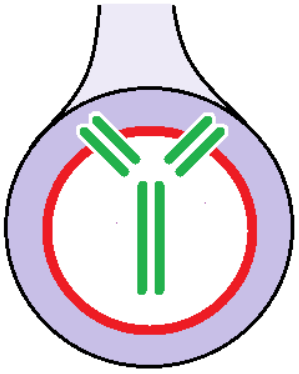
EVOLVD: Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients



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Protocol Synopsis

EVOLVD: Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients

Sponsor	Oslo University Hospital
Phase and study type	Phase IIIB, interventional, randomised controlled trial
Investigational Medical Product (including active comparator and placebo) :	Evolocumab or matching placebo
Centres:	Oslo University Hospital, Rikshospitalet, Oslo, Norway
Study Period:	Estimated date of first patient enrolled (study start) November 1st, 2018 Anticipated recruitment period: February 1st , 2019 – February 28th, 2022 Estimated date of last patient completed treatment: February 28th, 2023 Estimated date of last patient completed (last patient, last visit: Study end): March 31st , 2023
Treatment Duration:	12 months
Follow-up:	13 months (including treatment period)
Objectives	The main goal of this study is to evaluate the effect of the PCSK9 inhibitor Evolocumab on cardiac allograft vasculopathy in *de novo* heart transplant recipients. Secondary objectives are to assess the impact of treatment on: i) cholesterol levels, ii) renal function, iii) inflammation, iv) Quality of life, v) cardiac function as assessed by biomarkers and echocardiography, vi) the number of rejections, and (vii) safety and tolerability. As an exploratory outcome, we will assess the effect of treatment on clinical events (death, myocardial infarction, cerebral stroke, cancer, end stage renal disease)
Endpoints:	Primary endpoint: The primary endpoint will be the baseline-adjusted maximal intimal thickness as measured by coronary intravascular ultrasound (IVUS) after 12 months of treatment. Secondary endpoints: • Percent atheroma volume • Cardiac allograft vasculopathy (defined as mean a maximal intimal thickness ≥0.5 mm over the entire matched segment)

- LDL cholesterol
- Estimated glomerular filtration rate (eGFR)
- Quality of life as assessed by the SF36 and the EQ 5D 3L EuroQoL questionnaires, and the Beck's Depression Inventory
- N-terminal pro-B-type natriuretic peptide (NT-proBNP)
- Cardiac troponin T (TnT)
- The number of rejections
- The number of adverse events
- The number of major clinical adverse events, defined as death, myocardial infarction, percutaneous coronary intervention/coronary bypass surgery, cerebral stroke, cancer, end stage renal disease (exploratory endpoint)

Study Design:	This is a multicentre, multinational, dual arm, double blind, randomised, placebo-controlled trial.
Main Inclusion Criteria:	*De novo* heart transplant recipient.
Main Exclusion Criteria	Contraindications to study medication. Inability to perform coronary angiography with IVUS Estimated glomerular filtration rate < 20 ml/min Failure to obtain written informed consent
Sample Size:	130 patients
Efficacy Assessments:	Coronary IVUS, echocardiography, clinical assessment, blood samples for the assessment of lipid levels and inflammatory markers
Safety Assessments:	Physical examination. In-hospital observation for during the first dose of study drug administration. A 24-hour contact number will be provided. Repeat assessment after 1, 2, 3, 6, 9, 12, and 13 months.

List of abbreviations and definition of terms

Abbreviation or special term	Explanation
AE	Adverse event
CAV	Cardiac allograft vasculopathy
CRF	Case report form
CRP	C-reactive protein
DMC	Data monitoring committee
eGFR	Estimated glomerular filtration rate
GCP	Good clinical practice
ICH	International Conference on Harmonisation
IVUS	Intravascular ultrasound
LDL	Low density lipoprotein
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PCSK9	Proprotein convertase subtilisin/kexin type 9
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
TnT	Cardiac troponin T

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control; control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrolment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Investigational drug	The study drugs whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Randomisation number	A unique identifier on the label of each medication package in studies that dispense medication using an IVR system
Patient number	A unique identifier assigned to each patient who enrols in the study. In the EVOLVD study, the patient number equals the randomisation number
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrolment, randomisation, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomisation number	A unique identifier assigned to each randomised patient, corresponding to a specific treatment group assignment
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any control drugs
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

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1 Introduction

Heart transplantation is the treatment of choice for selected patients with end-stage heart failure.[1] World-wide, the median survival after transplantation is more than 11 years.[2] However, the longevity of the allograft is significantly limited by cardiac allograft vasculopathy.[3] This is a unique form of accelerated atherosclerosis that is characterised by a diffuse, progressive thickening of the arterial intima of the arteries in the allograft.[4]

Pravastatin reduces cholesterol levels and mitigates cardiac allograft vasculopathy in heart transplant recipients,[5, 6] and is recommended in the routine treatment of heart transplant recipients.[7] Despite the widespread use of statins, however, the prevalence of hyperlipidaemia reaches 88 % 5 years after heart transplantation.[2] Due to drug interactions,[8] statin-associated myopathy is widespread in transplant recipients. The high prevalence of statin-related side effects limits our ability to achieve optimum lipid levels in heart transplant recipients with statin therapy alone. On the other hand, there have been no randomised controlled trials to show that second-line lipid lowering drugs improve outcomes in these patients.[9]

Evolocumab is an inhibitor of the enzyme pro-protein convertase subtilisin–kexin type 9 (PCSK9). The PCSK9 inhibitors induce a massive reduction in low density lipoprotein (LDL) cholesterol.[10] Evolocumab lowers LDL cholesterol on top of statin therapy, and the additional reduction in LDL cholesterol translates to a reduced incidence of myocardial infarction and stroke in patients with coronary artery disease.[11]

1.1 Cardiac allograft vasculopathy

Cardiac allograft vasculopathy is a major impediment to long-term survival in heart transplant recipients.[12, 13] It is present in 48 % of heart transplant recipients within 10 years after transplantation,[2] and accounts for 30% of deaths occurring beyond the first year.[3] The pathophysiology of cardiac allograft vasculopathy is not fully elucidated. The aetiology is likely to be multifactorial. Classical risk factors for coronary artery disease are thought to contribute. Donor male gender, hypertension, and diabetes are risk factors for the development of vasculopathy in the allograft,[14] suggesting that pre-existing atherosclerosis predisposes to vasculopathy. Animal models have shown that hyperlipidaemia accelerates allograft vasculopathy.[15-17] In human heart transplant recipients, there is a clear link between cholesterol levels and the risk of developing allograft coronary artery disease.[18-20] In addition to traditional risk factors for atherosclerotic disease, low grade inflammation and chronic, antibody-mediated rejection are thought to contribute to the disease process.[12, 13]

Statin therapy reduces the prevalence of cardiac allograft vasculopathy in heart transplant recipients.[6] Research performed at the Scandinavian transplant centres has shown that early conversion from a calcineurin-based immunosuppressive regimen to a regimen based on everolimus, an inhibitor of the mechanistic target of rapamycin, alleviates cardiac allograft vasculopathy in *de novo* heart transplant recipients.[21] However, cardiac allograft vasculopathy remains a major obstacle in the effort to improve outcomes after heart transplantation.[4]

1.2 Cholesterol lowering and PCSK9 inhibitors

Serum levels of low density lipoprotein (LDL) cholesterol levels are strong predictors of atherosclerotic coronary artery disease.[22, 23] Inhibitors of the rate-limiting enzyme of human cholesterol synthesis, hydroxymethylglutaryl co-enzyme A (HMG CoA), called statins, were the first drugs to effectively lower serum cholesterol. Multiple trials have concluded that statin therapy significantly reduces the risk of myocardial infarction, stroke and mortality.[24-28]

Evolocumab is a fully human monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9).[29] Proprotein convertase subtilisin–kexin type 9 is an enzyme that binds to and degrades the low density lipoprotein (LDL) receptor and prohibits recycling of the LDL receptor to the cell surface. Evolocumab thus reduces circulating levels of LDL by increasing LDL clearance by

receptor mediated endocytosis.[10] Evolocumab lowers LDL cholesterol levels by approximately 60%. In the landmark FOURIER trial, 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 1.8 mmol/l or higher despite statin therapy were randomly allocated to treatment with evolocumab or matching placebo. In the evolocumab arm, there was a highly significant reduction in LDL cholesterol, and fewer cardiovascular clinical events.[11] To date, there have been no controlled trials to assess the effect of PCSK9-inhibitors on cardiac allograft vasculopathy.

