Clinical Trial Protocol

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

Study-name: **PACMAN-AMI**

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Signature Page

Study number	NCT03067844
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The Sponsor and the Coordinating Investigator and trial statistician have approved the current version of the protocol and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Coordinating Investigator & Sponsor:

Prof. Dr. Lorenz Räber, PhD

Place/Date	Signature

Local Subinvestigator

Place/Date	Signature

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STUDY SYNOPSIS

Study title	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
Study name	PACMAN-AMI
Category	Clinical trials of medicinal products, category B.
Hypothesis	Proprotein convertase subtilisin/kexin type-9 (PCSK9) inhibition (alirocumab) results in reduction of coronary plaque atheroma volume as assessed by intravascular ultrasound (IVUS) and favorable changes in plaque composition as assessed *in vivo* by means of near-infrared spectroscopy (NIRS) and optical coherence tomography (OCT) in patients with acute myocardial infarction treated with high-intensity statin therapy.
Study Objectives	**Primary objective** • To evaluate the effect of the PCSK9 inhibitor alirocumab on the change in percent atheroma volume (PAV) at week 52 in patients with acute myocardial infarction undergoing percutaneous coronary intervention (PCI) in the infarct-related artery and receiving guideline-recommended high-intensity statin therapy. **Secondary objectives** • To evaluate the effect of the PCSK9 inhibitor alirocumab compared with placebo after 52 weeks on the change in lipid core burden index (defined by NIRS), fibrous cap thickness and macrophage accumulation of coronary plaques (defined by OCT) in non-infarct-related coronary arteries. • To assess the effect of the PCSK9 inhibitor alirocumab compared with placebo after 52 weeks on the 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, Lp(a)], inflammatory biomarkers (hs-CRP, TNFa, IL1b, IL-6, MPO, cystatine, SIRT1, SIRT6) and other selected biomarkers (hs-TnT, NT-pro-BNP), and to explore possible associations with changes in coronary plaque characteristics
Primary Endpoint	• Change in PAV by greyscale IVUS from baseline to week 52
Secondary Endpoints	• Change in total lipid-core burden index ($LCBI_{total}$) as determined by NIRS from baseline to week 52

	• Change in maximum LCBI in any 4-mm segment (maxLCBI4mm) as determined by NIRS from baseline to week 52 • Change in minimal and mean fibrous cap thickness as determined by OCT from baseline to week 52 • Change in average angular extension (AAE) of macrophages as determined by OCT from baseline to week 52 • Change in normalized total atheroma volume (NTAV) by IVUS from baseline to week 52 • Change in LDL-cholesterol, hsCRP, hsTnT, NT-pro-BNP, lipid and inflammatory markers from baseline to week 52 and their association with indices of plaque progression/regression
Secondary clinical endpoints	• Any death • Cardiac death • Non-fatal myocardial infarction • Ischemia-driven coronary revascularization • Ischemic stroke/TIA
Safety endpoints	• Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), product complaints, laboratory data
Assessment of efficacy endpoints	2-vessel IVUS, NIRS and OCT of the proximal segments (≥50mm length) of two non-infarct-related coronary arteries after successful PCI of the culprit lesion at baseline (week 0) and after 52 weeks of treatment
Study design	Randomized, superiority, double blind, placebo-controlled, multicenter intracoronary imaging study
Study population	Patients presenting with acute myocardial infarction (non-ST-elevation myocardial infarction or acute ST-elevation myocardial infarction)
Study sample	294 patients (147 per treatment arm) See Appendix 1 for adjusted sample size and statistics Sample size powered for the primary endpoint, assuming a change in PAV of -0.5% in the placebo plus rosuvastatin 20mg/d arm and -1.8% in the alirocumab plus rosuvastatin 20mg/d arm, with a common standard deviation of 3.4%.

Patient eligibility **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 to undergo follow-up intracoronary imaging
Key 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.
Randomization	Double blind randomization in 1:1 ratio, stratified for (i.) study center; (ii.) presence of stable statin treatment within > 4weeks prior to enrollment; and (iii.) STEMI vs. NSTEMI.
Investigational products	alirocumab; placebo
Formulation	Active treatment: prefilled pen; sterile alirocumab drug product supplied at a concentration of 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose. Placebo: matched for content to verum except alirocumab

Route(s) of administration	Subcutaneous (SC); 1 injection of 1 mL in the abdomen, thigh, or outer area of upper arm (ie, deltoid region)
Dose regimen	Alirocumab 150 mg Q2W SC or placebo Q2W SC. Administration of the investigational product will start on day 1 / week 0 and end on week 50, respectively 52 dependent on end of study visit.
Background statin therapy	All patients will receive treatment with rosuvastatin 20mg/d starting on Day 1 and throughout the duration of the study (Week 52)
Assessment schedule	**V1 (Day 1 / Week 0)**: • Patient screening, enrolment and randomization • Medical History • Laboratory testing • Baseline intracoronary imaging (IVUS, NIR, OCT) • Administration of investigational product (first dose) • Patient training for self-administration of the investigational product **V2 (Week 2)**: • Administration of investigational product (second dose) • Patient training for self-administration of the investigational product • Safety assessment **V3 (Week 4)**: • Laboratory testing • Administration of investigational product (third dose) • Patient training for self-administration of the investigational product • Safety assessment **V4 (Week 8)**: • Telephone contact, safety assessment **V5 (Week 12)**: • Telephone contact, safety assessment **V6 (Week 24)**: • Safety assessment **V7 (Week 36)**: • Telephone contact, safety assessment **V8 (Week 48)**: • Telephone contact, safety assessment **V9 (Week 52 (-0/+14 days)**: • Laboratory testing • Follow-up intracoronary imaging (IVUS, NIR, OCT) • Safety assessment

Duration of study period	The duration of the study for each patient is approximately 12 months to include a 52-week treatment period and a 2-week period until final follow-up.
Study schedule	First Patient Enrolled: 03/2017 Last Patient Enrolled: 09/2020 Last Patient Visit: 09/ 2021
Study centers	• Bern University Hospital, Bern, Switzerland • University Hospital of Geneva, Geneva, Switzerland • Triemli Hopsital, Zurich, Switzerland • University Hospital Basel, Basel, Switzerland • University Hospital Vienna (AKH), Vienna, Austria • Erasmus Thoraxcentre Rotterdam, The Netherlands • Rigshospitalet, Copenhagen, Denmark • Radboud University, Nijmegen Medical Centre • University Hospital Zurich (USZ), Zurich, Switzerland
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, and the ICH-GCP as well as all national legal and regulatory requirements.

STUDY ADMINISTRATIVE STRUCTURE

Sponsor	Bern University Hospital, Inselspital, Department of Cardiology, Freiburgstrasse, 3010 Bern, Switzerland
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Principal investigator	Prof. Stephan Windecker, M.D. Chief Physician Department of Cardiology, Bern University Hospital Inselspital, 3011 Bern, Switzerland E-mail: stephan.windecker@insel.ch
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Consultant Biomarker	Prof. Christian Matter, M.D. Department of Cardiology, Zurich University Hospital, Switzerland E-mail: christian.matter@uzh.ch
Steering Committee Member	Prof. Francois Mach, M.D. Chief Physician Department of Cardiology, Geneva University Hospital, Switzerland Cardiovascular Research Laboratory 64 Avenue de la Roseraie 1211 Genève
Chair data management and analysis	Dik Heg, PhD Director Cardiovascular Statistics Institute of Social and Preventive Medicine University of Bern
Data management	Clinical Trials Unit Bern University

	Finkelhubelweg 11, 3010 Bern, Switzerland
Data Safety and Monitoring Board	*To be determined*
Intracoronary Imaging Core Labs	• IVUS / NIRS: Cardialysis BV, Westblaak 98, 3012 KM, Rotterdam, NL • OCT: Core Lab of Bern University Hospital
Clinical Event Adjudication Committee	*To be determined*
Study coordination	André Frenk, PhD, Cardiology Department, Bern University Hospital

LIST OF ABBREVIATIONS

AAE	Average angular extension
CAD	Coronary artery disease
CEC	Competent Ethics Committee
CRF	Case Report Form
CTU	Clinical Trials Unit
eCRF	Electronic Case Report Form
DSMB	Data Safety and Monitoring Board
EDC	Electronic Data Capture system
EEM	External elastic membrane
GCP	Good Clinical Practice
HDL-C	High-density lipoprotein cholesterol
hs-CRP	High sensitivity C-reactive protein
hs-TnT	High sensitivity troponin T
IEC	Independent Ethics Committee
IIT	Investigator-initiated Trial
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention to treat
IVUS	Intravascular Ultrasound
KEK	Kantonale Ethikkommission Bern, lead CEC
LCBI	Lipid-core burden index
LCP	Lipid core plaque
LDL-C	Low-density lipoprotein cholesterol
NET	Neutrophil extracellular trap
NIRS	Near infrared spectroscopy
NSTEMI	Non ST-Elevation Myocardial Infarct
NTAV	Normalized total atheroma volume
NT-pro--BNP	N-terminal B-natriuretic peptide
OCT	Optical Coherence Tomography
PAV	Percent atheroma volume
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
ROI	Region of interest
SAE	Serious adverse event
STEMI	ST-Elevation Myocardial Infarct
TCFA	Thin-cap fibroatheroma
TMF	Trial Master File

STUDY SCHEDULE

	Screening, Enrollment, Randomization	**Double-blind Treatment Period and Follow-up**							
Visit #	1 (Day 1 / Week 0)	2 (Week 2) +/- 3 days	3 (Week 4) +/- 3 days	4 (Week 8) +/- 10 days	5 (Week 12) +/- 10 days	6 (Week 24) +/- 3 days	7 (Week 36) +/- 10 days	8 (Week 48) +/- 10 days	9 (Week 52) +14 / -0 days End of study visit (within 2 weeks after the last IMP administration)
Mode of visit	In-hospital	Clinical visit	Clinical visit	Phone call	Phone call	Clinical visit	Phone call	Phone call	Clinical visit
Patient information and informed consent	X								
Review of inclusion/exclusion criteria	X								
Demographics	X								
Medical History	X								
Physical examination	X	X	X			X			X
Dietary recommendations	X	X	X	X	X	X	X	X	X
Randomization	X								
Injection training with dummy pen	X	X	X						
Distribute injection diary (Visit 1, day 1) and IMP instructions	X	X	X						
Double-blind dispensation and injection of investigational product at study site, document injection in diary	X	X	X						
Dispensation of drug (12 IMP pens, coolbox, container)			X			X			

Compliance check (diary, IMP count in container)						X			X
Review of concomitant medications	X	X	X	X	X	X	X	X	X
Safety: AE /SAE recording / product technical complaints	X	X	X	X	X	X	X	X	X
LDL assessment (Friedewald Formula)	X								
Laboratory Testing – Local testing at study site: • Hematology (hematocrit, hemoglobin, WBC count, platelet count) • Chemistry (HbA1c, sodium, potassium, creatinine) • CK, Troponine T including peak values	X								X
Laboratory Testing – Local testing at study site: • Liver panel (ALT, AST, ALP, total bilirubin) (please see section 6.1.4) • CK	X		X						X
Laboratory Testing – Central testing in dedicated biobank: • Total-C, LDL-C (Friedewald formula), 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) • hs-CRP, hs-TNT, NT-pro-BNP • TNFA, IL1B, IL-6, MPO, cystatine, SIRT1, SIRT6 • PCSK9 levels • NETs, DNAase activity	X		X						X
2-vessel intracoronary imaging (IVUS, NIRS, OCT)	X								X

