in the change in maxLCBI4mm of 193.3 between placebo and alirocumab if it was tested independently.

- Change in minimal cap thickness

For the change in minimal cap thickness from baseline to 52 weeks, we assumed: (i) a difference between PCSK9 arm and Placebo arm of 19.8μm for min cap thickness based on the observed difference in IBIS-4[7] and the expected reduction in LDL-C in PACMAN-AMI (-40% with placebo and -75% with alirocumab), (ii) a standard deviation of 44.8 (calculated from IBIS-4[7]); (iii) an intracluster correlation coefficient of approximately 0.57 (estimated from IBIS-4 data[7]); (iv) m=1.59 vessels per patient with fibroatheroma, according to the PACMAN-AMI matching substudy[8]), (v) 72% of the patients to show

any fibroatheroma (PACMAN-AMI matching substudy[8]). Considering a dropout rate of 10% at the week 52 imaging follow-up, an expected 72% of patients showing fibroatheroma, a total number of enrolled patients of n=294, and a significance level of alpha=2.5% using a two-sided test, the trial would provide a power of 85% to detect the expected difference in the change in min. cap thickness of 19.8µm between placebo and alirocumab if it was tested independently.

Supplementary references

1. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med. 2011;365(22):2078-2087.

2. Räber L, Taniwaki M, Zaugg S, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. Rur Heart J. 2015;36(8):490-500.

3. Nissen SE, Nicholls SJ, Sipahi I, et al; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006;295(13):1556-1565.

4. Nicholls SJ , Puri R, Anderson T, et al . Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. JAMA. 2016;316(22):2373-2384.

5. Kini AS, Baber U, Kovacic JC, et al. Changes in plaque lipid content after short-term intensive versus standard statin therapy: the YELLOW trial (reduction in yellow plaque by aggressive lipid-lowering therapy). J Am Coll Cardiol. 2013;62(1):21-29.

6. Waksman R, Di Mario C, Torguson R, et al. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: a prospective, cohort study. Lancet. 2019;394(10209):1629-1637.

7. Räber L, Koskinas KC, Yamaji K, et al. Changes in Coronary Plaque Composition in Patients With Acute Myocardial Infarction Treated With High-Intensity Statin Therapy (IBIS-4): A Serial Optical Coherence Tomography Study. JACC Cardiovasc Imaging. 2019;12:1518-1528.

8. Zanchin C, Ueki Y, Losdat S, et al. In vivo relationship between near-infrared spectroscopy-detected lipid-rich plaques and morphological plaque characteristics by optical coherence tomography and intravascular ultrasound: a multimodality intravascular imaging study. Eur Heart J Cardiovasc Imaging. 2021;22(7):824-834.

eTable 1. Inclusion and Exclusion Criteria

Inclusion criteria

- Male or female, age ≥18 years at screening
- Acute myocardial infarction: acute ST-segment elevation myocardial infarction (STEMI) with pain onset within ≤24h, or non-ST segment elevation myocardial infarction (NSTEMI), with at least one coronary segment (culprit lesion) requiring PCI
- LDL-C ≥70 mg/dL (≥1.8 mmol/L) assessed prior to, or during PCI in patients who have been receiving any stable statin regimen within ≥ 4 weeks prior to enrollment; OR LDL-C ≥125 mg/dL (≥3.2 mmol/L) in patients who are statin-naïve or have not been on stable statin regimen for ≥ 4 weeks prior to enrollment
- At least two major native coronary arteries ("target vessels") each meeting the following criteria for intracoronary imaging immediately following the qualifying PCI procedure:
  - Angiographic evidence of <50% reduction in lumen diameter by angiographic visual estimation
  - Target vessel deemed to be accessible to imaging catheters and suitable for intracoronary imaging in the proximal (50mm) segment ("target segment")
  - Target vessel may not be a bypass (saphenous vein or arterial) graft or a bypassed native vessel
  - Target vessel must not have undergone previous PCI within the target segment
  - Target vessel is not candidate for intervention at the time of qualifying PCI or over the following 6 months in the judgment of the Investigator
- Hemodynamic stability allowing the repetitive administration of nitroglycerine
- Ability to understand the requirements of the study and to provide informed consent
- Willingness of patient to undergo follow-up intracoronary imaging