1.3 Pre-Clinical & Clinical Experience with evolocumab

According to the Summary of Product Characteristics (SPC), available at www.medicines.org.uk, studies in animals have not shown evolocumab to affect embryonic development, be carcinogenic, or cause infertility. The carcinogenic potential of evolocumab was evaluated in a lifetime study conducted in hamsters at exposures up to 38-fold the recommended human doses of 140 mg every 2 weeks. The mutagenic potential of evolocumab has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes. There were no adverse effects on fertility at the highest dose in a fertility and early embryonic developmental toxicology study in exposed to 30-fold the recommended human doses of 140 mg every 2 weeks. In addition, there were no adverse evolocumab-related effects on surrogate markers of fertility in sexually mature monkeys.

There have been no trials to assess the safety of evolocumab in pregnancy, and according to the approved label, Repatha® should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab. The effect on breastfed infants has not been evaluated in controlled trials. Evolocumab has an effective half-life of 11- 17 days, and is eliminated through proteolysis in a non-saturable manner. Moderate renal dysfunction (estimated glomerular filtration rate [eGFR] > 30 ml/ min) is not associated with a significantly altered plasma half-life of evolocumab and is not a contraindication to treatment with Repatha®. Limited data are available in patients with severe renal impairment.

Repatha® has marketing approval in The United States and the EU for the treatment of hypercholesterolaemia at the doses intended for use in the EVOLVD trial. There is considerable clinical experience with evolocumab, including the large, phase IV FOURIER trial,[11] and the OSLER 1 open-label extension study.[30] The over-all favourable safety profile of evolocumab is evident from the low level of drug-related adverse events in these trials.

1.4 Known and potential risks and benefits

For potential risks and benefits, we refer to the approved label for evolocumab. Surveillance reports, observational studies, and some small randomised trials[31, 32] of statin therapy have suggested that statins (or the low levels of LDL cholesterol that result from their use) may be associated with impaired cognitive function. Also, there are well-known associations between statin use and myopathy, and between statin use and new-onset diabetes. The prevalence of statin-induced rhabdomyolysis has been negligible in large, randomised clinical trials,[27] but may be considerably higher in unselected populations, and particularly in patients who receive cyclosporine.[8] However, from the evidence so far, there is no reason to be concerned about neither cognitive function, nor myopathy with regard to treatment with evolocumab. In the FOURIER trial, no significant between-group differences were observed in the overall rates of adverse events, serious adverse events, or adverse events thought to be related to the study agent. The rates of muscle-related events were evenly distributed between the treatment arms.[11] In a separate study comprising 1204 of the patients enrolled in the FOURIER trial, neurocognitive function was assessed with the Cambridge Neuropsychological Test Automated Battery. There was no between-group difference in the change in neurocognitive function from baseline to the repeated assessment after a median of 19 months of treatment with evolocumab/ placebo.[33] There does not seem to be an increased risk of new-onset diabetes mellitus in patients treated with evolocumab.[34] Consistently, there has been a slightly increased incidence of injection-site reactions with evolocumab. In the

FOURIER trial, this minor adverse event occurred in 2.1% of patients allocated to evolocumab, and in 1.6% allocated to placebo.[11]

The benefit of PCSK9 inhibition in heart transplant recipients is unknown. Circumstantial evidence suggests that intensive LDL cholesterol lowering can reduce the incidence of allograft vasculopathy in heart transplant recipients. Furthermore, there is reason to believe that a reduced burden of coronary disease will improve outcomes in this population. The EVOLVD trial is designed to assess the hypothesis that treatment with 420 mg evolocumab subcutaneously every month for one year leads to a lower burden of cardiac allograft vasculopathy in *de novo* heart transplant recipients.

The main objective of the EVOLVD trial is to assess the effect of evolocumab on measures of cardiac allograft vasculopathy. While conventional coronary angiography is performed per current routine in our heart transplant recipient several weeks after heart transplantation and again one year after heart transplantation, in the EVOLVD trial, we plan to perform the first angiography up to eight weeks earlier, if there is no contraindication to coronary angiography at this time. In conjunction with the conventional exam, we will perform intravascular ultrasound and, in a subset of the patients, analyses of coronary physiology. The latter examination is more thoroughly described in Appendix B. We have no reason to believe that advancing the baseline angiography puts our patients at increased risk of complications. The addition of the IVUS and microcirculation measurements will add approximately 30 minutes to the procedure. The added measurements are associated with a minimal increase in risk on top of the conventional angiography.[35]

1.5 Rationale for the study and purpose

Cardiac allograft vasculopathy is an important cause of morbidity and mortality in heart transplant recipients. Our own data show that, although clinical coronary artery disease often manifests years after heart transplantation, there are substantial changes in the coronary artery intima thickness over the first year after transplantation, suggesting that the adverse process starts shortly after transplantation.[21] Moreover, our data suggest that, whereas early intervention can prevent long-term progression of cardiac allograft vasculopathy,[36] the same intervention is less effective when administered late after heart transplantation.[37] Thus, there seems to be a window of opportunity for preventive measures against cardiac allograft vasculopathy in *de-novo* transplant recipients.

The strong association between cholesterol levels and coronary heart disease in the general population, the high cholesterol levels in heart transplant recipients, the high prevalence of vasculopathy in the cardiac allograft, and the association between cholesterol levels and cardiac allograft vasculopathy together provide a strong rationale for aggressive cholesterol lowering in heart transplant recipients. Statins improve outcomes in heart transplant recipients, but their limited effect on post-transplant cholesterol levels, adverse effects, and drug interactions contribute to their not providing sufficient prophylaxis against post-transplant atherosclerotic disease.

Evolocumab is a well-tested drug with a favourable safety profile. It effectively reduces cholesterol levels on top of statin therapy in patients with coronary heart disease. We hypothesise that evolocumab on top of statin therapy will significantly lower LDL levels in *de novo* heart transplant recipients. We assume that this reduction in cholesterol levels will manifest as a reduced burden of cardiac allograft vasculopathy as measured by intracoronary ultrasound. Ultimately, we believe that a reduced burden of vasculopathy will translate to reduced morbidity and long-term mortality in heart transplant recipients. The EVOLVD trial is a randomised, placebo-controlled, double blind study designed to test the hypothesis that treatment with evolocumab can ameliorate cardiac allograft vasculopathy in heart transplant recipients.

1.6 Rationale for study endpoint

The ultimate endpoint for risk-reducing drugs is all-cause mortality. Currently, the one-year survival in heart transplant recipients is almost 90 %. Thus, for adequate power, an outcome-driven trial would require hundreds, possibly thousands of patients to show a difference between treatment

groups. With a mere 5000 patients receiving a cardiac allograft each year world-wide, designing a trial with coronary outcomes or mortality as primary endpoints simply is not feasible. Intima thickness as measured by IVUS is an established surrogate endpoint for coronary heart disease. Trials have shown that aggressive lipid-lowering treatment can alleviate, or even reverse, the atherosclerotic burden in patients with coronary heart disease.[38-40] In these trials, the primary efficacy endpoint has been the percentage atheroma volume, defined as

$$\frac{\text{the area enclosed by the external elastic membrane} - \text{the luminal area}}{\text{the area enclosed by the external elastic membrane}} * 100.$$[40]

On the other hand, in heart transplant recipients, it is the maximal coronary intima thickness that has been shown to be associated with outcome.[41, 42] These measures are closely correlated. Our own data show that IVUS measurements are reproducible and that the repeated measure variability in intima thickness is low.[21, 37] Furthermore, the measurement is not associated with significant risk on top of the risk associated with coronary angiography,[35] which is performed on a regular basis in heart transplant recipients.

2 Study objectives and related endpoints

The main goal of this study is to evaluate the effect of evolocumab administered subcutaneously every month for one year on the development of cardiac allograft vasculopathy in cardiac allograft recipients.

Secondary objectives are to assess the impact of treatment on: i) cholesterol levels, ii) renal function, iii) inflammation, iv) cardiac function as assessed by biomarkers and echocardiography, v) quality of life, vi) the number of allograft rejections, and (vii) safety and tolerability. As an exploratory endpoint, we will assess the impact of treatment on the number of major clinical events (death, myocardial infarction, percutaneous coronary intervention/coronary bypass surgery, cerebral stroke, cancer, and end stage renal disease).

2.1 Primary endpoint

The primary endpoint will be the baseline-adjusted maximal intimal thickness as measured by coronary intravascular ultrasound (IVUS) at end-of treatment, 12 months after randomisation. The maximal intima thickness is defined as the largest distance (in mm) from the intimal leading edge to the external elastic membrane.