1. BACKGROUND AND RATIONALE

1.1 Effect of lipid-lowering treatment on coronary atherosclerosis

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 they reduce cardiovascular mortality 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,[1-6] 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;[7] 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.[8,9] 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.[10,11] 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.[12-14]

1.2 PCSK9 inhibitors

Experimental studies have demonstrated that proprotein convertase subtilisin/kexin type 9 (PCSK9) reduces the hepatic uptake of LDL-C by increasing the lysosomal degradation of LDL receptors.[15] In humans, gain-of-function mutations of the PCSK9 are associated with hypercholesterolemia and increased risk of cardiovascular events, whereas loss-of-function mutations result in reduced plasma LDL-C levels and substantially lower cardiovascular risk.[16] Prompted by these observations and by robust experimental evidence elucidating the mechanistic role of PCSK9 in cholesterol homeostasis, monoclonal antibodies have been developed that bind to PCSK9 and thus prevent the degradation of LDL receptors, thereby resulting in reduction of LDL-C plasma levels. A growing number of studies of PCSK9 inhibitors in a wide spectrum of patients with hyperlipidemia on or off lipid-lowering therapy, familial hypercholesterolemia, and statin intolerance demonstrated consistent, profound, and sustained reductions in LDL-C with greater magnitude of reduction as compared with high-dose statin regimens (**Table 1**). Importantly, these favorable effects occurred while consistently maintaining a favorable safety profile.[17-29] Together these findings have rendered PCSK9 inhibitors a promising strategy for management of hypercholesterolemia.

Identification of PCSK9 expression in human atherosclerotic plaques[30] has raised the translational hypothesis of a direct favorable effect of PCSK9 inhibition on plaque biology beyond the potent LDL-C-lowering effect. Moreover, preclinical work has provided evidence of the implication of PCSK9 in regulating pathways of vascular inflammation and apoptosis within the plaque.[31] Because statin treatment increases the expression of PCSK9 in both normolipidemic and dyslipidemic subjects,[32] it

has been suggested that concomitant treatment with statins and PCSK9 inhibitors may exert a favorable synergistic effect on lipid uptake by atherosclerotic plaques in addition to the additive efficacy of the two regimens in lowering LDL-C levels.

Currently, while the efficacy of statins in moderately reducing coronary atheroma burden and favorably altering plaque composition has been established. Moreover, the GLAGOV (GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound) study is currently evaluating whether LDL-C lowering with evolocumab results in greater regression in atheroma volume by IVUS compared with placebo in patients with stable CAD receiving lipid-lowering therapy (ClinicalTrials.gov Identifier: NCT01813422). However, the effects of PCSK9 inhibition on coronary plaque morphology remain unknown. As clinical investigations are currently underway assessing the efficacy of PCSK9 inhibitors for prevention of cardiovascular events, it will be most valuable to investigate the impact of these agents on plaque burden, morphology and composition of heterogeneous coronary lesions in patients with acute myocardial infarction – a high-risk group of CAD patients who benefit mostly from aggressive lipid-lowering strategies.

Table 1. Summary of select clinical trials with PCSK9 inhibitors

First Author/Trial (Ref. #)	Publication Year	Population	N	Baseline LDL-C (mg/dl)	Percentage Change of LDL-C
Stein et al (17)	2012	Hypercholesterolemia	101	111 to 170	-38 to -65
Roth et al (18)	2012	LDL-C >100 following atorvastatin 10mg	61	120 to 132	-66 to -73
McKenney et al (19)	2012	LDL-C >100	152	123 to 132	-40 to -72
Stein et al (20)	2012	HeFH	62	140 to 170	-29 to -68
MENDEL (21)	2012	LDL-C 100-180	271	143	-37 to -53
Dias et al (22)	2012	Hypercholesterolemia	85	113	-24 to -75
RUTHERFORD (23)	2012	HeFH	111	151 to 162	-43 to -55
LAPLACE-TIMI 57 (24)	2012	LDL-C >85	553	120 to 128	-42 to -66
GAUSS (25)	2012	Statin intolerance	123	190 to 204	-41 to -63
Fitzgerald et al (26)	2013	Healthy volunteers	24	143	-14 to -36
Odyssey COMBO II (27)	2014	CVD or high CV-risk	720	109	- 51%
Odyssey Long Term (29)	2014	Hypercholesterolemia	2,341	122	-61%

HeFH: heterozygous familial hypercholesterolemia; HoFH: homozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein-cholesterol.

1.3 Intracoronary imaging for in vivo morphological assessment of coronary atherosclerosis

As our understanding of pathobiological mechanisms implicated in plaque progression and in the development of high-risk lesions has advanced, novel intracoronary imaging modalities have been developed that allow for detailed evaluation of human coronary atherosclerosis *in vivo*.[33] Intracoronary imaging modalities used for this purpose include intravascular ultrasound (IVUS), optical coherence tomography (OCT), and near infrared spectroscopy (NIRS). These modalities have shown substantial potential to quantify and characterize the risk profile of coronary atheroma. Importantly, combined use of these imaging tools can provide substantial incremental information for *in vivo* characterization of coronary lesions compared with the information obtained by each modality alone.

(i.) IVUS provides real-time, high-resolution tomographic images of the entire coronary vessel wall[34] and allows for accurate quantification of atherosclerotic plaque burden. IVUS performed serially at two consecutive time points currently represents the gold standard for assessment of plaque progression/regression over time, and also for evaluation of the effect of anti-atherosclerotic medications on plaque burden.[10,11,35] Of clinical importance, IVUS-derived measures of plaque progression are predictive of subsequent adverse outcomes in patients with CAD.[36]

(ii.) Based on the absorbance of light by organic molecules, NIRS has been extensively used for detailed analysis of the chemical composition of biological specimens.[37] NIRS has recently been applied to quantify lipid content in human coronary plaques *in vivo*. NIRS has shown very high correlation with histopathology – i.e., the gold standard for plaque tissue characterization – with a sensitivity and specificity of >90% for lipid detection in human atheroma.[38] Combining NIRS with IVUS has been shown to enhance plaque characterization in vivo as compared with the use of each modality alone.[39]

(iii.) OCT is a safe and effective modality for characterizing coronary atherosclerotic plaques *in vivo*.[40] OCT measures depth-resolved back reflection of infrared light with an axial and transverse resolution that is far superior compared to IVUS. With respect to discrimination of high-risk plaque, OCT has been validated against histology – the gold-standard for tissue characterization – for accurate evaluation of lipid content and macrophage infiltration, as well as for measurement of fibrous cap thickness.[41,42] Thereby, OCT enables not only the identification of macroscopic plaque characteristics, but also of microstructural characteristics which are well-recognized determinants of plaque vulnerability.

1.4. Ongoing relevant studies and gaps in evidence

In addition to recently published (**Table 1**) and ongoing trials assessing the LDL-C-lowering efficacy of PCSK9 inhibitors, the impact of PCSK9 inhibitors on clinical outcomes are also currently investigated. The phase 3 ODYSSEY program has been evaluating the efficacy of PCSK9 inhibition in different clinical settings. Within this program, a *post hoc* analysis of the ODYSSEY Long Term trial included 2,341 patients with hypercholesterolemia inadequately controlled by maximum tolerated statin therapy demonstrated a 54% reduction of major adverse cardiovascular events with the PCSK9 inhibitor alirocumab compared to placebo.[29] The ODYSSEY OUTCOME trial is currently assessing the effect of alirocumab on the occurrence of cardiovascular events (composite endpoint of coronary heart disease death, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in 18,000 patients randomized 4-52 weeks after an acute coronary syndrome event and are treated with high statin therapy (atorvastatin 40 or 80 or rosuvastatin 20 or 40) (ClinicalTrials.gov Identifier: NCT01663402). Furthermore, GLAGOV study, which is currently evaluating the effect of evolocumab on coronary atheroma volume as assessed by grayscale IVUS. Of note, and contrary to the present study, GLAGOV is including relatively lower-risk patients with stable CAD (i.e. not patients with acute myocardial infarction), and will not evaluate the clinically critical aspect of coronary plaque morphology and composition.

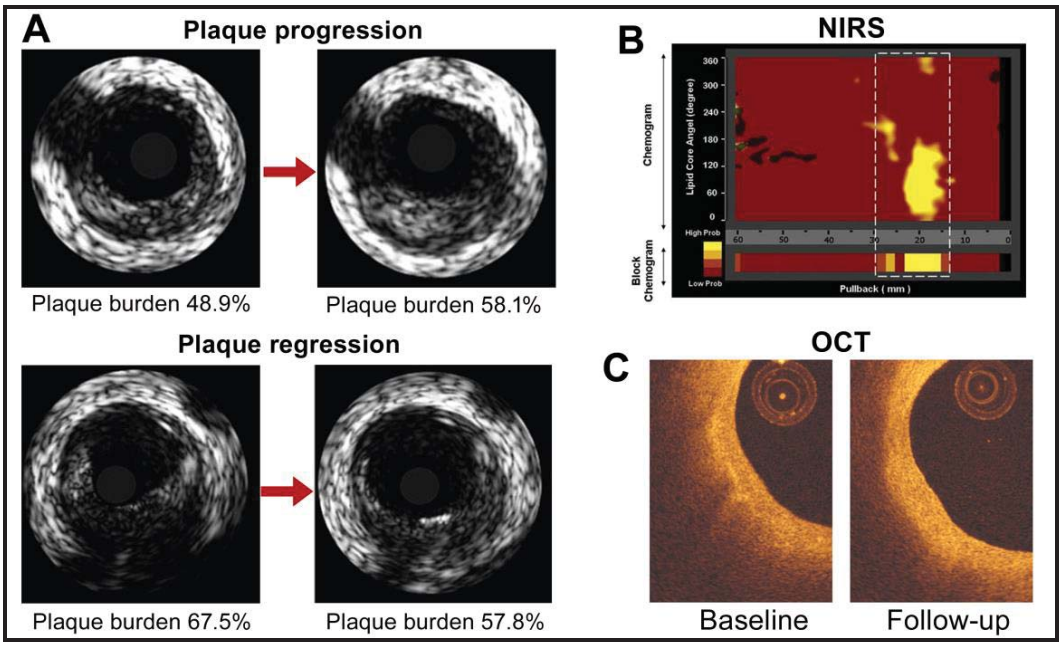

Figure 1. Use of intracoronary imaging modalities for in vivo assessment of coronary plaque progression and morphology. (**A**) Examples of plaque regression (upper panels) vs. regression (lower panels), as determined by IVUS, after 1 year of intensive statin therapy. (**B**) Example of a "chemogram" derived by NIRS for assessment of the lipid core burden index of a coronary plaque.(**C**) Images of serial OCT analyses for measurement of macrophage accumulation in a coronary plaque, defined as increased signal intensity within the fibrous cap accompanied by heterogeneous backward shadows. **A**: Modified from Räber L, et al. *Eur Heart J* 2015; 36:490-500. **B**: Adapted from Pu J, et al. *Eur Heart J* 2012; 33: 372–383. **C**: Unpublished data from ongoing analysis of our group.

