Statistical Analysis Plan

TRIAL FULL TITLE	Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients
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1 SAP Signatures

I give my approval for the Statistical analysis plan (SAP) for the EVOLVD trial dated 22nd June 2023

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Signature:

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Date:

22 June.2023

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4 Abbreviations and Definitions

Abbreviation or special term	Explanation
AE	Adverse event
eCRF	Electronic Case report form
CAV	Cardiac allograft vasculopathy
CI	Confidence interval
CRP	C-reactive protein
DSMB	Data safety monitoring board
EQ-5D-3L	EuroQoL five dimensions three levels [Questionnaire]
EQ VAS	EuroQoL visual analogue scale
EVOLVD	Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients
FAS	Full analysis set
GCP	Good clinical practice
ICH	International Conference on Harmonisation
KCCQSS	Kansas City Cardiomyopathy Questionnaire
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PCSK9	Proprotein convertase subtilisin–kexin type 9
PPS	Per protocol set
SAE	Serious adverse event
SD	Standard deviation
SF-36	Short form 36 [Questionnaire]
SS	Safety set
SUSAR	Suspected unexpected serious adverse reaction
TAVI	Transcatheter aortic valve implantation
TnT	Cardiac troponin T

5 Introduction

5.1 Preface

Cardiac allograft vasculopathy (CAV) is characterised by diffuse thickening of the arterial intima. It is partly thought to be caused by atheromatosis. Statins reduce the incidence of CAV and improve survival in heart transplant recipients. However, despite the use of statins, CAV is prevalent and remains the leading cause of death in long-term survivors of heart transplant. Inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) substantially reduce cholesterol levels but have not been tested in heart transplant recipients.

The Cholesterol lowering with EVOLocumab to prevent cardiac allograft Vasculopathy in De-novo heart transplant recipients (EVOLVD) trial is a Nordic, multicentre, parallel group, randomized, double-blind placebo-controlled trial designed to assess the effect of the PCSK9-inhibitor evolocumab, in addition to standard care, on coronary intima thickness in patients who have recently received a heart transplant.

5.2 Purpose of the analyses

The purpose of the analyses laid out in this analysis plan is to evaluate the efficacy and safety of the PCSK9-inhibitor evolocumab in *de novo* heart transplant recipients.

6 Study Objectives and Endpoints

6.1 Study Objectives

The main objective of this study is to evaluate the effect of the PCSK9 inhibitor Evolocumab vs placebo 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) cardiac function as assessed by biomarkers and echocardiography, iv) the number of rejections, and (v) safety and tolerability.

Exploratory objectives are to assess the effect of treatment on clinical events, defined as death, myocardial infarction, cerebral stroke, cancer, and end stage renal disease.

Additional objectives that will be explored in later substudies include – but are not limited to – the impact of treatment on (i) inflammation, (ii) HDL and total cholesterol, and (iii) quality of life.

6.2 Endpoints

In Sections 5.2.1 – 5.2.3, we present the endpoints that will be reported in the main publication of EVOLVD. Section 5.2.4 note some endpoints that will be reported in later substudies.

6.2.1 Primary endpoint

The primary endpoint of the EVOLVD trial is the baseline-adjusted maximal intimal thickness as measured by coronary intravascular ultrasound at 12 months' follow-up. The maximal intima thickness is defined as the largest distance (in mm) from the intimal leading edge to the external elastic membrane.

6.2.2 Secondary endpoints

1. Percent atheroma volume as measured by intracoronary ultrasound
2. LDL cholesterol
3. Estimated glomerular filtration rate
4. N-terminal pro-B-type natriuretic peptide
5. Cardiac troponin T

6.2.3 Safety endpoints

1. The number of patients with adverse events
2. The number of patients with serious adverse events, including
    a. Death
    b. Infections
    c. Any allograft rejection
    d. Treated allograft rejection
    e. Renal events (sustained eGFR < 15 ml/min/1.73m^2, renal replacement therapy or kidney transplant)
    f. Cardiovascular event (defined as percutaneous coronary intervention, myocardial infarction, or stroke.
3. The number of major clinical adverse events, defined as death, myocardial infarction, percutaneous coronary intervention/ coronary bypass surgery, cerebral stroke, cancer, or end-stage renal disease (exploratory endpoint)

6.2.4 Endpoints planned for later substudies

The following endpoints will be analysed and reported in later substudies:

- Cardiac allograft vasculopathy at 12 months
- Inflammation biomarkers
- HDL and total cholesterol
- Quality of life assessed by the SF-36 and 5D-EuroQoL questionnaires, and the Beck's Depression Inventory

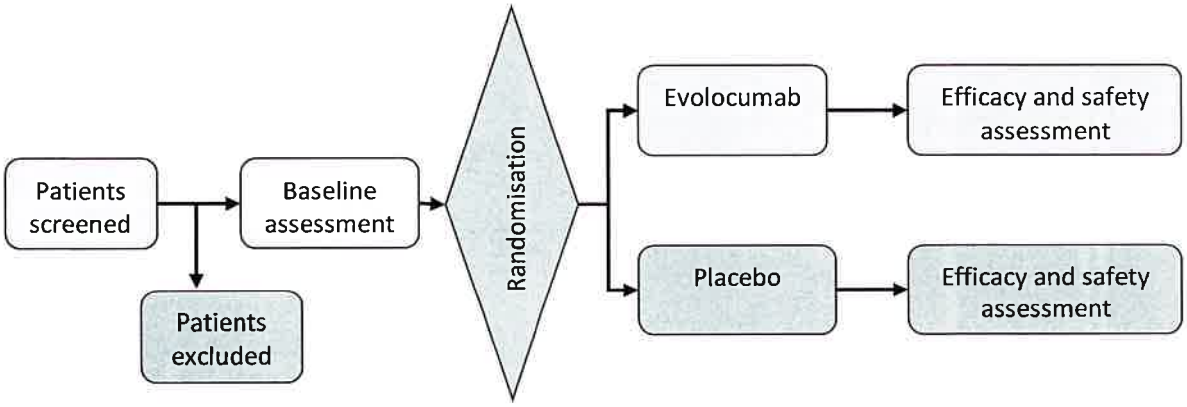
Table: Summary of objectives and endpoints for the main publication of EVOLVD

Primary objective	Primary endpoint	Data type	Method of analysis*
To evaluate the effect of the treatment on cardiac allograft vasculopathy	Maximal intimal thickness at 12 months	Continuous	ANCOVA, with adjustment for baseline values
	Secondary endpoints		
	Percent atheroma volume at 12 months	Continuous	ANCOVA, with adjustment for baseline values
	Cardiac allograft vasculopathy at 12 months	Continuous	ANCOVA, with adjustment for baseline values
Secondary objectives			
To assess the impact of treatment on cholesterol levels	LDL cholesterol at 12 months	Continuous	Linear mixed model, based on measurements at baseline, 1, 2, 3, 6, 9, and 12 months
To assess the impact of treatment on renal function	Estimated glomerular filtration rate at 12 months	Continuous	Linear mixed model, based on measurements at baseline, 1, 2, 3, 6, 9, and 12 months
To assess the impact of treatment on cardiac function	Cardiac troponin T at 12 months	Continuous	Linear mixed model, based on measurements at baseline, 1, 2, 3, 6, 9, and 12 months
	N-terminal pro-B-type natriuretic peptide at 12 months	Continuous	Linear mixed model, based on measurements at baseline, 1, 2, 3, 6, 9, and 12 months
Safety objectives	**Safety/exploratory endpoints**		
To assess the impact of treatment on rejections	The number of allograft rejections over 13 months' follow-up	Categorical	Descriptives
To assess the impact of treatment on safety and tolerability	The number and type of adverse events over 13 months' follow-up	Categorical	Descriptives
	The number of major clinical adverse events (death, myocardial infarction, percutaneous coronary intervention/ coronary bypass surgery, cerebral stroke, cancer, end-stage renal disease) over 12 months' follow-up	Categorical	Descriptives
*See Section 10 for details			

7 Study Methods

7.1 General Study Design and Plan

This is a phase II, multi-centre, randomised, placebo controlled, double blind, parallel group trial. The trial is conducted at the six Nordic transplant centres in Aarhus, Copenhagen, Helsinki, Gothenburg, Lund, and Oslo. Eligible patients are randomised 1:1 and allocated to subcutaneous evolocumab or matching placebo at baseline, after providing written informed consent and performing baseline exams. The patients start treatment with 420 mg evolocumab/placebo immediately after randomisation. The study is designed to show superiority regarding the primary endpoint in patients assigned to active treatment versus patients allocated to the placebo arm.