2.2 Secondary endpoints

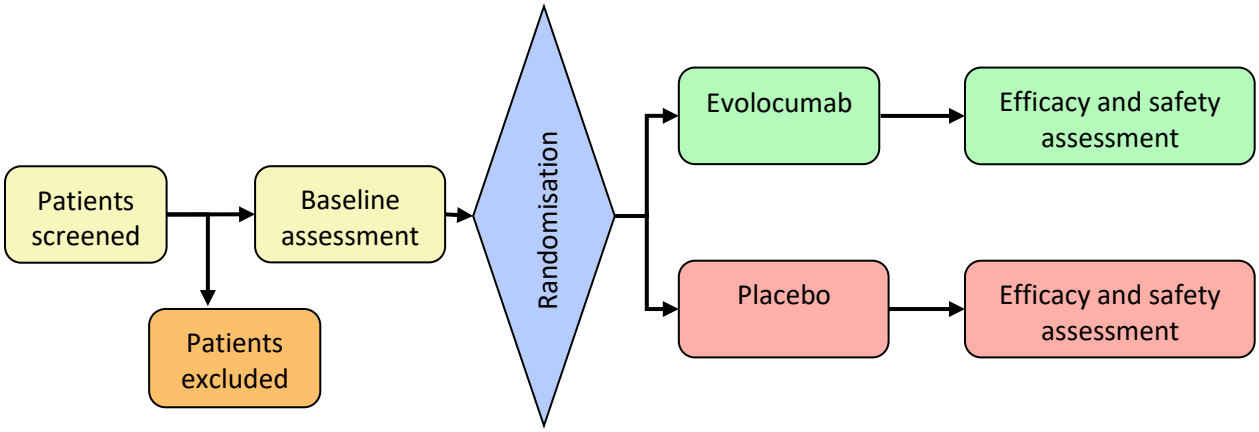
Secondary endpoints measured at 1 year will be the baseline-adjusted:

- Percent atheroma volume as measured by IVUS
- Cardiac allograft vasculopathy (defined as mean a maximal intimal thickness ≥0.5 mm over the entire matched segment)
- LDL cholesterol
- Estimated GFR
- Quality of life as assessed by the SF-36 and 5D EuroQoL questionnaires, and the Beck's Depression Inventory
- N-terminal pro-B-type natriuretic peptide (NT-proBNP)
- Cardiac troponin T (TnT)
- The number of allograft rejections
- The number of adverse events

- The number of major clinical adverse events, defined as death, myocardial infarction, percutaneous coronary intervention/coronary bypass surgery, cerebral stroke, cancer, end stage renal disease (exploratory endpoint)

3 Overall study design

This is a phase 3, double blind, randomised, placebo-controlled trial. Participants will be randomised in a 1:1 fashion to receive subcutaneous injections of 420 mg evolocumab or matching placebo every month for one year. The study is designed to show superiority regarding the primary endpoint in patients assigned to active treatment versus patients allocated to the placebo arm.



Study Period	Estimated date of first patient enrolled (study start) November 1st, 2018 Anticipated recruitment period: February 1st, 2019 – February 28th, 2022 Estimated date of last patient completed treatment: February 28th, 2023 Estimated date of last patient completed (last patient, last visit: Study end): March 31st, 2023
Treatment Duration:	12 months
Follow-up:	13 months

4 Study population

4.1 Selection of study population

The EVOLVD trial will be performed at six Scandinavian centres; Oslo University Hospital, Rikshospitalet; Oslo, Sahlgrenska University Hospital, Gothenburg, Sweden, Skåne University Hospital, Lund Sweden, Rigshospitalet, Copenhagen, Denmark, Aarhus University Hospital, Skejby, Denmark, and Helsinki University Hospital Heart and Lung Center, Helsinki, Finland. Together, these centres perform approximately 130 heart transplantations each year. We will recruit *de novo* heart transplant recipient who fulfil eligibility criteria (below) who are willing to participate, and who give written, informed consent. Eligible subjects will be asked for consent to participate in the trial by study personnel who are not in a position that can be perceived to undermine the voluntariness of a participant's consent to participate in research. The person who contacts the subject in the consent process should therefore be separate from the clinical team.

4.2 Number of patients

We aim to enrol 130 patients in this trial.

4.3 Inclusion criteria

Patients will be screened for eligibility during routine follow-up 4 – 8 weeks after heart transplantation.

All of the following conditions must apply prior to administering the investigational medicinal product:

- Heart transplant recipient within the last 4 – 8 weeks.
- Age between 18 and 70 years.
- Informed consent obtained and documented according to Good Clinical Practice (GCP), and national/regional regulations.
- No contraindications to coronary angiography with intravascular ultrasound
- Estimated glomerular filtration rate > 20 ml/min/1.73 m2 as assessed by the MDRD formula.[43]

4.4 Exclusion criteria

Patients will be excluded from the study if they meet any of the following criteria:

- Decompensated liver disease (Child-Pugh class C)
- Severe renal failure, i.e. eGFR < 20 ml/min/1.73 m2 or on renal replacement therapy
- Ongoing rejections or infections*
- Known sensitivity or intolerance to evolocumab or any of the excipients of Repatha®
- Prior use of PCSK9 inhibition treatment
- Indication for treatment with PCSK9 inhibitor
- Alcohol or drug abuse within 3 months of informed consent that would interfere with trial participation or any ongoing condition leading to decreased compliance with study procedures or study drug intake
- Participation in another clinical trial involving an investigational drug and/or follow-up within 30 days prior to enrolment.
- Pregnancy.
- The subject is a nursing woman
- Female subject who has either (1) not used at least one highly effective method of birth control** for at least 1 month prior to screening or (2) is not willing to use such a method during treatment and for an additional 15 weeks after the end of treatment, unless the subject is sterilised or postmenopausal†

*Only rejections with haemodynamic compromise and infections with hemodynamic consequences or infections that contraindicate coronary angiography with IVUS are to be regarded as exclusion criteria

**Highly effective methods of birth control include not having heterosexual intercourse or using birth control methods that work at least 99% of the time when used correctly, including combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); intrauterine device or intrauterine hormone-releasing system; bilateral tubal occlusion; and a vasectomised partner. Sexual abstinence is a reliable method of birth control in women who are highly unlikely to establish a sexual relationship to a new partner over the course of the trial only. The reliability of sexual abstinence needs to be re-evaluated over the duration of the trial and with due consideration to the preferred and usual lifestyle of the subject.

† Menopause is defined as 12 months of spontaneous and continuous amenorrhea with a follicle stimulating hormone (FSH) level > 40 IU/L (or according to the definition of "postmenopausal range" for the laboratory involved) in a female < 55 years old unless the subject has undergone bilateral oophorectomy

5 Treatment

For this study, subcutaneous evolocumab (Repatha®) and matching placebo are defined as investigational medicinal products.

5.1 Drug identity, supply and storage

Medication and comparator
Active drug: Evolocumab for subcutaneous injection.
Placebo: The placebo is presented in an identical prefilled autoinjector. It is supplied as a sterile, single use, preservative free solution for subcutaneous injection in a disposable, spring based prefilled autoinjector. The prefilled autoinjector contains a 1.0 mL deliverable volume of 1.1% (w/v) sodium carboxymethylcellulose, 250 mM proline, 10 mM acetate, and 0.01% (w/v) polysorbate 80, pH 5.0.

5.1.1 Supply, packaging, labelling, handling, storage and accountability

The manufacturer supplies study drugs to the investigators on site. It is labelled with information according to local regulation. The study medication will be stored in a locked refrigerator (2-8°C), protected from unintended use. All study medications supplied for this trial will be retained in a safe place at all times of the study. Only personnel authorised by the principal investigator should dispense the study medication, and the accountability is the responsibility of investigator. An up to date study medication inventory (dispensing records) will be maintained at all times.

5.2 Dosage and administration

After the participant has provided informed consent, he or she will be randomised to receive subcutaneous evolocumab (Repatha®) or matching placebo. The randomisation process will be performed online via the commercially available electronic case report form (eCRF) system called Viedoc®. The investigational drug, evolocumab/placebo, will be administered subcutaneously once monthly in abdomen, thigh, or upper arm for the duration of the treatment period (one year). 420 mg evolocumab/placebo will be administered by giving 3 injections consecutively within 30 minutes using the single-use prefilled autoinjector.

5.3 Duration of therapy

The investigational medicinal products will be administered subcutaneously every month for one year. No other study-specific intervention will be provided.

5.4 Monitoring during drug administration

The first dose(s) of study drug will be administered in a hospital setting. A study nurse will instruct the patients on how to self-administer the drug. The patients will self-administer the subcutaneous injections.

5.5 Concomitant medication

All concomitant medication will be recorded in the patient's file and CRF. Study participation does not preclude administration of drugs that are provided on clinical indication. On the contrary, study participants will receive standard-of-care treatment as recommended in prevailing guidelines.