Against this background of ongoing large-scale studies assessing the efficacy of PCSK9 inhibition for reduction of LDL-C levels and, subsequently, for reduction of adverse cardiovascular events, there is currently a gap of evidence regarding the impact of this highly effective LDL-C-lowering medical intervention on changes in plaque morphology and composition particularly among patients at highest risk, notably those with acute myocardial infarction undergoing PCI.

The clinical efficacy of PCSK9 inhibitors is expected to provide new opportunities for management of hypercholesterolemia. A growing body of evidence has demonstrated that pharmacological PCSK9 inhibition results in profound, sustained reductions of LDL-C levels in a manner that is synergistic to the effect of high-dose statin regimens. It is increasingly appreciated that certain morphological coronary plaque characteristics (increased lipid content, thin fibrous caps) rather than merely large plaque size determine a lesion's risk to rupture and trigger acute coronary events. While statins – the standard for LDL-C reduction – have demonstrated a favorable effect in retarding plaque progression or even achieving moderate atheroma regression and in stabilizing plaque composition, a residual risk still exists. Plaque progression, development of new high-risk coronary lesions, and subsequently new coronary events still occur despite intensive statin treatment. Against a background of currently ongoing studies assessing the efficacy of PCSK9 inhibition for prevention of adverse cardiovascular events, it remains to be determined whether the profound lipid-lowering efficacy of PCSK9 inhibition may translate into favorable effects on the morphology of the plaque, i.e., of the anatomical substrate and trigger of adverse cardiac events.

1.5 Study relevance and expected impact

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 current paradigm for management of dyslipidemia and for prevention of CAD anatomic and clinical progression. The present analysis, utilizing a multimodality approach of intracoronary imaging, aims to uniquely investigate the effect of PCSK9 inhibition on important aspects of coronary plaque burden, morphology and composition in humans 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 in a background of evidence of the efficacy of PCSK9 inhibitors in reducing LDL-C levels and of ongoing analyses assessing possible translation of this potent lipid-lowering potential into improved clinical outcomes. Considering the alarmingly 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, innovative treatment strategy in favorably affecting both plaque progression and plaque composition in a high-risk populations of patients who already experienced myocardial infarction and who derive the greatest benefit from aggressive lipid-lowering and other anti-atherosclerotic medications.

Acute myocardial infarction causes a systemic inflammatory reaction, which promotes inflammation and thereby induces plaque growth at non-culprit lesion sites as demonstrated in preclinical models. In addition, patients with myocardial infarction are known to harbor more vulnerable plaques in their non-infarct related arteries compared to stable CAD patients, thereby indicating an ideal population to study the PCSK9-mediated effects on atherosclerosis. As an additional feature, a multi-vessel assessment will be obtained in the proposed study, as plaque progression in the entire coronary artery tree is of greater interest compared to assessment of only a single selected arterial segment. Cardiovascular events are not limited to one single vessel segment and in this study we will focus specifically on selecting the clinically most relevant vessel regions, that is, according to previous pathology studies,[8,43] the proximal portions of the major coronary arteries where most rupture-prone TCFAs are located and where the consequences of a myocardial infarction are highest based on the large amount of myocardium at risk.

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) 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.

2.2 Secondary objectives (please see also Appendix 1 to protocol)

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

- To assess the effect of alirocumab 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.

2.3 Safety objective

- To evaluate adverse events in patients treated with alirocumab.

3. RESEARCH PLAN

3.1 Study Design

This is a prospective, randomized, superiority, double-blind (assessor and patients blinded to treatment), placebo-controlled, parallel-group, multi-center study to evaluate the effect of 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. Number of patients

A total of 294 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 as detailed in **section 4**. Justification of the sample size is described in: .

Please see Appendix 1 to Protocol for adjusted sample size

3.3 Number of centers

The study will be conducted at 9 centers in Switzerland (5), Austria (1), Netherlands (2), Denmark (1).

3.4 Expected study duration

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.

3.5 Interim safety analysis

Interim safety analyses will be conducted based on the reported frequency of SAE and AESI by the DSMB. The timing and frequency of these analyses will be determined by the members of the DSMB (at least one).

4. PATIENT ELIGIBILITY

4.1 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 to undergo follow-up intracoronary imaging

4.2 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 defined by the following criteria: inability to tolerate at least 2 different statins (one statin at the lowest starting average daily dose and the other statin at any dose); intolerance associated with confirmed, intolerable statin-related adverse effect(s) or significant biomarker abnormalities; symptom or biomarker changes resolution or significant improvement upon dose decrease or discontinuation; and symptoms or biomarker changes not attributable to established predispositions such as drug-drug interactions and recognized conditions increasing the risk of 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

4.3. Emergency unblinding procedure

In case of a medical reason for emergency unblinding, the investigator will contact the pharmacist on call at the Bern University Hospital. The unblinding procedure will be activated upon reception of a corresponding form per Fax (Number +41 31 632 47 90) from the requesting investigator. The pharmacist has access to the randomization list linking the patient's study number with the randomly allocated treatment.

4.4 Justification of LDL-C criteria for eligibility

The rationale for the LDL-C eligibility thresholds in conjunction with pre-enrollment statin treatment status is in line with previous studies with PCSK9 inhibitors, also accounting for specific patient selection criteria uniquely applicable in the present study. In previous studies, PCSK9 inhibitors were administered either instead of a statin (e.g. due to statin intolerance) or on top of maximum tolerated statin therapy if LDL-C levels were above target levels as determined by individual patient cardiovascular risk. In those previous PCSK9 studies, a lipid-stabilizing period was applied and PCSK9 inhibitor treatment was initiated if LDL-C levels remained above targets despite maximally tolerated statin therapy with or without other lipid-modifying agents. In contrast, in the present study a lipid-stabilizing phase is not feasible as a result of the enrolment of patients in the acute setting of myocardial infarction, and due to the performance of the baseline intracoronary imaging evaluation (a prerequisite to proceed to randomization) during the clinically indicated cardiac catheterization in the acute clinical setting. This study will therefore require that patients either have LDL-C levels at screening above the guideline-recommended target of 70 mg/dL (1.8 mmol/L)[44,45] while on prior stable statin treatment, or are on no prior statin treatment and have LDL-C levels ≥125 mg/dL (≥3.2 mmol/L). The latter approach accounts for the fact that, in patients with LDL-C levels ≥125 mg/dl (3.2 mmol) without concurrent treatment, LDL-C levels would still remain above target despite an estimated mean 43% reduction reportedly achievable with rosuvastatin 20mg (protocol-mandated background statin therapy throughout the study period for both treatment arms). Although a lipid-stabilizing phase is not feasible in the present study, the advantage of the present approach will be the possibility to uniquely investigate changes in coronary atheroma burden and composition in response to PCSK9 inhibitor treatment in high-risk patients in the acute phase of myocardial infarction who are expected to derive maximal benefit from the treatment (as suggested by earlier studies with statins).

5. PATIENT SELECTION AND ENROLLMENT

5.1 PATIENT SCREENING

Patients undergoing clinically indicated PCI for acute myocardial infarction (STEMI or NSTEMI) will be screened for clinical and anatomic eligibility for study participation. STEMI will be defined by symptom onset within 24 hours and ST-segment elevation of ≥1 mm in 2 or more contiguous leads, true posterior MI, or new left bundle branch block. NSTEMI will be defined as chest pain >30 min and rise of troponin. Study enrollment will require evidence of two major, non-infarct-related coronary arteries (defined as “target vessels” for the purpose of intracoronary imaging) without significant lesions in their proximal (50mm) segments (significant lesions defined as >50% reduction in lumen diameter by angiographic visual estimation). Patients will either need to be on any stable statin treatment for ≥4 weeks prior to study enrollment and have an LDL-C value of ≥70 mg/dL (1.8 mmol/L) determined prior to, or during PCI, OR have an LDL-C value of ≥125 mg/dL (3.2 mmol/L) if they are stain-naïve or have not been on a stable (≥4 weeks) statin regimen. Among patients considered to be potential study candidates based on all other inclusion and exclusion criteria, LDL-C levels will be measured rapidly from blood samples drawn after the diagnostic angiography and before completion of the qualifying PCI. For this purpose, a validated, point-of-care assay available at each participating study center will be used for prompt measurement of LDL-C levels to determine eligibility for enrollment.

5.2 Patient enrollment

Patient who fulfil all inclusion criteria (including LDL-C levels), do not meet any of the exclusion criteria, and sign the informed consent form will be considered enrolled and will undergo intracoronary imaging. All patients will be specifically asked if they consent to inclusion of their blood samples in the biobank. Patients who do not meet all inclusion criteria or meet any exclusion criteria will be considered screen failures and cannot be rescreened. Due to the particular situation of patients suffering from a heart attack with STEMI and the emergency need for treatment, a specific informed consent process will be applied (see also under 13.3 "Patient information and informed consent"):

- If the patient is conscious and in a position to take an informed decision, he/she will be asked for consent prior to the randomization.
- If the patient is conscious but, according to the treating cardiologist, not in position to read, interpret and sign the informed consent form, an oral consent will be asked for and documented in the informed consent form. As soon as possible after the intervention, the patient will be asked to confirm his/her decision by signing the informed consent form.
- Unconscious patients will not be included in the study.

Eligible patients will be considered enrolled once the consenting form has been signed and they will subsequently receive a unique Secutrial identifier, assigned by a web-based database system. The identifier will remain constant throughout the entire clinical study. Additionally, a blinded randomization identifier will be assigned when the patient is randomized. Randomization of enrolled patients will be performed only in patients with successful 2-vessel intracoronary imaging (or exceptionally also two regions of interest in the same vessel, e.g. in case of minimal caliber of one of the two non-infarct related vessels two ROI may be obtained in the larger non-infarct related vessel.), defined as successful imaging of the 2 imaging target vessels, at minimum by means of IVUS (modality used for the study's primary endpoint). Intracoronary imaging will be performed as deemed clinically feasible and safe by treating operators, aiming at successful imaging but without compromising patient safety according to physician's judgment. Imaging will be performed preferably immediately after PCI and latest within 24 hours after PCI. A screening log of all enrolled patients who undergo (successful or unsuccessful) intracoronary imaging will be maintained on the database A total of 220 enrolled patients will be randomized. Justification of the sample size calculation is described in Section 13.1.

5.3 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; 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 will be generated by an independent statistician and concealed using a central randomization 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
- Placebo Q2W SC at 1.0 ml via an autoinjector

Treatment with the investigational product (IP) (alirocumab or placebo) will start on Day 1 (Week 0) and finish on Week 50. This treatment will be on top of evidence-based optimal medical treatment, including rosuvastatin 20mg/day throughout the entire study period of 52 weeks (described in detail in **section 6.2**).

A patient is considered randomized once randomization to IP (alirocumab or placebo) is completed. 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**).

Every effort will be made that treatment assignment is un-blinded only when knowledge of the treatment is judged to be essential for patient safety. Unblinding for other reasons will be considered a protocol violation. The steering committee will be informed before any unblinding procedure is effective.