Exclusion criteria

- Left-main disease, defined as ≥50% reduction in lumen diameter of the left main coronary artery by angiographic visual estimation
- Three-vessel disease, defined as ≥70% reduction in lumen diameter of three major epicardial coronary arteries by angiographic visual estimation or in major branches of one or more of these arteries, irrespective of the localization (proximal 50mm or more distal localization) of the obstructive lesions
- History of coronary artery bypass surgery
- TIMI flow <2 of the infarct-related artery after PCI

- Unstable clinical status (hemodynamic or electrical instability)
- Significant coronary calcification or tortuosity deemed to preclude IVUS, NIRS and OCT evaluation
- Uncontrolled cardiac arrhythmia, defined as recurrent and symptomatic ventricular tachycardia or atrial fibrillation with rapid ventricular response not controlled by medications in the past 3 months prior to screening
- Severe renal dysfunction, defined by estimated glomerular filtration rate <30 ml/min/1.73m^2
- Active liver disease or hepatic dysfunction
- Known intolerance to rosuvastatin OR known statin intolerance
- Known allergy to contrast medium, heparin, aspirin, ticagrelor or prasugrel
- Known sensitivity to any substances to be administered, including known statin intolerance
- Patients who previously received alirocumab or other PCSK9 inhibitor
- Patient who received cholesterol ester transfer protein inhibitors in the past 12 months prior to screening
- Treatment with systemic steroids or systemic cyclosporine in the past 3 months
- Known active infection or major hematologic, metabolic, or endocrine dysfunction in the judgment of the Investigator
- Planned surgery within 12 months
- Patients who will not be available for study-required visits in the judgment of the Investigator
- Current enrollment in another investigational device or drug study
- History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer
- Estimated life expectancy less than 1 year
- Female of childbearing potential (age <50 years and last menstruation within the last 12 months), who did not undergo tubal ligation, ovariectomy or hysterectomy.

eTable 2. Pre-Specified Secondary Endpoints not Reported in the Present Manuscript

- High-sensitivity troponin T
- N-terminal B-type natriuretic peptide
- Tumor-necrosis factor a
- Interleukin-1b
- Interleukin-6
- Cystatine
- Myeloperoxidase
- Sirtuin-1
- Sirtuin-6
- PCSK9

eTable 3. Medications at Discharge after Hospitalization for the Index Event

Medication	**Alirocumab** n=148	**Placebo** n=152
Statin	147 (99.3%)	151 (99.3%)
Rosuvastatin 20mg	141 (95.3%)	142 (93.4%)
High-intensity statin therapy[a]	144 (97.3%)	148 (97.4%)
Ezetimibe	0 (0.0%)	0 (0.0%)
Any antiplatelet drug	147 (99.3%)	151 (99.3%)
Dual antiplatelet therapy	144 (97.3%)	150 (98.7%)
Aspirin	144 (97.3%)	150 (98.7%)
Clopidogrel	8 (5.4%)	8 (5.3%)
Ticagrelor	115 (77.7%)	122 (80.3%)
Prasugrel	24 (16.2%)	21 (13.8%)
Novel oral anticoagulant	4 (2.7%)	4 (2.6%)
Vitamin K antagonist	4 (2.7%)	3 (2.0%)
ACE inhibitor	109 (73.6%)	105 (69.1%)
ARB	15 (10.1%)	21 (13.8%)
β-blocker	116 (78.4%)	126 (82.9%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

In the alirocumab group, one missing value in all variables. In the placebo group, one patient excluded short after randomization has missing values in all variables.