We routinely use induction therapy at the time of heart transplantation. We introduce maintenance immunosuppressive therapy consisting of a combination of a calcineurin inhibitor, mofetil mycophenolate and steroids on the first post-operative day with gradual tapering of the calcineurin inhibitor and steroid doses over the first year. In selected patients, we add everolimus with reduction of the calcineurin inhibitor dose or complete cessation of calcineurin inhibitor treatment. We perform regular bioptic controls as recommended by the International Society of Heart and Lung Transplantation (ISHLT). We administer trimethoprim-sulpha o.d. for the first 6

months after heart transplantation according to current recommendations. In patients with blood pressure consistently above 140/90, we provide anti-hypertensive treatment.

Pravastatin 40 mg o.d. is routinely introduced during the first five postoperative days and continued indefinitely unless there are contraindications to statin use, or there is a need to escalate treatment. To keep investigators blinded to treatment allocation, we will not perform measurements of blood lipids for the during the treatment phase.

5.5.1 Birth control

Female participants who are not postmenopausal or sterilised, must agree to use highly effective methods of birth control for at least 1 month prior to screening, during treatment with the investigational drug (evolocumab/placebo) and for an additional 15 weeks after the end of treatment. Highly effective methods of birth control include not having heterosexual intercourse or using birth control methods that work at least 99% of the time when used correctly, including combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); intrauterine device or intrauterine hormone-releasing system; bilateral tubal occlusion; and a vasectomised partner, provided that the partner is the sole partner of the female trial participant and that the vasectomised partner has received medical assessment of the surgical success. Sexual abstinence is a reliable method of birth control in women who are highly unlikely to establish a sexual relationship to a new partner over the course of the trial only. The reliability of sexual abstinence needs to be re-evaluated over the duration of the trial and with due consideration to the preferred and usual lifestyle of the subject.

5.6 Drug accountability

The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. The manufacturer (AMGEN®) provides the active study drug and matching placebo. The first dose(s) of the study drug or matching placebo will be administered by trained hospital personnel. The patients will receive full information on how to administer the drug subcutaneously, and will administer the subsequent injections themselves. The manufacturer supplies study medication to the investigators on site. It will be labelled with information according to local regulation. The study medication will be stored in locked refrigerators (2-8°C), protected from unintended use. All study medications supplied for this study must be retained in a safe place at all times of the study. Only personnel authorised by the principal investigator should dispense the study medication, and the accountability is the responsibility of the investigators. A study medication inventory (dispensing records) for all medication dispensed must be maintained at all sites at all times and must always be kept up to date. Used study medication can be send to destruction before the monitor double-checks used study medication if two study nurses verify that the used study medication has been dispensed to the correct subject with the correct KIT number. The nurses have to sign the Master drug accountability log as well as the Subjects drug accountability log. Study medication must be destroyed as per local guidelines and documented in the Site file. Any abnormalities must be documented on both logs and filed in the Site file.

5.7 Drug labelling

The investigational product will have a label permanently affixed to the outside and will be labelled according with ICH/GCP and national regulations, stating that the material is for clinical trial / investigational use only and should be kept out of reach of children. The label will also specify batch number and expiry date.

The boxes containing evolocumab/placebo will have an affixed label stating (in the local language) that box contains injection pens filled with 140 mg evolocumab (Repatha®) or placebo for clinical investigation in the EVOLVD trial, that the drug is meant for monthly subcutaneous injection, and that it should be stored refrigerated at 2° - 8°C in the original carton to protect from light and kept out of sight and reach of children.

Label example (in Norwegian):

Injeksjonsvæske, oppløsning
Subkutan bruk
Oppbevares i originalpakningen
Følg den anbefalte doseringen eller se
protokoll for bruksanvisning.
Til klinisk utprøving
Oppbevares utilgjengelig for barn
Må ikke fryses
Må ikke ristes
Senteradresse: _____
Senterets telefonnr.: _____

5.8 Subject identification

Each study participant is identified by a unique subject identification number that is assigned after the subject signs the informed consent form. A unique randomisation code is generated through the online randomisation process. Once assigned, the subject identification number and the randomisation code cannot be reused for any other subject. The same primary identifiers will be used throughout the study.

5.9 Study drug allocation

Amgen will deliver study drugs to each site. A list identifying each kit number as active drug/placebo will be provided. Unblinded personnel not participating as study investigators or taking care of the study participants must sort the study drugs into containers containing active drug or placebo according to this list. The list must not be seen by blinded study personnel. The study drugs must be stored and handled according to the trial protocol and the Standard Operating Procedure (SOP) detailing study drug storage and accountability.

Once randomisation has been performed in the eCRF, a randomisation number specific to that study participant is generated. This number must be presented to the unblinded study personnel who have access to the study drugs. The unblinded personnel will also be in the possession of a drug allocation list generated by the Research Support Services at Oslo University Hospital linking each randomisation number to active treatment or placebo. This list must not be seen by blinded study personnel. Based on the randomisation number, the unblinded personnel will pick a study drug box with the correct treatment (active drug or placebo), write down the corresponding kit number on the drug allocation list. The blinded study personnel must enter the kit number in the eCRF. There is an internal control procedure embedded in the eCRF that will generate an error message if the kit number selected does not correspond to the treatment to which the patient has been randomised.

Each time the study participant needs more study drug, the blinded investigator or study nurse must present the randomisation number to the unblinded study personnel, who will dispense new boxes. All the corresponding kit numbers must be recorded on the drug allocation list (by the

unblinded personnel) and in the eCRF. Several boxes can be dispensed at once, providing that the intended date of use does not exceed the drug expiry date.

6 Study procedures

6.1 Flow chart

Study phases	Pre-treatment		Treatment							Follow-up
			Baseline	1 month	2 months	3 months	6 months	9 months	12 months	13 months
Eligibility	x									
Consent	x									
Vital signs	x		(x)	x	x	x	x	x	x	
Physical exam	x		(x)			x			x	
Study drug administration			x	x	x	x	x	x		
Coronary angiography with IVUS			x						x	
Echocardiography			x						x	
Blood samples		**Randomisation**	x	x	x	x	x	x	x	
Quality of life			x						x	
Clinical events			x	x	x	x	x	x	x	x
Safety	x		(x)	x	x	x	x	x	x	x
Microcirculation (optional)			x						x	

6.2 By visit

Study participants will be recruited from the pool of recently transplanted cardiac allograft recipients who attend regular follow-up at the participating centres. Typically, the patients are still hospitalised or visit the participating hospital on a near-daily basis over the first 8 weeks after heart transplantation. Subsequent visits and study drug injections can be performed within ± 14 days of the optimal interval. If it is necessary to perform a visit or an injection more than one week before or after the optimal time, on should aim to adjust the preceding and following visits in order to avoid very short or very long intervals between injections. Regarding the 12 month visit (12 months after randomization), we recommend postponing the regular 1 year control for the 12 month visit and clinical visit to coincide.

6.2.1 Screening visit

Informed consent

Voluntary, written informed consent (Appendix A) must have been obtained for each subject before any study specific procedure is initiated. At this time, the patient will be registered in the eCRF, and a unique identifier will be assigned.

The following tests will be performed at screening:

Physical examination

A physical examination (including examination of heart, lungs, abdomen, neck and assessment of peripheral circulation and oedema) must be performed; vital signs (blood pressure, and heart rate); and height and weight must be recorded.

Medical history

A medical history must be obtained, and age; gender; NYHA functional status; risk factors (hypertension, smoking, and diabetes mellitus); reason for and time since heart transplantation; and concomitant disease must be recorded. The time from organ harvest to aortic clamp removal minus the time on a warm perfusion device should be registered at centres that employ the Transmedic OCS® warm perfusion (or an equivalent) transport device. However, the centres are asked to keep a record of total ischaemia time (i.e. from harvest to aortic clamp removal) in case this information is needed at a later time.

The investigators should use clinical common sense when selecting which co-morbidities to list.

- Co-morbidities that affect the prognosis in heart transplant recipients, such as diabetes, COPD, and renal insufficiency must be registered.
- Co-morbidities relevant to the development of cardiac allograft vasculopathy, such as overt hypercholesterolemia and hypertension must also be listed.
- Likewise, diseases that may be relevant to the development of complications, such as immunodeficiency or recurring infections, should be listed.
- Chronic diseases that require treatment or that are likely to affect the participants' quality of life, such as thyroid disease, skin diseases like psoriasis, gastrointestinal diseases etc., should also be listed.

On the other hand, diseases and conditions that are either resolved (cured cancer without remission over the last five years, corrected orthopaedic disorders, previous surgery, intercurrent diseases) or diseases unlikely to affect outcomes or quality of life (like refraction abnormalities, minor loss of hearing, minor skin conditions) need not be mentioned.

Concomitant medication

All concomitant medication used by the participant within 28 days of the start of treatment must be recorded in the CRF by generic name and dose.