6. TREATMENT INTERVENTIONS

6.1 Investigational products

Investigational products in this study include alirocumab and placebo.

6.1.1 Composition and storage

Alirocumab 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. The dosage is in keeping with phase-3 studies with alirocumab.[29] 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.

Detailed information regarding storage will be contained in an IP manual that will be sent to each participating center. Investigators or other authorized persons (e.g., pharmacists) are responsible for storing the IP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures. Control of storage conditions, especially control of temperature (refrigerated storage) and information on in-use stability should be managed according to the rules provided by the product manufacturer. The product will be stored at the investigational site in an appropriate locked room, under the responsibility of the Investigator, and kept in a refrigerator between +2°C and +8°C (36°F to 46°F) at the site. The temperature of the site refrigerator should be checked daily and recorded on a log sheet.

6.1.2 Route and method of administration

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 IP 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.

6.1.3 Timing of administration

IP administration will be will be performed between Day 1/Week 0 and Week 50. IP administration will be initiated on Day 1/Week 0 during hospitalization for the index event, and will next be performed at planned visits at Week 2 and Week 4 at the Investigator site by qualified staff member. During these visits, patients will be trained for self-administration and noted in the injection diary distributed during the first visit (day 1). As the injection are scheduled to take place on visits including blood withdrawal, the IP will be administered after the blood sampling has been completed.

Following Week 4 (i.e., starting at Week 6), the IP will be self-administered at home once every 2 weeks up to Week 52 in accordance with instructions previously given to patients and noted in the injection diary. The IP may also be administered by another designated person (such as a spouse, relative, etc.). In this case, it must be ensured that this person has been adequately trained by the study staff prior to administering the injection. For patients or designated persons who do not feel comfortable to proceed to self-administration after Week 4, the IP may be administered on the investigational site at Weeks 6 and 8 (or later, if the patient wished so) with continuing patient training. In exceptional cases, if a patient prefers to have the injection performed at the study site and provisions are able to be made to accommodate the administration of injections at the site, it may also be allowed.

It is acceptable to have a window period of ±3 days for IP administration. If an injection is delayed by more than 7 days from the planned date, then the patient should return to the original schedule of administration without administering delayed injections. If a planned injection is delayed by less than or equal to 7 days, then the patient should administer the delayed injection and then resume the original schedule of alirocumab administration. Patients who completely miss a scheduled dose of the IP will be instructed to continue and administered the next dose as scheduled. Consecutive injections should not be administered within less than 7 calendar days.

Each patient will receive a diary to record the injections. The diary will be prepared by the study nurse and handed out to the patient during the visit at week 4. The patient will be asked to record each injection and asked to bring the diary with her/him for each visit.

6.1.4 Withholding of investigational product

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) as described in **Appendix A** and **B**.

6.1.5 Drug accountability

The Sponsor will establish and maintain adequate records from shipment to the sites until return or disposal including the physical location, dates (receipt, expiry, use, return), lot/batch number and quantities (received, used, destroyed).

Sites will be responsible for local accountability and its proper documentation of the IP, from the reception, distribution to the patient, returns from the patient to the destruction of the remaining lock stock if any.

6.2. Background medical therapy (non-investigational treatment)

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.

6.3 Prohibited concomitant medications

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)

6.4 Lifestyle and dietary habits

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 (**section 8.1**). Lifestyle and dietary habits as well as level of physical exercise should be maintained stable if possible throughout the entire study duration, if feasible.

7. STUDY PROCEDURES

7.1 Randomization visit (Day 1 / Week 0)

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. 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 (**section 5.3**).

The initial diagnostic procedure and PCI procedure will be performed by the usual clinical team in the catheterization laboratory by current standards and institutional protocols. Data that will be recorded at baseline include clinical and demographic data, use of medications, 12-lead ECG, angiographic data, IVUS, NIRS, and OCT pullback. 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 as detailed in **section 9.3.2**. 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.

The time frame between Week 0 (first administration of the IP) and Week 52 (last administration of the IP, follow-up intracoronary imaging) comprises the "treatment period" (**Figure 2**).

- The following data will be obtained and procedures performed on Day 1 / Week 0, which is the period from study enrollment and randomization up to 24 hours (patients will remain in-

hospital for a minimum of 24h, if subsequently transferred to other referring hospitals, or a minimum of 48h, if discharged from the study centers): Administer IP

- Training patient (or other designated person, if applicable) for self-injection using a dummy auto-injector pen (to be applied in an injection site other that the one used for IP administration) and distribute injection diary.
- Obtain fasting blood samples for the following measurements (to be performed at local investigation site lab):
  - Hematology: blood cell count including hematocrit, hemoglobin, RBC count, WBC count with differential count and platelets
  - Chemistry: plasma glucose, HbA1c, sodium, potassium, creatinine
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CK
- Obtain blood sample for the following measurements (samples to be transferred to biobank and measures to be performed centrally):
  - 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)
  - hs-CRP, hs-TNT, NT-pro-BNP
  - Other biomarkers specified in **section 9.3.2** (**Table 2**)

Lipid levels will be assessed by the central lab and blinded to patients, physicians, investigators and site staff.

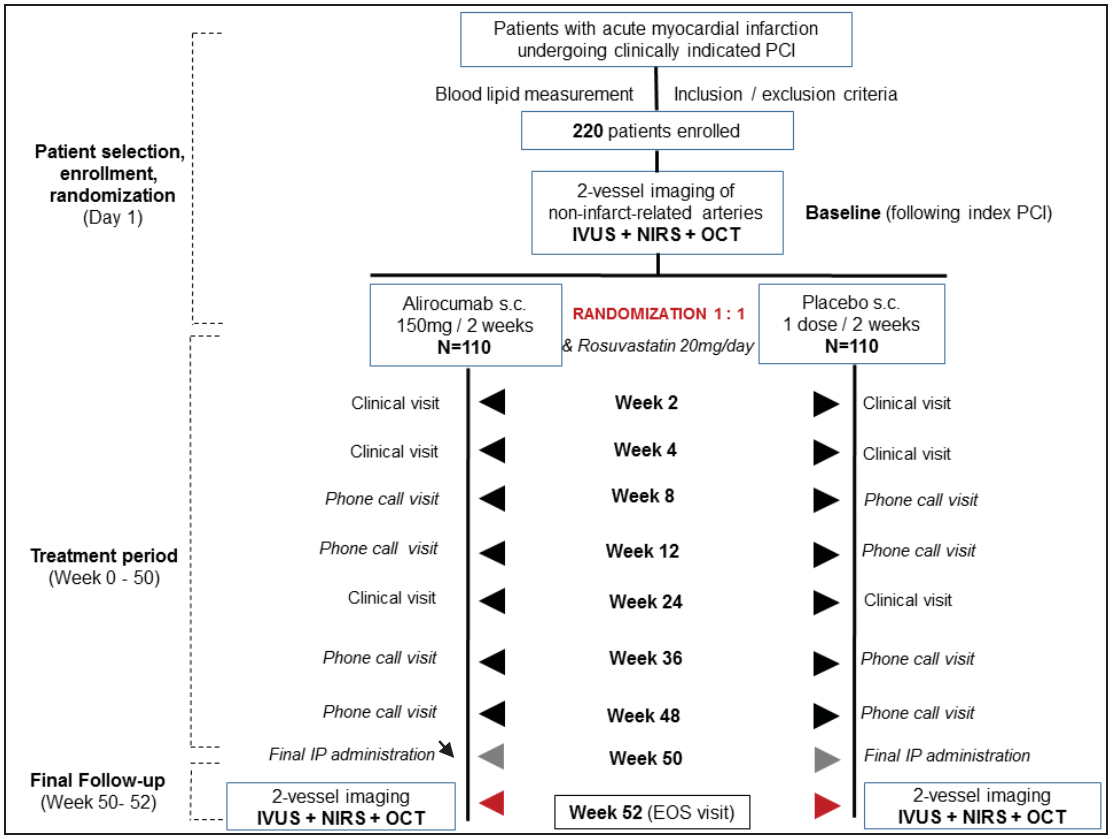

Figure 2. Schematic presentation of study flow.

7.2 Week 2 (clinical visit)

At Week 2 clinical visit, the following data will be obtained and procedures performed:

- Vital signs (blood pressure, heart rate)
- Record AEs / product complaints
- Record concomitant medications including statin treatment
- Reinforce dietary recommendations (adherence to ATP III TLC diet)
- Encourage patient to maintain stable physical activity level
- Administer IP and document injection in diary
- Review injection instructions (within diary)
- Training patient (or other designated person, if applicable) for self-injection using a dummy auto-injector pen

7.3 Week 4 (clinical visit)

The following data will be obtained and procedures performed:

- Vital signs (blood pressure, heart rate)
- Record AEs / product complaints
- Record concomitant medications including statin treatment
- Reinforce dietary recommendations (adherence to ATP III TLC diet)
- Encourage patient to maintain stable physical activity level
- Administer IP and document injection in diary
- Training patient (or other designated person, if applicable) for self-injection using dummy auto-injector pen
- Dispensation of 12 IMPs, coolbox, container for used IMPs
- Review injection instructions
- Obtain fasting blood samples for the following measurements (to be performed at local investigation site lab):
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CK
- Obtain fasting blood sample for the following measurements (samples to be transferred to biobank and measures to be performed centrally):
  - 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)
  - hs-CRP, hs-TNT, NT-pro-BNP
  - Other biomarkers specified in **section 9.3.2** (**Table 2**)

If a patient is not in fasting conditions, no blood sample will be collected and a new appointment will be given the day after or as close as possible to this date with instruction to be fasted.

7.4 Week 8 (phone call)

The following data will be obtained:

- Collect AEs / product complaints
- Record concomitant medications including statin treatment

7.5 Week 12 (phone call)
The following data will be obtained:

- Collect AEs / product complaints
- Record concomitant medications including statin treatment

7.6 Week 24 (clinical visit)
The following data will be obtained and procedures performed:

- Vital signs (blood pressure, heart rate)
- Record AEs / product complaints
- Record concomitant medications including statin treatment
- Reinforce dietary recommendations (adherence to ATP III TLC diet)
- Encourage patient to maintain stable physical activity level
- Check compliance by diary document ation and returned IMPs in container
- Dispensation of 12 IMPs, coolbox and container for used IMPs

7.7 Week 36 (phone call)
The following data will be obtained:

- Collect AEs / product complaints
- Record concomitant medications including statin treatment

7.8 Week 48 (phone call)
The following data will be obtained:

- Collect AEs / product complaints
- Record concomitant medications including statin treatment

7.9 Week 52 (end-of-study clinical visit) +14 days*/ -0 days
The following data will be obtained and procedures performed:

- Patient admission, performance of follow-up intracoronary imaging (IVUS, NIRS, OCT)
- Vital signs (blood pressure, heart rate)
- Record AEs / cardiovascular events / product complaints
- Record concomitant medications including statin treatment
- Check compliance by diary documentation and returned IMPs in containerReinforce dietary recommendations (adherence to ATP III TLC diet)
- Encourage patient to maintain stable physical activity level
- Obtain fasting blood samples for the following measurements (to be performed at local investigation site lab):
  - Hematology: blood cell count including hematocrit, hemoglobin, RBC count, WBC count with differential count and platelets
  - Chemistry: plasma glucose, sodium, potassium, creatinine

- Liver panel (ALT, AST, ALP, and total bilirubin)
- CK

- Obtain fasting blood sample for the following measurements (samples to be transferred to biobank and measures to be performed centrally):
  - 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)
  - hs-CRP, hs-TNT, NT-pro-BNP
  - Other biomarkers specified in **section 9.3.2** (**Table 2**)

If a patient is not in fasting conditions, no blood sample will be collected and a new appointment will be given the day after or as close as possible to this date with instruction to be fasted.