7.1.1 Treatment Duration

12 months

7.1.2 Follow-up

13 months (including treatment duration)

7.1.3 Randomisation and treatment allocation

Treatment is allocated according to a computer based balanced, permuted block randomisation (in a 1:1: ratio for the two study arms). Treatment allocation is performed online on a password-protected platform designed for study purposes (Viedoc™) once eligibility has been confirmed, the informed consent has been signed and baseline assessments have been performed. Randomisation is stratified by centre.

7.1.4 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.

7.1.5 Trial procedures

Study phases	Pre-treatment		Treatment (months)							Follow-up
			Baseline	1	2	3	6	9	12	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		Randomisation	x	x	x	x	x	x		
Coronary angiography with IVUS			x						x	
Echocardiography			x						x	
Blood samples			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	

7.1 Number of patients

We aim to enrol 130 patients in this trial.

7.2 Inclusion criteria

Patients will be screened for eligibility during routine follow-up 4 – 8 weeks after heart transplantation.
All 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.[1]

7.3 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

7.4 Randomisation and Blinding

The Research Support Unit at Oslo University Hospital generated a balanced, permuted, variable block size randomisation list (in a 1:1: ratio for the two study arms). We used a computerised randomisation procedure for treatment allocation. Random treatment allocation was executed on the online, password-protected platform designed for study purposes (Viedoc™) once eligibility had been confirmed and the informed consent had been signed. Study nurses who were blinded to study drug content administered identical-looking drug packages to the patients according to the randomisation number generated for each patient. The investigator or study nurse who randomised the patient was responsible for presenting the randomisation number to the designated unblinded personnel dispensing the study drug and registering the corresponding kit-number in the eCRF. The study drug was not administered/ dispensed to the patient before the kit number had been entered in the eCRF and no error message was generated. The study participants (patients) and all study personnel, including investigators, personnel assessing outcomes, study nurses, data analysts and treating physicians and nurses, are blinded to allocation to study drug.

7.5 Study Variables

7.5.1 Primary endpoint:

The primary endpoint, the maximal intracoronary intima thickness, is measured as the largest distance from the intimal leading edge to the external elastic membrane on matched slices of the same coronary vessel (Figure 1). All intracoronary ultrasound analyses will be conducted after trial closure at 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 intravascular ultrasound (IVUS) images by the American College of Cardiology and European Society of Cardiology.