Laboratory analyses

Fasting blood samples will be obtained to determine: Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CK; CRP; NT-proBNP; total cholesterol; LDL cholesterol, high density lipoprotein cholesterol and triglycerides. Serum hCG must be measured in women of childbearing potential[‡]. These are to be considered safety and descriptive parameters: Efficacy-samples must be collected at randomisation.

6.2.2 Randomisation and Baseline Procedures (Day 1)

After confirmation of eligibility, baseline efficacy measurements can be made, and the online randomisation process can be performed. If more than 72 hours have passed since the screening visit, the physical exam should be repeated, vital signs recorded anew, and safety blood samples should be repeated.

Quality of life

Self-reported, health-related quality of life will be gauged with the SF-36, the Beck's depression inventory, and EQ 5D 3L questionnaires. We will allow subjects to complete the quality of life assessments before study procedures are performed.

Coronary angiography with intravascular ultrasound

Per routine, we perform coronary angiography approximately 12 weeks after heart transplantation to assess the allograft vessels. For the EVOLVD trial, we will ask the participants to have this "baseline" angiography within 4 to 8 weeks after heart transplant. The baseline IVUS, which is performed for study-specific purposes only, must be performed before study-specific treatment is started. We surmise that, to obtain the wanted effect on coronary artery intima thickness, aggressive cholesterol lowering treatment should start as soon as possible after heart transplantation. We therefore want to advance the baseline coronary angiography, so that it is performed shortly after enrolment.

Measurements of cardiac microcirculation (optional: See Appendix B)

In a subset of approximately 80 patients, we aim to assess cardiac microcirculation. For description of rationale and methods, see Appendix B.

Echocardiography

A comprehensive echocardiographic exam for study purposes must be performed prior to study drug administration. A copy of this exam will be stored in the clinical imaging archive under the patient's real name for reasons of safety.

Blood samples

Blood for efficacy analyses (specified later) must be collected, drawn and appropriately labelled and stored in a dedicated biobank for later analysis.

Randomisation

The randomisation code will be generated online on the eCRF (Viedoc®) platform

Study drug injection

The first study drug injection, starting on day 1, will be performed by a dedicated study nurse, who will also provide training for self-administration of the study drug.

6.2.3 Visits one, two, three, six and nine months after start of treatment

These visits are for assessing lipid levels and safety. At these visits, we will assess:

Medical history

A medical history must be obtained, and NYHA functional status; well-being; adverse events; and concomitant disease must be recorded.

Concomitant medication

[‡] A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

All concomitant medication used by the participant since the last visit must be recorded in the CRF by generic name and dose. Routine changes in doses of immunosuppressants need not be recorded in the eCRF. If the dose has been changed in response to a perceived clinical or biochemical complication, this event should be recorded as an adverse event.

Laboratory analyses

Fasting blood samples will be obtained to determine: Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CK; CRP; TnT and NT-proBNP (safety). Trough levels of immunosuppressive drugs must be measured. Blood for efficacy analyses must be collected, appropriately labelled and stored in a dedicated biobank for later analysis. Serum hCG must be measured in women of childbearing potential who have stopped menstruating after randomisation.

Safety assessment

Any untoward medical event (i.e. any AE, SAE or SUSAR) since the last visit must be recorded in the eCRF and the patient medical record.

Study drug dispensing

The study drug should be injected by the participant under the supervision of a study nurse on the visits 1, 2, and 3 months after start of treatment. At 3 months, injection pens for the next two injections will be dispensed by the study nurse, and the patients will receive information on when and how to perform the next injections. At 6 and 9 months, supervised injections should be made, and again study drugs must be dispensed for the intervening months.

6.2.4 End of treatment visit

This study visit 12 months after heart transplant is designed to assess efficacy and safety.

Quality of life

Self-reported, health-related quality of life will be gauged with the SF-36, the Beck's depression inventory, and EQ 5D 3L questionnaires. We will allow subjects to complete the quality of life assessments before study procedures are performed.

Medical history

A medical history must be repeated, and NYHA functional status; any change in risk factors (hypertension, smoking, diabetes mellitus), and concomitant disease must be recorded. Any medical events since inclusion in trial must be evaluated. Current well-being, symptoms, potential side effects and physical capacity must be assessed.

Physical examination

A physical examination must be performed, and results (including examination of heart, lungs, abdomen, neck and assessment of peripheral circulation and oedema); vital signs (blood pressure, and heart rate); and height and weight must be recorded.

Concomitant medication

All concomitant medication (incl. vitamins, herbal preparation and other "over-the-counter" drugs) used by the participant since the last visit must be recorded in the CRF by generic name and dose. Routine changes in doses of immunosuppressants need not be recorded in the eCRF. If the dose has been changed in response to a perceived clinical or biochemical complication, this event should be recorded as an adverse event.

Laboratory analyses

Fasting blood samples will be obtained to determine: Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CK; CRP; TnT and NT-proBNP; total cholesterol; LDL cholesterol, high density lipoprotein cholesterol and triglycerides(safety). Blood for efficacy analyses must be collected, appropriately labelled and stored in a dedicated biobank for later analysis.

Coronary angiography with intravascular ultrasound

Per routine, we perform coronary angiography approximately 12 months after heart transplantation. For the EVOLVD trial, we perform the main efficacy assessment, the 12-month IVUS, at the 12-month follow-up visit.

Echocardiography

A comprehensive echocardiographic exam for study purposes must be performed at the end of treatment. A copy of this exam will be stored in the clinical imaging archive under the patient's real name for reasons of safety.

Safety assessment

Any untoward medical event (i.e. any AE, SAE or SUSAR) since the last visit must be recorded in the eCRF and the patient medical record.

Measurements of cardiac microcirculation (optional)

In patients who have been had microcirculatory measurements at baseline, we wish to repeat this measurement after one year's treatment

6.2.5 13 months safety control

At 13 months, we will perform a telephone interview to assess clinical events and safety:

Medical history

A medical history must be repeated, and NYHA functional status; any change in risk factors (hypertension, smoking, diabetes mellitus), and concomitant disease must be recorded. Any medical events since inclusion in trial must be evaluated. Current well-being, symptoms, potential side effects and physical capacity must be assessed.

Safety assessment

Any untoward medical event (i.e. any AE, SAE or SUSAR) since the last visit must be recorded in the eCRF and the patient medical record.

Laboratory analyses

Serum hCG must be measured in women of childbearing potential.

6.3 Criteria for patient discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient for this study are:

- Voluntary discontinuation: participating patients are free to discontinue his/her participation in the study at any point in time, without prejudice to further treatment.
- Major protocol deviation
- Incorrect randomisation, i.e. the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Patient's non-compliance to study treatment and/or procedures

6.4 Procedures for discontinuation

6.4.1 Study drug discontinuation

The study participants may discontinue study drug treatment at any time according to their preferences. The investigator may also advise study drug discontinuation in case of side effects, if adverse effects of the treatment are suspected, or if contraindications to the continued use of evolocumab arise. Study drug discontinuation and the reason why must be documented in the eCRF as well as in the hospital record. Efforts should be made to make ensure that adherence to the study protocol is kept up even though the patient no longer takes the study drug. All available data will be used in the intention to treat analysis, unless the patient specifically disagrees to let the investigator use his or her data.

6.4.2 Patient discontinuation

Patient withdrawal must be documented in the CRF as well as in hospital records. If possible, a final assessment should be obtained (end of study visit). The reason for discontinuation is recorded. The investigator is obliged to follow up any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal or unknown. Patients who withdraw will be included in the intention-to treat analysis.

6.4.3 Trial discontinuation

The whole trial may be discontinued at the discretion of the primary investigator or the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients
- Cancellation of drug development

The sponsor and principal investigator will inform all investigators, the relevant Competent Authorities and Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

7 Assessments

7.1 Assessment of efficacy

Efficacy will be evaluated through assessments of cardiac allograft vasculopathy; clinical events, blood tests of lipids, renal function, cardiac biomarkers, and inflammation; echocardiography; self-assessed quality of life; and cognitive function. All efficacy assessments will be made prior to administration of the first study drug dose, and at the end-of-treatment visit after twelve months. The results will be reported as baseline-adjusted between-group differences. Efficacy samples for the determination of blood lipids, renal function, and clinical events will be collected at 1, 2, 3, 6, 9, and 12 months, and analysed retrospectively. Cardiac biomarkers (NT-proBNP and TnT), will be analysed as safety parameters as well as efficacy parameters.