* Should it is not be possible to schedule the final visit on week 52, a maximal delay of 14 days may be acceptable. 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. STUDY PROCEDURES

8.1 Intracoronary imaging

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 PCIImaging should only be performed during maximal vasodilatation (repetitive administration of 100-200µg intracoronary nitroglycerin prior every pullback) and ACT is kept >250 sec during the entire imaging procedure. The starting position of both the IVUS-NIRS catheter and the OCT catheter have to be documented by radiography and on a dedicated CRF.

Patients will be readmitted at 52 weeks for catheterization and repeat intracoronary imaging using IVUS, NIRS and OCT of the same regions of interest ("target segments") of the two proximal non-infarct-related arteries ("target vessels") imaged at baseline. Prior to imaging, the operator has to review carefully the baseline recording to achieve a maximal overlap of the acquired pullbacks. Imaging will be performed at follow-up applying the same technical standards (material, procedures) and by the same operator, to the extent possible, as at baseline. In addition, OCT of the stented segment will be performed during the 52-week follow up (see Appendix 1 to protocol). Following the procedure, patients will continue treatment with dual antiplatelet therapy (aspirin plus a P2Y12 inhibitor) for a minimum of 3 additional weeks, which can be extended according to clinical indication.

During the intracoronary imaging procedure at both baseline and follow-up, it will be ensured that activated clotting time (ACT) remains >250 sec by means of adequate heparin administration.

8.1.1 IVUS acquisition

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 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.

8.1.2 IVUS analysis

The independent Corlab Cardialysis, Rotterdam, NL, will randomly allocate a code to the baseline and follow-up pullbacks in order to ensure blinding of the analysts to the temporal sequence and treatment allocation of paired images. The largest common region of interest (ROI) available from the two serial recordings will be assessed with the help of a dedicated matching software and identified as much common matching points within the pullbacks (e.g. side branches, calcifications). Within the matched ROI, the lumen and external elastic membrane will be measured in every frame (approximately 0.4 mm) (QIVUS, Medis, Leiden, The Netherlands). Analyses will be performed in accordance to current expert recommendations[46] as previously reported by our group.[47,48]

IVUS analyses will be performed in accordance to current recommended standards.[54] 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 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).[54]

8.1.3 Near-infrared spectroscopy (NIRS) acquisition

Using the same protocol as for IVUS imaging, NIRS will be performed at baseline and at follow-up using a 3.2-F NIRS catheter (InfraReDx, Inc.). The catheter will be advanced into the distal coronary artery and withdrawn by an automated mechanical pullback at 0.5 mm/s and 240 rotations/min. Raw spectra will be acquired at a rate of 40 Hz (one spectrum every 25 msec).

8.1.4 Near-infrared spectroscopy analysis

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. 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.[49] 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 ($maxLCBI_{4mm}$).[55] The secondary endpoint

for the present study will be the change in $LCBI_{total}$ between baseline and follow-up investigation.[38,55] Co-registration of IVUS, NIRS, and coronary angiography will be accomplished by matching the angiographic, IVUS, and NIRS data independently via landmark fiduciary points and the position of the IVUS and NIRS imaging catheter recorded on the coronary angiograms, accounting for the pull-back speed on the IVUS and NIRS catheters. The corresponding IVUS and NIRS segments will be determined and compared at baseline and follow-up.

8.1.5 OCT acquisition

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. After administration of intra coronary nitroglycerin, motorized pullback OCT imaging at a pullback speed of 36mm/s for a total of 75mm will be performed using a 2.7Fr C7 Dragonfly imaging catheter (Dragon Fly Duo, LightLab, St. Jude Medical, St. Paul, MN, USA). During the pullback, automated injector such as ACIST is mandatory to be used for quality reason, with an injection rate of >4.0ml/s for the left coronary artery and >3.0 ml/s for the right coronary artery depending on the vessel size. The position of the imaging catheter and probe will be filmed. As much as possible of the proximal non-infarct-related arteries will be imaged, with a minimum of 50mm as measured from the respective ostia.

8.1.6 OCT analysis

OCT images will be analyzed offline at every single frame (0.4 mm) using proprietary software (QCUCMS Medis, Leiden) as previously reported by our group.[50-52] Each plaque will be classified as lipid-rich, fibrous or fibro-calcific.[40,53] Macrophage infiltration will be defined as bright spots with increased signal intensity within the plaque accompanied by heterogeneous backward shadows, and macrophage accumulation will be quantified.[41.42] Cap thickness will be assessed using a dedicated cap measurement program. 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 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.

8.2 Intercurrent angiography

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.

8.3 Biomarker sampling and analyses

Blood samples will be collected from all patients at the time point of enrollment (Day 1), and at clinical visits at Weeks 4 and 52. A first part of the planned analyses will be performed locally at each study site, and a second part will be performed in a dedicated central lab University Hospital Bern and at University hospital Kings College London. .

8.3.1 Analyses at local study sites

8.3.1.1 Potential study candidates. Blood will be drawn from potential study candidates following diagnostic coronary angiography for rapid measurement of LDL-C levels ("baseline blood draw #1"). The LDL-C measurement will be used as an inclusion criterion to determine eligibility for enrollment (**section 4.1** and **7.1.1**).

8.3.1.2 Enrolled patients. Once enrollment is confirmed, blood will be drawn ("baseline blood draw #2") to measure following parameters: hematocrit, hemoglobin, RBC count, WBC count, platelets, plasma glucose, sodium, potassium, ALT, AST, ALP, total bilirubin, CK levels. CK peak after revascularization should be obtained every 8 hours to assess peak levels (clinically relevant in the setting of acute myocardial infarction). Blood draw will be performed from venous sheaths placed routinely in patients with acute myocardial infarction, so as to avoid multiple punctures pre-enrollment (status "potential study candidate") and post enrollment (status "enrolled patient"). The same parameters will be measured on scheduled visits at Weeks 4 and 52.

8.3.2 Analyses at central lab

Samples will be collected on day 1 (post enrollment, during "baseline blood draw #2" as described above), Weeks 4 and 52 in routine blood tubes, serum, heparin-coated and EDTA-coated plasma tubes of 10 ml vacutainers. The study site personnel will carry the samples to the local laboratory where samples will be centrifuged immediately, aliquoted and frozen at -80°C for subsequent analyses. Samples from all study sites will be transferred to a fully automated central biobank at the University Hospital in Bern. Samples will be destroyed after study end, i.e. latest five years after the last visit of the last patient has been completed.

The following blood samples will be collected: serum (4 aliquots of 500 µL and 4 aliquots of 250 µL), EDTA-Plasma (4 aliquots of 500 µL and 4 aliquots of 250 µL) and heparin-plasma (4 aliquots of 500 µL and 4 aliquots of 250 µL).

Following analyses will be performed (**Table 2**):

See Appendix 1 for early and late effects of Alirocumab on Apolipoproteins

Table 2. Planned biomarker analyses.

Key biomarkers	• Cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides, Lp (a), Apo A1, Apo B, ratio Apo B/Apo A-1, Apo C-III, Lp(a) • hs-CRP, hs-troponin T, NT-proBNP • TNFa, IL1b, IL-6, MPO, cystatine, SIRT1, SIRT6 • PCSK9 levels	• Planned to be analysed in Bern and Zurich
Neutrophil extracellular trap (NET)	• DNAase activity	• Planned to be analysed in Vienna

A. Key biomarkers

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).

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.

B. Neutrophil extracellular trap formation - DNase activity

The rationale for measuring markers of neutrophil extracellular trap (NET) formation and its counterpart, DNase activity is that endoluminal NET formation has emerged as a major component of acute atherothrombosis.[54] Surrogate markers of NET predict cardiovascular events. Oxidized LDL is a trigger for NET release.[55,56] We hypothesize that specific reduction of oxidized LDL by means of alirocumab reduces neutrophil activation, NET burden and coronary plaque progression.

For the measurement of nucleosomes (DNA-histone complexes), an ELISA - cell death detection kit (Roche Diagnostics GmbH, Germany) will be used. Optical density (OD) values will be set in proportion to the internal positive control and expressed as arbitrary nucleosome units/ml (NU/ml). The intra-assay positive control equals 1000 NU/ml. For the measurement of MPO-DNA complexes, a mouse anti-human myeloperoxidase antibody (AbD Serotec) will be coated. Results will be given as expressed as arbitrary MPO-DNA units/ml (NU/ml) in proportion to the internal control. For the measurement of citrullinated histone 3, a mouse anti-human histone 3 antibody (Abcam) will be used. Results will be given as expressed as arbitrary citH3 units/ml (NU/ml) in proportion to the internal control. For detection of double stranded DNA (dsDNA) in patient plasma, we will employ a Quant-iT PicoGreen dsDNA Assay (Invitrogen, USA) on 96-well microplates. Fluorescence will be measured by a Varioskan Flash microplate reader (Thermo Scientific, USA) and normalized to the provided standard (1000 ng/ml). Endogenous DNase activity will be measured employing a DNase Activity Assay (Orgentec Diagnostika GmbH, Mainz, Germany).

This analysis has the following aims:

- To compare NET surrogate markers and NETosis at baseline and Week 52 following treatment with alirocumab vs. placebo

- To correlate data on NETs with changes in coronary plaque burden and composition

9. STUDY OUTCOMES

9.1 Primary Endpoint

- The primary endpoint is the change in percent atheroma volume (PAV) as determined by IVUS, between baseline and 52-week follow-up from matched regions of interest. This endpoint is used for the pre-specified sample size calculation.

Justification of primary endpoint selection

The selection of PAV as the primary endpoint is consistent with previous serial IVUS studies assessing plaque regression in response to statin treatment,[10,11] as well as with the GLAGOV study assessing the effect of evolocumab on coronary atherosclerosis. Among different IVUS measures of disease burden, change in PAV (i.e. percentage of vessel wall volume occupied by atheroma) is recommended due to smaller variability compared with other endpoints that may be sensitive to pullback length differences.[33]

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, maxLCBI4mm at BL, hsCRP on treatment levels.