[a] Defined as atorvastatin ≥40mg or rosuvastatin ≥20mg.

eTable 4. Medications at 52-Week Follow-up

Medication	**Alirocumab** n=131	**Placebo** n=135
Statin	128 (97.7%)	134 (99.3%)
Rosuvastatin 20mg	115 (87.8%)	126 (93.3%)
High-intensity statin therapy[a]	116 (88.5%)	128 (94.8%)
Ezetimibe	2 (1.5%)	3 (2.2%)
Any antiplatelet drug	129 (98.5%)	135 (100%)
Dual antiplatelet therapy	106 (80.9%)	125 (92.6%)
Aspirin	124 (94.7%)	134 (99.3%)
Clopidogrel	9 (6.9%)	9 (6.7%)
Ticagrelor	82 (62.6%)	97 (71.9%)
Prasugrel	20 (15.3%)	20 (14.8%)
Novel oral anticoagulant	7 (5.3%)	4 (3.0%)
Vitamin K antagonist	3 (2.3%)	0 (0.0%)
ACE inhibitor	71 (54.2%)	77 (57.0%)
ARB	32 (24.4%)	30 (22.2%)
β-blocker	104 (79.4%)	99 (73.3%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

[a] Defined as atorvastatin ≥40mg or rosuvastatin ≥20mg.

eTable 5. Baseline Characteristics of Patients in the Randomized Population Who Received Study Drug With and Without Serial IVUS Imaging

Characteristics	Serial IVUS (n=265)	No serial IVUS (n=35)
Age (y)	57.8 (9.3)	64.0 (11.1)
Female sex	43 (16.2%)	13 (37.1%)
Body mass index[a]	28.0 (4.3)	25.9 (4.3)
Diabetes mellitus	26 (9.8%)	5 (14.3%)
Arterial hypertension	113 (42.6%)	17 (48.6%)
Current smoking	129 (48.7%)	13 (37.1%)
Family history of CAD	88 (33.2%)	10 (28.6%)
Previous myocardial infarction	6 (2.3%)	1 (2.9%)
Previous PCI	7 (2.6%)	0 (0.0%)
Peripheral arterial disease	5 (1.9%)	1 (2.9%)
Type of acute myocardial infarction		
NSTEMI	122 (46.0%)	20 (57.1%)
STEMI	143 (54.0%)	15 (42.9%)
Baseline medications		
Antiplatelet therapy	26 (9.8%)	5 (14.3%)
Statin	34 (12.8%)	3 (8.6%)
High-intensity statin[b]	18 (6.8%)	2 (5.7%)
Ezetimibe	1 (0.4%)	0 (0.0%)
β-blocker	24 (9.1%)	5 (14.3%)
ACE inhibitor	21 (7.9%)	3 (8.6%)
ARB	32 (12.1%)	9 (25.7%)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; IVUS, intravascular ultrasound; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation acute myocardial infarction.

Values are count (%) or mean (SD).

In the patient population without serial IVUS, one patient excluded short after randomization has missing values in all variables except “Age” and ”Type of acute myocardial infarction”. One additional value was missing for BMI in the patient population without serial IVUS.

[a] Calculated as weight in kilograms divided by height in meters squared

[b] Atorvastatin ≥40mg or rosuvastatin ≥20mg.

eTable 6. Clinical and Biochemical Adverse Events

	Alirocumab N=147[a]	**Placebo N=151[a]**
Any adverse event	104 (70.7%)	110 (72.8%)
Serious adverse event[b]	47 (32.0%)	50 (33.1%)
Adverse events resulting in study drug discontinuation	2 (1.4%)	0 (0.0%)
Cardiovascular events		
Coronary revascularization – ischemia driven[c]	12 (8.2%)	28 (18.5%)
Revascularization of *de novo* lesion – ischemia driven[c]	7 (4.8%)	17 (11.3%)
Target-lesion revascularization[d] – ischemia driven[c]	5 (3.4%)	12 (7.9%)
All-Cause death	2 (1.4%)	1 (0.7%)
Cardiac death	2 (1.4%)	0 (0.0%)
Myocardial infarction	2 (1.4%)	3 (2.0%)
Stroke / TIA	0 (0.0%)	1 (0.7%)
Adverse events of special interest		
Local injection site reaction	9 (6.1%)	5 (3.3%)
General allergic reaction	5 (3.4%)	0 (0.0%)
Neurocognitive event	3 (2.0%)	0 (0.0%)
ALT increase > 3x ULN	1 (0.7%)	0 (0.0%)

Abbreviations: ALT, alanine transaminase; TIA, transient ischemic attack; ULN, upper limit of normal.
Only the first event of each type per patient is included.