7.1.1 Intravascular ultrasound (IVUS)

Intravascular ultrasound examination of the same major epicardial coronary artery (preferentially the left-anterior descending coronary artery) will be performed during routine coronary angiography at 4 – 8 weeks after heart transplantation and at end-of-treatment one year after randomisation. In patients who have completed at least 6 months of study drug treatment, we will allow the second IVUS exam (used for assessment of the primary endpoint) to be performed at the time of study discontinuation for subjects who are unable to complete 12 months of treatment. All IVUS analysis will be conducted after trial closure by a core laboratory (Oslo University Hospital, Rikshospitalet, Oslo, Norway) by personnel blinded to patient treatment. Precise matching of the IVUS recordings at baseline and at 12 months will be performed and contour detection of both the lumen and external elastic membrane will be performed at approximately 1 mm intervals using validated software (QIVUS, v.3.0, Medis medical imaging systems, Leiden, the Netherlands). Borders will be reviewed by two independent operators according to the guidelines for acquisition and analysis of IVUS images by the American College of Cardiology and European Society of Cardiology.[44] The primary IVUS efficacy variable will be the mean change in the maximal intimal thickness between matched slices from baseline to 12 months as this parameter is an established predictor of all-cause mortality, myocardial infarction and angiographic abnormalities among HTx recipients.[42] In accordance with established guidelines, the largest distance from the intimal leading edge to the

EEM is defined as the maximal intimal thickness.[44] Secondary IVUS variables are: (i) incidence of cardiac allograft vasculopathy (defined as mean a maximal intimal thickness ≥0.5 mm over the entire matched segment) and (ii) normalised total atheroma volume.

7.1.2 Echocardiography

Top specified cardiac ultrasound devices will be used for echocardiographic imaging. Patients are examined in the lateral recumbent position after > 5 minutes of rest at baseline, and after 12 months. The heart is visualised by the standard ultrasonic techniques and imaging planes as recommended by the European society of echocardiography[45] providing a comprehensive hemodynamic and valvular assessment. In addition to apical recordings of the left ventricle, parasternal short axis cine loops at the mid-papillary level are recorded. Tissue Doppler examinations are performed from the three apical planes by using colour coding, and single pulsed Doppler at the septal and lateral mitral ring. Two-dimensional imaging from the apical position should be performed in the three standard planes in two imaging depths: One encompassing the ventricle(s) and atria, and one with the sector encompassing the left ventricle only, ensuring that the mitral plane is within the imaging sector throughout the cardiac cycle. Two-dimensional images should be optimised for speckle tracking analysis by 1) ensuring that 200 msec is recorded before and after each cine loop 2) keeping the frame rate above 50 frames/s and 3) ensuring that the sector encompasses the full thickness of the myocardium.

At least three heart beats (at least five in atrial fibrillation) are recorded with each registration. Recordings are performed before treatment and after 3 months, prior to study drug discontinuation. Blinded analysis of echocardiographic data will be performed off line using EchoPac (GE Vingmed). The following recordings should be obtained:

Projection:	Parameter:	
Parasternal long axis	Cine loop	Left ventricle
		Zoom LVOT (3 different recordings, only at baseline)
	M-mode	Mid left ventricular
	Colour Doppler	Left ventricular outflow tract
		Mitral valve
Parasternal short axis	Cine loop	Left ventricle at the level of the papillary muscle
		Left ventricle at mid-ventricular level
		Aortic valve
	Colour Doppler	Aortic valve and right ventricular outflow tract
Apical 4chamber / 5 chamber	Cine loop	Four-chamber including atria
		Four-chamber zoom left ventricle*
		Four-chamber zoom right ventricle
	Colour Doppler	Mitral valve
		Aortic valve
		Tricuspid valve
	Doppler	Mitral valve tip (pulsed wave)
		Mitral regurgitation jet (continuous wave)
		Pulmonary vein (pulsed wave)
		Left ventricular outflow tract (pulsed wave)
		Aortic flow velocity (continuous wave)
		Tricuspid regurgitation jet (continuous wave)
	Tissue Doppler	Colour TVI left ventricle

		Colour TVI right ventricle TVI pulsed wave mitral annulus septum TVI pulsed wave mitral annulus anterolateral wall
Apical 2 chamber	Cine loop	Two-chamber including left atrium Two-chamber zoom left ventricle*
	Tissue Doppler	Colour TVI left ventricle
Apical long axis	Cine loop	Apical long-axis including left atrium Apical long-axis zoom left ventricle*
	Colour Doppler	Mitral valve Aortic valve

*Settings ideal for speckle tracking: Patient in breath-hold for three consecutive heart beats. Frame rate above 50 beats per min. The sector should include full thickness of ventricular wall. On the other hand, the left ventricle should fill entire sector (no "dead space"). Depth set so as to include mitral annulus at any time trough heart cycle. LVOT: Left ventricular outflow tract; TVI: Tissue velocity imaging.

7.1.3 Quality of life

Quality of life will be examined at baseline and at the end of treatment using three validated questionnaires; the SF36 (version 1)[46], the Beck's depression inventory, and the EQ 5D 3L EuroQoL questionnaires.[47] The SF-36v2 is a 36-item general health-related quality of life instrument that has 36 questions that contribute to 8 domains or scale scores of physical functioning, role-physical, bodily pain, general health, vitality, social functioning, and role-emotional and mental health.[46] The EQ 5D 3L EuroQoL questionnaire consists of 2 pages, the EQ-5D descriptive system and the EQ visual analogue scale. The Beck depression inventory is a 21-question multiple-choice self-report inventory for measuring the severity of depression. The test is rated on a 4-point scale ranging from 0 to 3 based on severity of each item. The maximum total score is 63.

7.1.4 Blood samples

We will collect fasting blood samples for biobanking at baseline, and at every subsequent visit. For biobanking, 18 ml blood should be collected in tubes containing EDTA, 6 ml in tubes with citrate and 6 ml in tubes without additives. The tubes with EDTA and citrate should be put on ice immediately and be centrifuged at 3700 rotations/min for 20 minutes. The tubes without additives should be left at room temperature for 1-2 hours prior to centrifugation at 3500 rotations/min for 15 minutes. The tubes containing citrate as the anticoagulant should be put on ice immediately. The resulting plasma and serum, respectively, should be stored in multiple aliquots (at least four aliquots of serum and six aliquots of plasma per patient per visit), and labelled with the unique trial subject number, and the letter A signifying baseline, and the letter B signifying the 1-month visit etc. The samples should be stored at -80 degrees Celsius until analysis.

Blood samples for safety will be collected at screening, and 1, 2, 3, 6, 9, and 12 months after randomisation. These blood samples will be collected and analysed at the study sites as per clinical routine. The glomerular filtration rate (in in ml/min/1.73 m^2) will be estimated by the MDRD formula: 175 x (SCr)-1.154 x (age)-0.203 x 0.742 [if female] x 1.212 [if black], where SCr is serum creatinine in mg/dl, and age is measured in years.[43] C-reactive protein, NT-proBNP, and troponin T-values will be used for endpoint analyses. Blood lipids must be assessed after end-of treatment only, to avoid what will effectively amount to study drug allocation unblinding. To avoid bias, the investigators will be blinded to the lipid analyses.

NT-proBNP will be assayed on a MODULAR platform (Roche Diagnostics, Basel, Switzerland). Plasma levels of CRP will be determined by a high-sensitivity particle-enhanced immunoturbidimetric assay (Tina-quant CRP [Latex] HS, Roche Diagnostic, Basel, Switzerland). TnT will be assessed using a high-sensitive immunoassay (Roche hs-TnT).

7.1.5 Biobanking

A dedicated biobank will be established at Oslo University Hospital, Rikshospitalet under the auspices of Professor Lars Gullestad. Blood samples for efficacy can be stored at each centre at -80 degrees in dedicated freezers until analysis. Blood samples for tertiary/exploratory efficacy analyses, including vasoactive peptides, markers of endothelial function and inflammatory markers, must be shipped to the core laboratory at Oslo University Hospital for analysis.

7.1.6 Cardiac microcirculation

In selected patients, we will perform a substudy where we perform measurements of the cardiac microcirculation. See Appendix B.

7.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. Significant findings that are present prior to the signing of informed consent must be included in the relevant medical history/ current medical condition page of the CRF. For details on AE collection and reporting, refer to Section 8.

For the assessment schedule, refer to Flow chart in Section 6.1.

Study-specific physical examinations will be performed at baseline and at 1, 2, 3, 6, and 12 months. Vital signs including heart rate and blood pressure will be recorded.

Blood samples for safety analyses will be drawn at baseline and after 1, 2, 3, 6, 9, and 12 months. Local laboratory cut-points for normal values will be used for safety analyses. Haemoglobin; white blood cell count, platelet count; serum potassium; serum sodium; glucose, glycosylated haemoglobin (HbA1c); creatinine; ALT; bilirubin; albumin; INR; CRP; TnT; and NT-proBNP. For the EVOLVD trial, we will not perform routine measurements of total cholesterol; LDL cholesterol, HDL cholesterol or other blood lipids for the duration of the treatment period. Instead, the biobank samples will be analysed regarding blood lipids retrospectively for efficacy and compliance assessments.