9.2 Secondary Endpoints

9.2.1 Secondary imaging endpoints

Pre-specified secondary imaging endpoints are measures of change between baseline and 52-week (12-month) follow-up from the matched ROI:

- Change in lipid-core burden index ($LCBI_{total}$) as determined by NIRS, between baseline and 12-month follow-up from matched ROI
- Change in maximum LCBI in any 4-mm segment ($maxLCBI_{4mm}$) as determined by NIRS
- Change in minimal and fibrous mean cap thickness as determined by OCT
- 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)

9.2.2 Secondary biomarker endpoints

- Change in LDL-cholesterol, hs-CRP, hs-TnT and NT-pro-BNP as well as lipid and inflammatory markers (**Table 2**) between baseline (Week 0), Week 4, and Week 52
- Association between levels of biomarkers and changes in plaque characteristics as described in the primary and secondary imaging endpoints

9.2.3 Secondary clinical endpoints

- Death
- Cardiac death

- Myocardial infarction
- Any coronary revascularization
- Stroke, transient ischemic attack

The definition of cardiac death includes any death due to immediate cardiac cause, procedure-related deaths, and death of unknown cause. The diagnosis of MI requires ischemic signs or symptoms and new pathological Q-waves in ≥2 contiguous electrocardiogram leads. In the absence of Q-waves, the diagnosis of MI is based on an elevation in CK to ≥2× upper limit of normal and an elevation of CK-MB or troponin to ≥3× upper limit of normal.

Any patient who develops a major adverse cardiac event during the follow-up period should be evaluated by the Investigator. Case Report Form for Event and data regarding any adverse events will be sent to the Clinical Event Committee. The Clinical Event Committee, consisting of cardiologists not participating in the trial, will review and adjudicate all major adverse cardiac events. The members of the Clinical Event Committee will be blinded to the patient's treatment allocation.

9.2.4 Secondary safety endpoints

- Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), product complaints, laboratory data (refer to **Section 10** for details).

10. DEFINITION AND REPORTING OF ADVERSE EVENTS

10.1 Definitions of adverse events

An adverse event (AE) is any untoward medical occurrence or clinical investigation in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.2 Definitions serious adverse event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

• Results in death, or

• Is life-threatening, or

• Requires inpatient hospitalization or prolongation of existing hospitalization, or

• Results in persistent or significant disability/incapacity, or

• Is a congenital anomaly/birth defect

• Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (i.e., specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

10.3 Definitions of suspected, unexpected, serious adverse reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for drugs that are not yet approved and Product Information for approved drugs, respectively).

The DSMB will evaluate any SAE that has been reported regarding seriousness, causality and expectedness. If the event is categorized as "possibly", "probably" or "definitively" related to the investigational product and is both serious and unexpected, it will be classified as a potential SUSAR. A potential SUSAR will require unblinding to determine a SUSAR. The DSMB will provide an overall assessment of benefit and harm given the observed rates of SAE at that time.

10.4 Definitions of adverse events of special interest

An adverse event of special interest **(**AESI) is an AE (serious or non-serious) of scientific and medical concern for which ongoing monitoring and immediate notification to Sanofi PV is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

Adverse events of special interest (AESI) in this study include the following:

AESI	Definition
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.

10.5. Safety instructions related to investigational product

10.5.1 Local tolerability (local injection site reactions)

In case the Investigator or patient recognizes any signs of local intolerability, this should be treated and followed-up as per the Investigator's medical judgment. Specific electronic CRF screens are to be filled in. Local symptoms should be reported in the "local injection site reaction" section. If the injection site reaction progresses, both "local injection site reaction" and "general allergic reaction" of the form should be completed.

10.5.2 Allergic adverse events requiring consultation and local injection site reactions that are allergic and requiring consultation

Specific e-CRF screens are to be filled in to assess allergic reactions or allergic-like reactions requiring consultation with another physician that may occur. Transient injection site reactions, irritant in nature, that may occur but do not require intervention and are of dubious significance would not be considered to be allergic reactions. Adverse events that are obviously not of allergic origin (e.g., local injection site reactions related to mechanics of injection) should only be recorded on the Local Injection Site Reaction Complementary Form.

The IP should be immediately interrupted (temporarily discontinued) if there is a suspicion of an allergic event related to the IP. Re-initiation of the IP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met.

The Investigator should exercise medical judgment concerning the handling of all background/ concomitant medications potentially related to an allergic event.

10.5.3 Allergic adverse event with cutaneous involvement

Adverse events (AE) with cutaneous involvement which are obviously of allergic origin or injection site reactions which progress/expand/worsen should be evaluated by a dermatologist as soon as possible, and preferably within one week of the site first becoming aware of the event. The Investigator should evaluate the patient for possible etiologies (e.g., new medications) and extracutaneous symptoms and signs. An unscheduled assessment for hematology, chemistry, liver panel should be obtained. If possible, the site will take pictures of the skin lesions in order to provide the patient with them for the dermatologist's visit. If the photos are obtained, then copies should be kept as source documents which may later be collected and transmitted to Sanofi PV. The Investigator will provide a summary of the patient's case, reason for consultation, and information being requested to the consulting dermatologist.

A full consultation report should be sent by the dermatologist to the Investigator. The full report should contain, at a minimum, the following information; a detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [e.g.,

scattered, grouped, linear], distribution, color, consistency, presence of pruritus or pain, and other clinical signs) and in case a skin biopsy (including histopathology and immunofluorescence) was done (if it was deemed necessary as per the dermatologist's or Investigator's medical judgment), the results of this investigation with, if applicable, a specific diagnosis of the AE. The Investigator will fax the full report and the corrected AE form if necessary, to the monitoring team representative within 24 hours and Sanofi PV.

10.5.4 Acute allergic injection reactions

Acute allergic injection reaction (which are considered under the category of general allergic reactions) is defined as any AE that occurs during or shortly after injection of the IP characterized by - but not limited to - hypotension, bronchoconstriction, urticaria, edema, angioedema, nausea, vomiting. Emergency equipment and medication for the treatment of these potential adverse effects (e.g., antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and epinephrine) must be available for immediate use for the injection at the inclusion visit.

Patients will be observed at the investigational site for at least 30 minutes following the injection that takes place at hospital. Patients should be treated symptomatically if any AEs are observed. Patients are to remain at the site until any acute injection reaction is assessed as stable, at the Investigator's discretion. General Allergic Reaction and/or Local Injection Site Reaction Complementary Form will have to be completed.

10.5.4. Neurocognitive side effects

In case of a suspected neurocognitive side effects (<0.2%), the study patients would be referred to a neurologist for further clinical evaluation prior to the next scheduled IMP administration.

10.6 Reporting of adverse events/ SUSAR/AESI

AE and SAE will be consistently documented.

The local Investigator will report all Serious Adverse Events (SAEs) regardless of the relationship to the investigated medicinal product and all Adverse Events of Special Interest (AESIs) (a) to the Sponsor/Coordinating Investigator within 24 hours of becoming aware of the event. If the event is fatal, it must be reported by the local Investigator to the responsible Ethics Committee within 7 days or according local regulations and requirements.

A SUSAR needs to be reported to the responsible Ethics Committee and to the health/ regulatory authorities (via Sponsor / Coordinating Investigator) within 7 days if the event is fatal, or else within 15 days (all other events) or according local regulations and requirements. The Sponsor / Coordinating Investigator must inform all Investigators participating in the clinical study of the occurrence of a SUSAR.

All SAEs will be followed until the event has resolved (with or without sequelae). All deaths, regardless of underlying cause and relationship to study drug, will be reported as SAEs up to the last visit of the patient.

This reporting requirement is applicable to SAEs/AESIs that occur during the designated study period. If the Investigator is notified of an SAE/AESI after the end of the study and the Investigator feels that this SAE is causally related to the study drug, the Investigator should report this event through the process described above in this paragraph.

All Serious Adverse Events (SAEs) regardless of the relationship to the investigated medicinal product and all Adverse Events of Special Interest (AESIs) must be transmitted to Sanofi PV within 1 business day of the Sponsor's awareness. The Sponsor/Coordinating Investigator must provide to Sanofi, upon request, results of any relevant complementary exams performed to obtain the final diagnosis of any SAE or AESI (e.g. hospital discharge summary, autopsy, consultation).

11. SAFETY AND FEASIBILITY OF INTRACORONARY IMAGING IN THE SETTING OF ACUTE MYOCARDIAL INFARCTION

At baseline (Day 1), study procedures for intracoronary imaging (IVUS, NIRS, OCT) are expected to increase the length of the cardiac catheterization by approximately 30-40 minutes. Potential, generally acknowledged risks of cardiac catheterization include a risk of death, myocardial infarction, or stroke of approximately 1 in 1000. However, the index cardiac catheterization and PCI will be performed only for clinical indications (acute myocardial infarction) and not for the purposes of the study. The incremental risks are only those associated with the intracoronary imaging procedures; importantly, IVUS is generally a very safe and routine clinical procedure. The study will require no additional in-hospital time. The repeat cardiac catheterization at Week 52 is associated with similar risk as the initial procedure (approximately 1 in 1000 of life threatening complications or a small risk of coronary artery damage by IVUS less than 1%).

Our group has specifically tested the feasibility, procedural and long-term safety of intracoronary imaging with OCT and IVUS in patients with acute STEMI undergoing primary PCI in the setting of the IBIS-4 study.[35] Imaging of the non-infarct-related artery at baseline and follow-up was successful in 88.7% and 95.6%, respectively, of patients using OCT and in 90.5% and 93.3%, respectively, using IVUS. Peri-procedural complications occurred less than 2.0% of OCT (arrhythmia, resolved with electroconversion) and none during IVUS, and there were no differences throughout 2 years as compared with a control group of 485 STEMI patients undergoing primary PCI without additional imaging in terms of major adverse cardiac events (16.7% vs 13.3%, adjusted HR1.40; 95%CI 0.77-2.52; p=0.27). These data demonstrated that multi-modality three-vessel intracoronary imaging in STEMI patients undergoing primary PCI is feasible and can be performed safely without a significant impact on cardiovascular events at long-term follow-up.[57] Similar to IBIS-4, two catheters will be used (IVUS-NIRS combined catheter and OCT catheter). Consistently, we expect that performance of intracoronary imaging will be at least as safe in the present study that will also enroll relatively lower-risk patients with NSTEMI.

12. STATISTICAL CONSIDERATIONS

12.1 Pre-specified sample size calculation

12.1.1 Evidence of effect sizes on PAV. Previous serial IVUS studies assessing the effect of different statin doses on PAV by IVUS showed a dose-response relation between changes of PAV and doses of statin (and consequently, magnitude of LDL-C reduction). In the CAMELOT trial, a PAV increase of +1.3% was seen in placebo patients who received standard-of-care statin regimens.[58] Hong et al.[59] found that rosuvastatin 20mg resulted in -0.46% reduction of PAV at 11 months. Using a higher-dosed statin regimen, we recently reported a 43% reduction of LDL-C at 13 months with rosuvastatin

40mg and a PAV reduction of -0.90% at 13 months.[35] Consistently, a 53% LDL reduction and -0.98% PAV reduction at 24 months with rosuvastatin 40mg was reported in the ASTEROID trial,[10] and a 44% LDL-C reduction and -1.23% PAV reduction was found in the SATURN trial at 24 months.[11] Of note, a sub-analysis of our data from the IBIS4 trial demonstrated that patients with more pronounced (above-median) LDL-C reduction had an average PAV reduction of -1.66 %, whereas in patients with less pronounced (below-median) LDL-C reduction the decrease of PAV was only -0.16%.[35] This finding indicates that differences in the magnitude of LDL-C reduction are associated with a difference of the order of ±1.5% in PAV change within a single cohort. Of note, the addition of ezetimibe to atorvastatin in the PRECISE-IVUS trial resulted in incremental LDL-C lowering and PAV reduction compared with treatment with atorvastatin alone, an effect that was most pronounced in patients with acute coronary syndromes (i.e., similar to patients in the present study) as compared with patients with stable coronary artery disease.[60]

12.1.2 Rationale for expected effect size in each treatment arm. In summary, the observed range of PAV change over 1-2 years is in the range -1.2% to +1.3% in previous statin trials, with highest-dose statin regimens consistently associated with a PAV reduction of the order -0.90% to -1.23%. Along this line, the addition of alirocumab to maximally tolerated statin doses resulted in an incremental LDL-C reduction by 29.8% as compared to patients treated with maximal tolerated statin doses plus ezetimibe, with the proportion of patients reaching the LDL-C target of 70 mg/dl (1.8 mmol/L) being 77% vs. 45.6% and the proportion of patients reaching the extremely low LDL-C target of 50 mg/dl (1.3 mmol/L) being 60.3% vs. 14.2%, respectively.[27] Given the substantial incremental LDL-C reduction with alirocumab on top of maximally tolerated statin doses, we consider that a reduction in PAV beyond -1.23% is possible and we assume an expected PAV reduction of -1.8% in the PCSK9 inhibitor arm after 1 year. For the placebo arm of the proposed study that will receive rosuvastatin 20mg, the results by Hong et al[59] provide a reasonable benchmark to assume a moderate expected PAV reduction of -0.5%.