Results expressed a count (percentage).

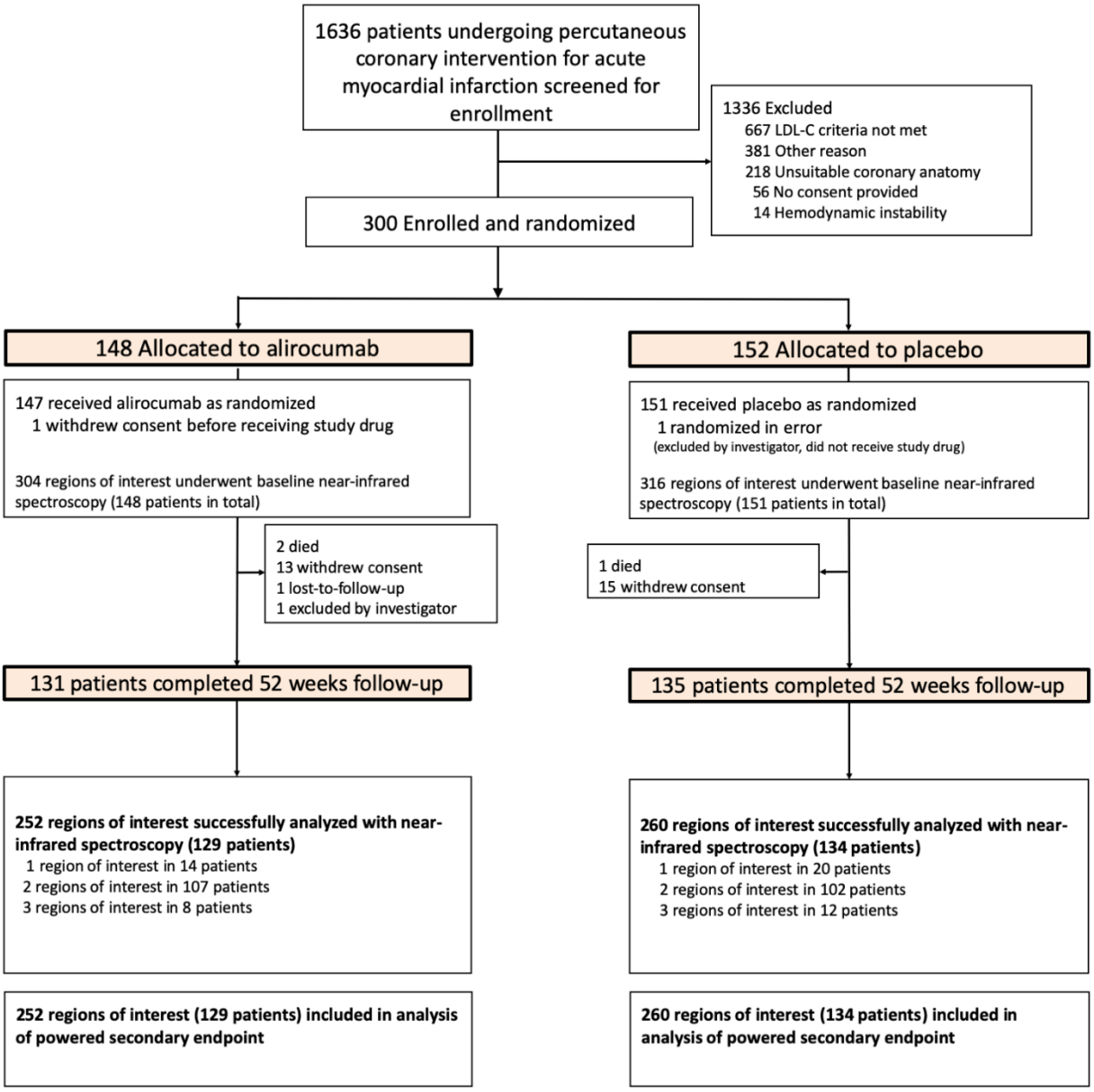
[a] Includes patients who received at least one dose of the study drug.
[b] Serious adverse events were defined as events that resulted in death; or were life-threatening; or required inpatient hospitalization or prolongation of existing hospitalization; or resulted in persistent or significant disability/incapacity; or were congenital anomaly/birth defects; or were medically important events.
[c] Ischemia driven revascularization was defined as revascularization in the presence of angina symptoms and >50% stenosis by quantitative coronary angiography; or >70% stenosis by quantitative coronary angiography in the absence of angina; or a positive fractional flow reserve (<0.80).
[d] Indicates revascularization in a stent implanted during index coronary intervention.