8 Safety monitoring and reporting

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE). Each patient will be instructed to contact the investigator immediately should they manifest any signs or symptoms they perceive as serious. When judging whether an adverse event is unexpected or not, the Repatha® Summary of Product Characteristic (SPC) will be used as reference safety information.

The methods for the collection of safety data are described below.

8.1 Definitions

8.1.1 Adverse event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The term AE is used to include both serious and non-serious AEs.

If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

8.1.2 Adverse events of special interest (AESI)

In general, AESIs are AEs that occur in categories of special interest with regard to determining the benefit/risk profile and overall safety of a drug. Whereas there have been no particular safety concern in the large, randomised, placebo-controlled trials involving evolocumab, the clinical experience with this drug outside of controlled trials is yet limited. In particular, we will monitor any pregnancy that may arise during the trial. However, pregnancies during the first year after heart transplantation are extremely rare, and we will demand that female participants of fertile potential use at least one highly effective method of birth control for the duration of the treatment phase. Immunosuppressants used after heart transplantation have a narrow therapeutic range and are sensitive to drug interactions. While there is no pharmacokinetic or pharmacodynamic reason to expect interactions with evolocumab, we will monitor levels of immunosuppressive drugs closely.

8.1.3 Serious adverse event (SAE)

Any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- In itself requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalisation for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated adverse event warranting hospitalisation.

8.1.4 Suspected unexpected serious adverse reaction (SUSAR)

Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered;

Unexpected Adverse Reaction: an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

Suspected Unexpected Serious Adverse Reaction: SAE (see section 8.1.2) that is unexpected as defined in section 8.2 and possibly related to the investigational medicinal products. When judging whether a possibly study drug related serious adverse event is unexpected or not, the Repatha® SPC will be used as reference safety information.

8.2 Time period for reporting adverse events and serious adverse events

For each patient the he standard time period for collecting and recording AE and SAEs will begin at the start of study treatment and will continue for 30 day after end-of treatment (at which time approximately 30 days will have passed since the last study drug injection). We will proactively follow up all AEs and SAEs for each patient during the course of the study; events will be followed up to resolution, unless the event is considered to be unlikely to resolve due to the underlying disease. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. Mandatory reporting of new AEs ends 30 days after the end-of-treatment visit.

8.3 Recording of adverse events

If the patient has experienced adverse event(s), the investigator will record the following information in the CRF:

The **nature of the event**(s) will be described by the investigator in precise standard medical terminology (i.e. not necessarily the exact words used by the patient).

The **duration of the event** will be described in terms of event onset date and event ended data.

The **intensity** of the adverse event will be categorised as mild / moderate / severe / life-threatening / death according to Common Terminology Criteria for Adverse Events version 4.0:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life;
- Severe: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activities of daily life;
- Life-threatening consequences: urgent intervention indicated.

The **causal relationship** of the event to the study medication will be assessed as one of the following:

- Unrelated: There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.
- Unlikely: There is a temporal relationship to investigational product administration, but there is not a reasonable causal relationship between the investigational product and the AE.
- Possible: There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.
- Probable: There is a reasonable causal relationship between the investigational product and the AE. The event responds to dechallenge. Rechallenge is not required.

Definite: There is a reasonable causal relationship between the investigational product and the AE. Action taken: **Which investigations/medical procedures/treatments that are initiated as a result of the adverse event.**

The **outcome** of the adverse event – whether the event is resolved or still ongoing.

It is important to distinguish between seriousness and severity of AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 8.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but is not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

8.4 Reporting procedure

8.4.1 Adverse events, adverse events of special interest and serious adverse events

All adverse events and serious adverse events that should be reported as defined in section 8.1.1 will be recorded in the patient's CRF. SAEs must be reported by the investigator to the sponsor, Oslo University Hospital, within 24 hours after the site has gained knowledge of the SAE. The Serious Adverse Event Report Form must be completed, documented in the eCRF, signed and sent to Lars Gullestad. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique trial code numbers assigned to the latter. The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness

8.4.2 Suspected unexpected serious adverse reactions

SUSARs will be reported to the National Competent Authorities in each participating country and the local Ethics Committee according to national regulations. The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Norwegian Medicines Agency and the Regional Committee for Medical and Health Research Ethics in any case no later than seven (7) days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight (8) days. The sponsor shall ensure that suspected adverse reactions that are serious and unexpected are reported to the Norwegian Medicines Agency and the Regional Committee for Medical and Health Research Ethics within 15 days of the sponsor after knowledge of the event. The sponsor shall inform all investigators of the trial substance in question of suspected adverse reactions that are serious and unexpected. An account of any interruption in treatment or any breaking of the treatment code, the investigator's assessment of the causal relationship, and consequences for further testing shall accompany the notification of suspected adverse reactions pursuant to the first and second paragraphs. SUSARs will be reported to the drug manufacturer, Amgen® at time of regulatory submission.

The National Competent Authorities may require that individual reports of adverse events described in collective reports should also be submitted. The sponsor shall keep detailed records of all adverse events that are reported to him by the investigator. The records shall be submitted to the National Competent Authorities on request. Amgen® will receive annual safety reports and a Final (End of Study) Report, including unblinded data for blinded studies and reports of unauthorised use of a marketed product.

8.4.3 Annual safety report

Once a year throughout the clinical trial, the sponsor will provide the Norwegian Medicines Agency with an annual safety report. The format will comply with national requirements.

8.4.4 Clinical study report

The adverse events and serious adverse events occurring during the study will be discussed in the safety evaluation part of the Clinical Study Report.

8.5 Procedures in case of emergency

The investigator is responsible for assuring that there are procedures and expertise available to cope with emergencies during the study (see also section 10.2.3).

8.6 Safety monitoring

A data safety monitoring committee will be appointed to assess trial safety. The committee consist of an independent clinician and a statistician. It will receive reports summarising patient recruitment and the number of AEs / SAEs after the first 20 patients have been randomised, and again after 50 % and 100 % of patient enrolment. The data safety monitoring committee will receive additional information on demand and can advise temporary or permanent stop in patient enrolment. The committee will have access to the randomisation code, and can, if they so choose, perform an interim analysis regarding the number of adverse events and serious adverse events. The data safety monitoring committee is independent from the sponsor and will be composed of individuals with no competing interest with regard to the study investigational products or study outcome.

9 Data management and monitoring

9.1 Electronic case report forms (eCRFs)

The designated investigator staff will enter the data required by the protocol into the electronic Case report form (eCRF). The Principal Investigator is responsible for assuring that data entered into the eCRF are complete, accurate, and that entry is performed in a timely manner. If any assessments are omitted, the reason for such omissions will be noted in the eCRFs. Corrections, with the reason for the corrections will also be recorded. After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site. An online eCRF will be used in this trial.

9.2 Source data

Some data will be recorded directly into the eCRF, which, together with the patient medical record, is to be considered the source data. All data important for patient safety and continued care must be duplicated in the patient's medical record as described below. Study-specific imaging data and blood analyses are independent source data.

The medical records of each patient should clearly describe at least:

- That the patient is participating in the study
- The patient's study identification number
- Date when the informed consent was obtained from the patient;
- Results of all assessments confirming a patient's eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);
- Surgical history, as relevant;
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- Treatments provided, changes in treatments during the study and the time points for the changes;
- Visits to the clinic / telephone contacts during the study, including those for study purposes only;
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments;
- Date of, and reason for, discontinuation from study treatment;
- Date of, and reason for, withdrawal from study;
- Date of death and cause of death, if available.

9.3 Study monitoring

The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check that the study is conducted as approved by the Ethics committee and adheres to GCP guidelines.

Sponsor's representatives (e.g. monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

9.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc.) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorised personnel.

9.5 Database management

Data will be entered into the eCRF without delay and stored in the dedicated and secured online platform (Viedoc®). Data will be extracted from Viedoc for analysis, and the extracted data will be

stored in dedicated, secure areas at the participating centres. Data will be stored in a de-identified manner, where each study participant is recognisable by his/her unique trial subject number. The data will be stored until Dec 31st, 2040 in compliance with local regulations, or until the patient requires that his/her data are deleted. Data in the eCRF will be handled according to GCP. Only the personnel authorised to enter and/or analyse data (i.e. investigators) will have access to the database.