12.1.3 Sample size calculation. This is a superiority trial powered on 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 SATURN[11]: 3.0%, IBIS4[35]: 3.4%, ASTEROID[10]: 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). See Appendix 1 for adjusted sample size and statistics

12.1.4 Pre-specified protocol amendment with revised sample sized calculation. The GLAGOV study is currently testing the effect of evolocumab on PAV regression by IVUS in a multi-center study including 968 patients. Study outcomes are expected to be presented in Q4, 2016. In case GLAGOV 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. No amendment will be made in the present study if the GLAGOV findings exceed our present assumptions regarding PAV regression.

See Appendix 1 for adjusted sample size and statistics

12.2 Pre-specified statistical analysis of endpoints.

The primary analysis aims at comparing the active treatment (alirocumab) group with the placebo group in terms of the primary endpoint. The primary endpoint is defined at vessel level (matched ROI within vessels) and will therefore 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. 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. 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;[49] if necessary, an adequate transformation will be used prior to deriving the change and estimating the p-values. Primary analyses will be based on the intention to treat principle (ITT). A sensitivity analysis for patients with missing data will be conducted and baseline characteristics will be compared with those of patients with complete data.

See Appendix 1 for adjusted sample size and statistics

13. REGULATORY ASPECTS

13.1 Study registration

This study is registered on Clinicaltrials.gov. The identification number is NCT03067844.

13.2 Categorisation of study

This interventional study is a clinical trial with medicinal product. The risk category is B, as the medicinal product is authorized in Switzerland and will be used in an indication at variance from that specified in the prescribing information (ClinO, Art. 19). International Categorization according local guidelines/ laws.

13.3 Patient information and informed consent

Prior to patient enrolment into the study, the Investigator will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The participant will be informed that his/her medical records may be examined by authorised individuals other than their treating physician. The consenting Investigator must allow the patient to ask questions and provide adequate time for the patient to decide whether or not he/she would like to participate.

Due to the particular situation of patients suffering from a heart attack with STEMI and the emergency need for treatment, the following informed consent process will be applied:

- If the patient is conscious and in a position to take an informed decision, the patient will be asked for consent prior to the randomization.
- If the patient is conscious but, according to the treating cardiologist, not in position to read,

interpret and sign the informed consent form, an oral consent will be asked for. This oral consent will be documented in the informed consent form. As soon as possible after the intervention, the patient will be asked to confirm his/her decision by signing the informed consent form. If the consent is revoked, the health-related personal data of the patient collected up to the time of withdrawal will be anonymized after data evaluation has been completed. In case of death after oral consent but prior to the signed informed consent, the collected data will be anonymized after data evaluation has been completed.

- Unconscious patients will not be included in the study.

All study participants will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Due to the specific character of the study, the patients will be informed about the study and asked for participation by the treating interventional cardiologist immediately after the diagnostic angiography as this is the precondition to assess patient eligibility. Obtaining consent prior to angiography is not possible as it is expected that less than ≈5% of patients undergoing diagnostic angiography will be eligible for study inclusion. Obtaining consent in the operating room appears justified as the PCI procedure and the devices used are approved (CE marked) and in a clinical setting outside the study, the Investigator may also decide to perform OCT or IVUS to guide PCI as supported by current guidelines for myocardial revascularization. Furthermore, rescheduling the coronary intervention is not advisable as it may increases patient's risk (e.g. in case of acute coronary syndrome or unstable angina) and would potentially increase the risk for periprocedural complication (e.g. repetitive punctures or changing access sheath etc.) The Investigator must clearly document the process of obtaining informed consent in the subject's source documents by indicating the exact time, when the patient was provided with the specific study information. It is the Investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP, EC requirements and country specific regulations.

The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study specific procedure.

13.4 Patient privacy and confidentiality

All data and information collected during this study related to the participating patient will comply with the standards for protection of privacy based on applicable local/ national requirements for patient's confidentiality. All data used in the analysis and summary of this study will be encoded, and without reference to specific study patient names. Access to study patient files will be limited to authorized personnel of the Investigator and research staff as well as authorized personnel responsible for monitoring of the data. Authorized personnel from competent authority have the right to inspect the records pertinent to this study. Patients will be informed that anonymized data from the study may be transferred to the company that provides the drug and funding for additional analyses under applicable data privacy law.

13.5 Early termination of the study

The Principle Investigator (and any competent authority) may terminate the study prematurely according to certain circumstances, such as:

- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk,
- early evidence of benefit or harm of the experimental intervention.

The DSMB will have the responsibility for recommending early termination of the study to the

Sponsor / Coordinating Investigator which will have ultimate authority/responsibility for making the decision. The criteria that the DSMB will follow to determine whether/when to recommend termination of the study will be based on:

- results of any interim analysis;
- results of parallel clinical studies;

In such a case, the CEC will be informed within 15 days and a final report will be provided within 1 year.

13.6 Consent withdrawal, patient removal and replacement

All patient have the right to withdraw fully or partially from the study at any time and for any reason, without any consequences on the patient's subsequent clinical care. Patients may withdraw consent in case they do not wish to continue receiving investigational treatment, do not wish or are unable to continue study participation (follow-up visits, planned study-related procedures). Patient data of all randomized patients up to consent withdrawal will be included for study analyses based on the intention-to-treat principle. The Investigator should ask the patient about the possibility of performing all or part of the procedures included in the final study visit. All efforts will be made to complete observations as thoroughly as possible up to the date of withdrawal.

Patients may wish to discontinue receiving the IP. If this occurs, Investigators should encourage these patients to continue with data collection, including study endpoints and adverse events. If a patient refuses further follow-up examinations (drop-out) or is lost-to follow-up, the reason for dropping out or loss will be recorded and the patient will be censored at the time when the last follow-up examination took place.

Reasons for patient removal from protocol-required IP or study procedures may include clinical indication as judged by the Investigator, or occurrence of adverse events related to the IP or study procedures.

There will be no replacement of randomized patients in this study.

13.7 Study schedule and milestones

The planned study scheduling is as follows:

Achievement	**Time-point / Time frame**
Time from initial protocol submission to ethical approval	**6 months**
First patient enrolled	36 months enrollment period
Last patient enrolled (N=294)	**42 months**
	12 months follow-up
Last patient follow-up	**54 months**
	6 months imaging data analysis
Core lab analysis completed	**60 months**
Final report	**66 months** (5.5 years)

13.8 Protocol amendments

The Principle Investigator and the Local Investigators are allowed to provide suggestions for a protocol amendment. Substantial amendments will only be implemented after approval of the CEC. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol. Refer also to **Section 12.1.4** for pre-specified protocol amendments with regard to study sample justification.

Under emergency circumstances, deviations from the protocol may proceed without prior approval of the sponsor and the CEC when necessary to protect the rights, safety and well-being of patients or when the change(s) involves only logistical or administrative aspects of the trial. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible. All amendments judged to be non-substantial by the Principle Investigator (administrative, logistical) will be communicated to the CEC within the Annual Safety Report (ASR).

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

14. QUALITY ASSURANCE AND CONTROL

14.1 Data collection, Case report forms, and database

Investigators will maintain information in the patient's medical records to corroborate data collected on the case report forms. At minimum, the following list of information will be maintained and made available as required by monitors and/or regulatory inspectors:

- Original signed copy of the patient informed consent (PIC)
- Medical history/physical condition of the study patient before involvement in the study sufficient to verify investigational plan entry criteria (if not already present)
- Medical records
- Assigned patient number
- AE/SAE reported and their resolution, including supporting documents such as discharge summaries, investigation reports, lab results.
- Study patient's condition upon completion of or withdrawal from the study.

Patient data will be collected using paper Case Report Form (CRF) at the index procedure, and during all planned study visits. Specific form for AE/SAE will be available. Only the Local Investigator will be able to decode the patient's name. All required data will be accurately recorded by authorized personnel on Case Report Forms (CRFs). Appropriate training will be ensured by the Coordinating Investigator.

14.1.1 Data handling and record keeping / archiving / Data Management System (Hardware and software)

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (secuTrial). The EDC system is activated for the trial only after successfully passing a formal test procedure. The confidentiality of patients' health related data and documents that could identify subjects will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects will be identified only by their assigned study number and year of birth on all CRFs and other records and documents submitted.
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number) on each subject.
- The investigator will maintain all study documents in strict confidence.
- CRF entries will be performed by authorized persons and it will be assured that any authorized person can be identified.

All data entered in the CRFs are stored on a Linux server in a dedicated Oracle database. Responsibility for hosting the EDC system and the database lies with Inselspital Bern.

14.1.2 Confidentiality, data protection (data security, access and back-up)

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.

All data entered into the CRFs are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail). A multi-level back-up system is implemented.

14.1.3 Archiving and Destruction (Analysis and archiving)

At interim and final analyses, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in special archive tables. The study database with all archive tables will be securely stored by Inselspital Bern. The sponsor also keeps the Trial Master File and interim and final reports both in electronic and in hard copy form for at least 10 years.

14.1.4 Electronic and Central Data Validation

Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant. In addition central data reviews will be performed on a regular basis to ensure completeness of the data collected and accuracy of the primary outcome data.

14.2 Blood samples at core lab

The blood samples sent to the Core Lab (Biobank, University Hospital Bern) will be destroyed after study end, i.e. latest five years after the last visit to the last patient has been completed.