eTable 7. Complications Related to Intracoronary Imaging Procedures

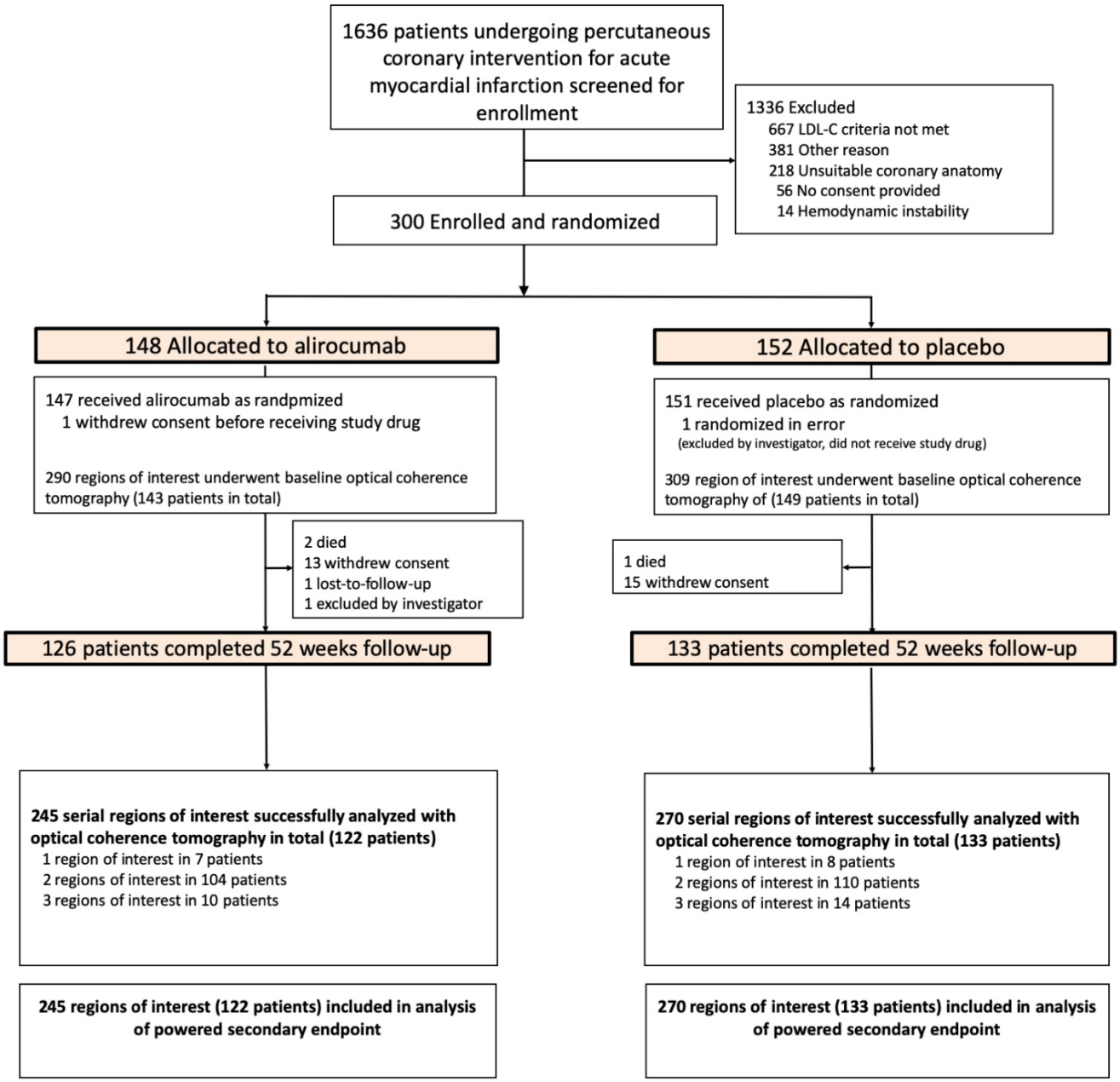
Imaging related complications	Number of patients (%)*	Alirocumab	Placebo
Any	7 (2.3)	4	3
Arrhythmia	3 (1.0)	1	2
Air embolism	2 (0.7)	1	1
Spasm	2 (0.7)	2	0
Perforation	0	0	0
Dissection	0	0	0