9.6 Biobanking

A biobank will be established at the Dept. of Cardiology, Oslo University Hospital, Rikshospitalet for the analysis of serum and plasma. The samples will be stored in multiple aliquots and labelled with the unique trial subject number, and the letter A signifying baseline, and the letter B signifying the visit at one month, C signifying 2 months etc. The samples will be stored at -80 degrees Celsius in a dedicated research freezer. The material is scheduled for destruction by Dec 31st, 2040. Professor Lars Gullestad at Oslo University Hospital, Rikshospitalet will be responsible for the biobank. Biochemical analyses may be performed at other participating centres, and the samples may be shipped between countries for storage and analyses.

10 Statistical methods and data analysis

10.1 Determination of sample size

This trial is designed to assess the effect of evolocumab on intima thickness as measured by coronary IVUS. The sample size of the present study is based calculations relating to the primary outcome, the change in maximal intima thickness from baseline to one year. In the SCHEDULE trial, we observed an increase in the maximal intima thickness of 0.08 +/- 0.12 mm in the placebo group, whereas the corresponding increase was 0.03 +/- 0.06 mm in the everolimus arm.[21] Intensive cholesterol reduction has been shown to actually reverse the atherosclerotic volume in previous trials. We therefore hope to achieve a 0.05 mm between-group difference in the change in the intima thickness in the EVOLVD trial. With an estimated 0.09 mm standard deviation, we will require 51 patients in each arm with a power of 80%, at a two sided alpha level of 5%. To increase the chances of reaching the primary and secondary outcomes, and to compensate for uncertainties in this calculation, we will ensure that 120 patients complete the one-year follow-up. To allow for a dropout rate of 5 - 10% we aim to include 130 patients.

In the SCHEDULE trial, the mean increase in the percent atheroma volume was 1.3 ± 2.3 percentage points in the everolimus arm versus 4.2 ± 5.0 percentage points in the cyclosporine group. Provided that evolocumab can produce a similar reduction in the progression of the atheroma volume, with an estimated standard deviation of 3.7 percentage points, we will need just 26 patients in each arm to detect a between-group difference in the important secondary outcome, the change in percent atheroma volume, with an α of 5 % and a power of 0.8.

10.2 Randomisation

10.2.1 Allocation- sequence generation

Balanced, permuted block randomisation (in a 1:1: ratio for the two study arms) will be performed online in Viedoc and stratified by centre.

10.2.2 Allocation- procedure to randomise a patient

We will use a computerised randomisation procedure for treatment allocation. Random treatment allocation will be executed on the online, password-protected platform designed for study purposes (Viedoc™) once eligibility has been confirmed and the informed consent has been signed.

10.2.3 Blinding and emergency un-blinding

The study participants (patients) and all study personnel, including investigators, personnel assessing outcomes, study nurses, data analysts and treating physicians and nurses, will be blinded to study drug allocation.

Un-blinding will be performed in the event of AEs where knowledge of the type of drug might be of importance to the personnel treating the patients, and in the event of SUSARS. Un-blinding will be performed by personnel with the designated role of performing unblinding, and the result will immediately be reported to the primary investigator, who will then take the required action(s). The eCRF is designed to handle emergency unblinding by allowing investigators to take on different roles, one of which is the role of emergency unblinder. When taking on this role, the investigator can unmask study drug assignment for a particular patient without further compromising the integrity of the randomisation list. Emergency unblinding is traceable in the eCRF system and will only be performed if requested by an investigator, and only if required to make important medical decisions for the patient in question. Two of the study personnel at the sponsor site only, will be given the emergency unblinding role. Their telephone numbers will be distributed among the study personnel. At least one of the designated emergency unblinders will be available at any time on a 24-hour basis. Unless unavoidable, other investigators and the personnel assessing outcomes, should not be made aware of treatment allocation.

10.3 Population for Analysis

The following populations will be considered for the analyses:

- Intention to treat (ITT) population: All randomised participants, regardless of protocol adherence.
- Safety population: All patients who have been enrolled in the trial, and who have received at least one dose of the investigational medicinal product (evolocumab or placebo).
- Per-protocol population (PP): Includes all subjects who have completed 12 months of treatment.

10.4 Planned analyses

The main statistical analysis is planned when the last patient has completed the end-of-treatment visit 12 months after randomisation. The number severity of adverse events will be assessed consecutively.

Deviation from the original statistical plan will be described and justified in the Clinical Study Report. Amendments to plan can be done until the day of database lock.

10.5 Statistical analysis

All statistical tests will be performed using a two-sided 5 % level of significance. Continuous efficacy variables will be analysed using baseline-adjusted ANCOVA for comparisons between the treatment arms. If necessary, values will be log-transformed to meet the assumptions of the tests. All analyses will primarily be analysed according to the intention-to-treat principle. The number of major clinical events will be analysed using descriptive statistics. Between-group differences in ordinal categorical variables, such as NYHA class, will be analysed using ordinal logistic regression, whereas the count variables will be assessed by Poisson regression. Demographic, efficacy and safety data will be summarised by treatment group using means, minimums, medians, maximums, interquartile ranges and standard deviations for continuous variables and frequency counts and percentages for categorical variables. Per protocol analyses will be performed using the same methods as for the intention-to-treat analyses.

The primary endpoint, the between-group difference in the baseline-adjusted intima thickness at 12 months, will be calculated by baseline-adjusted ANCOVA according to the intention-to-treat principle, the statistical null-hypothesis being that the intima thickness does not differ between the two treatment arms. Secondary analyses will be made according to the per-protocol-principle as baseline-adjusted absolute values after end-of-treatment.

Key, secondary endpoints:

The secondary endpoints "Percent atheroma volume as measured by IVUS" and "Cardiac allograft vasculopathy" will be tested, at a two-sided alpha level of 0.05, in a hierarchical fashion.The baseline-adjusted between-group difference in the atheroma volume, eGFR, quality of life, and biomarkers reflecting cardiac function, blood lipids, and inflammation will be calculated by ANCOVA according to the intention to treat principle. The statistical null-hypotheses are that the changes in these characteristics do not differ between patients allocated to evolocumab and patients allocated to placebo.

Secondary per protocol analyses will be performed using the same methods as for the intention-to-treat analyses. Exploratory analyses will be made for efficacy variables stratified by centre.

Safety analyses will include tabulation of type and frequency of all adverse events. Any serious adverse events will be reported with comprehensive narratives. Any value of safety laboratory parameters outside normal ranges will be identified.

Missing data will be omitted from analyses, i.e. there will be no imputation or estimation of missing values. However, a comparison of the baseline characteristics of those with an intima thickness measurement at 12 months and the baseline characteristics of those without a value will be performed to assess any bias introduced due to missing data. Statistical analyses will be performed in IBM SPSS Statistics version 21 or later.

11 Study management

11.1 Investigator delegation procedure

The principal investigator is responsible for making and updating a "delegation of tasks" listing all the involved co-workers and their role in the project. He will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

11.3 Study amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

11.4 Audit and inspections

Authorised representatives of a Competent Authority and Ethics Committee may visit the centre to perform inspections, including source data verification. Likewise, the representatives from sponsor may visit the centre to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these

activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (ICH/GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 Ethical and regulatory requirements

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics committee approval

The study protocol, including the patient information and informed consent form to be used, must be approved by the regional ethics committee in each participating country before enrolment begins in the particular country.

The investigator is responsible for informing the regional ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol as per national requirements.

12.2 Other regulatory approvals

The protocol will be submitted and approved by the applicable, national competent authorities before commencement of the study. The protocol will also be registered on www.clinicaltrials.gov before inclusion of the first patient.

12.3 Informed consent procedure

The investigator is responsible for giving the patients full and adequate verbal and written information about the nature, purpose, and potential risks and benefits of the study. Study participants will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

It will be emphasised that study participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Written informed consent must be obtained for all study participants before enrolment in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent form will be given to the patients. The signed and dated consent forms will be filed in the Investigator Site File binder.

12.4 Subject identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal number, full names and last known addresses.

The patients will be identified in the eCRFs by a study-specific, unique identification number.

13 Trial sponsorship and financing

The EVOLVD trial is an investigator-sponsored (ISS) study which receives funding from Amgen®. Amgen has also provided the study drug. The funding sources have had no role in the design of the study; neither will they participate in the implementation of the trial, in the analyses of the results, or

in the decision to publish. The investigators take sole responsibility for the integrity of the data, the writing of the manuscript and the dissemination of the results.

14 Trial insurance

The Principal investigator has insurance coverage for this study through membership of the Drug Liability Association.

15 Publication policy

Upon study completion and finalisation of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results. We will allow for a separate publication of baseline characteristics once all subjects have been enrolled.

The results of this study will also be submitted to the Competent Authorities and the Regional Ethics Committees according to EU and national regulations. All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors. The funding sources have had no role in the conception of the study; neither will they participate in the implementation of the trial, in the analyses of the results, or in the decision to publish.

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