14.3 Intracoronary imaging data handling

IVUS, OCT, and NIRS data will be stored in the media as “native” format (raw data) in the local hospitals and will be sent to an independent Core Laboratory (Inselspital (OCT); Cardialysis BV, Westblaak 98, 3012 KM, Rotterdam, NL (IVUS NIRS)). Only the patient ID provided by web-based system is indicated on the records. Patient’s name and date of birth will be anonymized an concealed as for the treatment allocation and acquisition time point. All angiography and OCT pullbacks at baselines and 12-month follow-up will be sent to the Core Laboratory (Bern University Hospital, Switzerland). IVUS and NIRS pullbacks will be sent to a separate Core Laboratory (Cardialysis, Rotterdam, NL). Analyses will be performed only serially (both baseline and follow-up pullback available). However, the independent Core Laboratory will verify the quality of the IVUS and NIRS baseline recording and provide immediate feedback on the acquisition quality to the site and the

steering committee. In case of insufficient quality of the recordings, repetitive trainings will be organized on site and in case of persisting quality issues, the center or individual physicians may be excluded from the trial. Similarly, Bern University Core Lab will verify the baseline OCT recordings and analyze OCT pullbacks only serially.

14.4 Record retention at study sites

Investigators must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents. Investigators should retain the study documents at least 10 years after the completion or discontinuation of the clinical trial. Applicable regulatory requirements should be taken into account in the event that a longer period is required.

14.5 Handling of data and blood samples in case of withdrawal of consent

Patients can withdraw their consent at any time without justification. The data and samples collected up to this point will be analyzed and anonymized after study end, i.e. latest five years after the last visit to the last patient has been completed. No further data or samples will be collected.

14.6 Monitoring

Monitoring will verify that the rights and well-being of the patients are protected, the trial is conducted according to GCP and that the protocol is followed. A specific monitoring plan will be developed. The dates of the visits will be recorded by the monitor in a log kept at the site. The source data/documents should be accessible to monitors and questions should be answered during monitoring. The Local Investigator and their relevant personnel should be available during monitoring visit and possible audits and sufficient time should be devoted to the process. The progress of the study will be monitored by:

- Ensuring completed eCRFs match source documents, and resolution of any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data.
- Periodic on-site visits and, if necessary, remote monitoring of data.
- Frequent telephone or email communications between the investigator and assigned study site monitors.
- Appropriate computer edit programs will be run to verify the accuracy of the database.

14.7 Audits and inspections

The source data/documents are accessible to auditors/inspectors (also CEC and Competent Authorities) and questions will be answered during inspections. All involved parties must keep the participant data strictly confidential.

15. ETHICAL CONSIDERATIONS

15.1 Competent Ethics Committee (CEC)

The study will be submitted to the competent ethics committee (CEC), the Kantonale Ethikkommission (KEK) in Bern, Switzerland. The KEK will act as the lead CEC.

The responsible Investigator at each site (Local Investigator) ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study

according local requirements.

15.2 Ethical conduct of the study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

16. PUBLICATION AND DISSEMINATION POLICY

One or several manuscripts will be prepared for publication in reputable scientific journals regardless of positive or negative results. The publication of the principal results from any single center experience within the trial is not allowed until both the preparation and publication of the multi-center results as appropriate. All publications will follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors.

17. FUNDING AND SUPPORT

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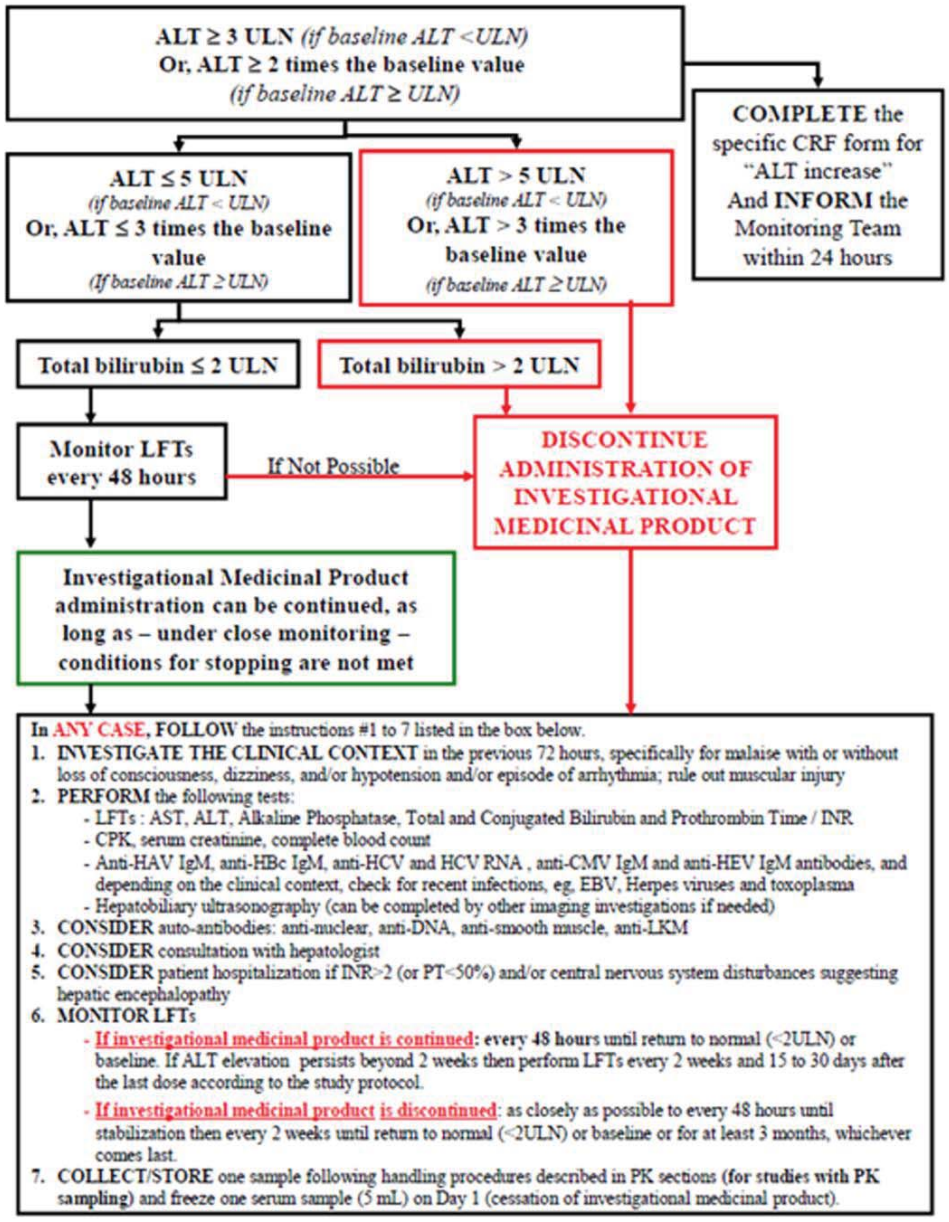
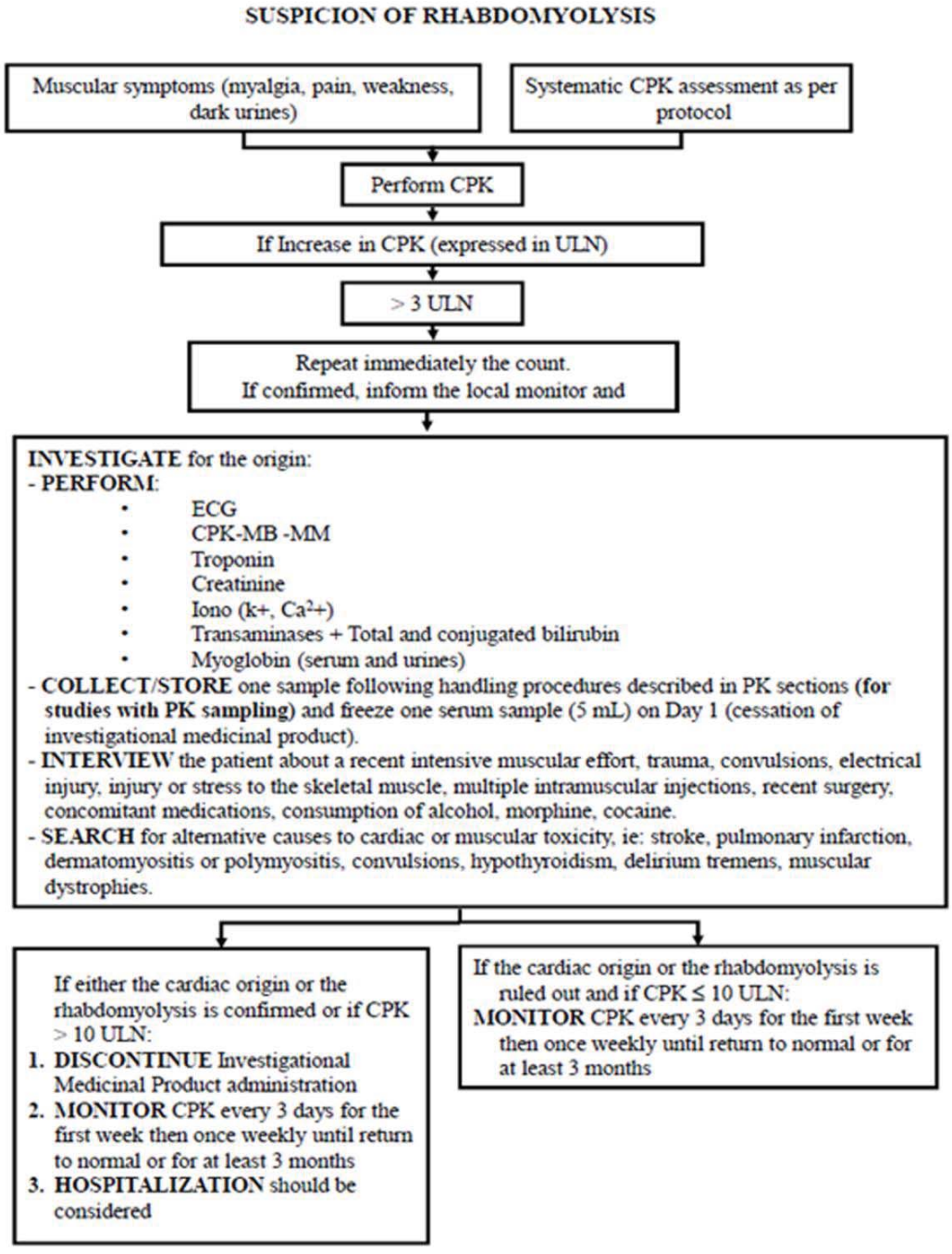
19. APPENDICES

APPENDIX A. General guidance for the follow-up of laboratory abnormalities: elevation in liver enzymes (concerns specifically the mandatory 4 week liver enzyme blood sampling).



Note: ALT ≥ 3 ULN (if baseline ALT < ULN) or ALT ≥ 2 times the baseline value (if baseline ALT ≥ ULN) should be notified within 24 hours to the monitoring team. In addition, if ALT < 3 ULN meets a seriousness criterion, the event should be notified within 24 hours to the monitoring team.

APPENDIX B. General guidance for the follow-up of laboratory abnormalities: elevation in creatine kinase levels.



Suspicion of rhabdomyolysis is to be recorded as an AE only if it meets any of the following:
• Symptomatic
• Requiring either corrective treatment or consultation
• Leading to IMP discontinuation or modification of dosing
• Fulfilling a seriousness criterion (in that case, the event [SAE] should be reported within 24 hours to the monitoring team).