*in a total of 567 imaging procedures (baseline and week 52)

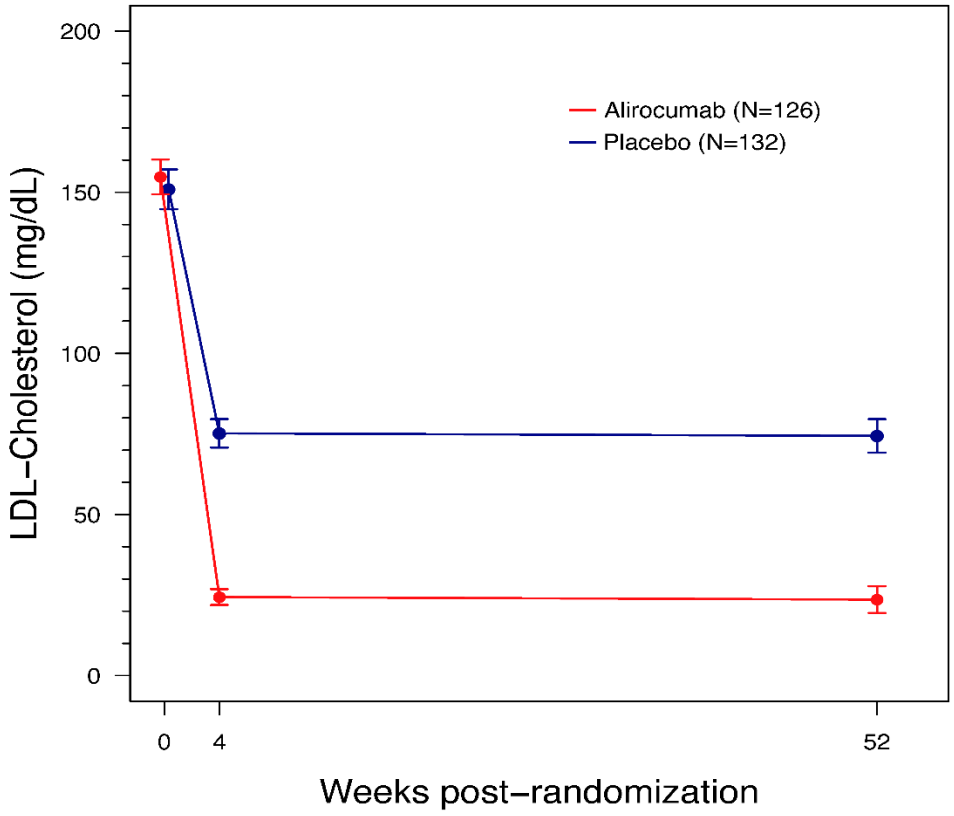
eFigure 1. Flow of Patients in the PACMAN-AMI Randomized Clinical Trial with Respect to Imaging with Near-Infrared Spectroscopy



eFigure 2. Flow of Patients in the PACMAN-AMI Randomized Clinical Trial with Respect to Imaging with Optical Coherence Tomography



eFigure 3. Mean Low-Density Lipoprotein Cholesterol Levels During the Trial



Values are means and 95% confidence intervals. Sample size: 259 patients (7 missing due to missing LDL-C values).

To convert LDL-C values to mmol/L, multiply by 0.0259.