Figure 1

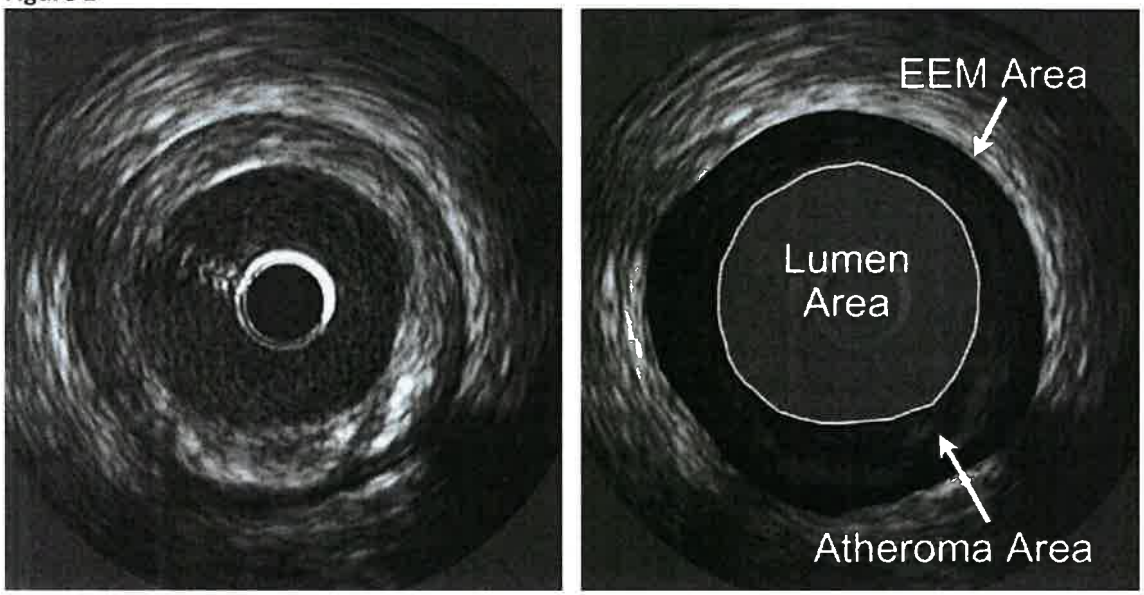


Illustration of single slice of coronary ultrasound images. Multiple slices are recorded at constant intervals along a coronary vessel and matched (baseline/follow-up) for direct comparison. The primary endpoint of the trial is the maximal intima thickness, measured from the external elastic membrane (EMM) to the luminal border. The percent atheroma volume is the percentage of the intima area (EMM area – lumen area) that contains lipids (different echogenicity than the healthy intimal area) across the entire matched segment of the coronary artery. (E From Stephen J. Nicholls et al, Relationship Between Cardiovascular Risk Factors and Atherosclerotic Disease Burden Measured by Intravascular Ultrasound. JACC 2006:47;1967-75.

7.5.2 Secondary endpoints:

The secondary endpoints "percent atheroma volume" and "cardiac allograft vasculopathy" will be analysed on matched sections of the IVUS images of the coronary vessel with contour detection of the lumen and external elastic membrane for each mm. "Percent atheroma volume" expresses the summation of atheroma areas in proportion to the area between the lumen and the external elastic membrane (in percent) (Figure). "Cardiac allograft vasculopathy" is defined as the extent to which the mean maximal intimal thickness is ≥0.5 mm over the entire matched segment.

8 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 (SD 0.12) mm in the placebo group, whereas the corresponding increase was 0.03 (SD 0.06) mm in the everolimus arm.[2] Intensive cholesterol reduction has been shown to actually reverse the atherosclerotic volume in previous trials.[3,4] 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 aim for 120 patients to complete the one-year follow-up. To allow for a dropout rate of 5 - 10%, we plan to include 130 patients.

9 General Considerations

9.1 Timing of analyses

The final analysis will be performed after the last patient has completed the last follow-up visit 12 months after randomisation, and all data have been transferred to a separate file. The data must have met the cleaning and approval requirements of the primary investigator, and this Statistical Analysis Plan must have been finalised and approved by the primary investigator. Only when these requirements have been met, will database lock occur, and the randomisation code be opened.

9.2 Populations for analysis

9.2.1 Full analysis set (modified intention-to-treat population)

The full analysis set (FAS) will include all patients who were randomised and who (irrespective of receipt of actual treatment) had intracoronary ultrasound adequate for the determination of coronary intima thickness at baseline and at the 12 months follow-up. The adequacy of the ultrasound examination must be determined before database lock and the randomisation code is opened. The primary analysis of the primary endpoint (and all secondary endpoints) will be carried out on the FAS.

9.2.2 Per Protocol set

The per protocol set (PPS) will include all patients who received the study drug with compliance > 80% during the treatment period (see Section 9.4) and who have valid data for the baseline and the 12-months follow-up measurements. A secondary analysis of the primary endpoint will be performed on the PPS.

9.2.3 Safety set

The safety set (SS) will include all patients who received any study treatment (including control) but excluding subjects who drop out prior to receiving treatment.

Each patient's inclusion or exclusion status regarding each analysis population must be determined prior to breaking the blind. The status must be documented in the final database prior to breaking the blind.

9.3 Covariates and Subgroups

The analyses of the primary and secondary endpoints will not be adjusted for baseline characteristics; however, the primary endpoint and key secondary endpoints will be calculated as baseline-adjusted values (i.e., the analyses of the 12 months measurements will be adjusted for the baseline measurements in ANCOVA analyses) as specified in Section 10. Adjustment will also be made for the stratification factor in the randomisation (centre).

We will perform binary subgroup analyses of the primary endpoint stratified by gender; age above/below median; baseline LDL cholesterol above/below median; baseline intima thickness above/below median; ischaemic reason for transplant; baseline CRP above/below median; and baseline creatinine above/below median. A forest plot will be used to communicate the results. The

subgroup analyses are exploratory, and the trial is not powered to show differences across subgroups.

9.4 Missing Data

Because the measurements of the primary endpoint and key secondary endpoints are collected twice only, and the endpoint analyses will be baseline adjusted ANCOVA, there will be no imputation of missing data in the primary analyses, which will be analysed on the FAS. However, to elucidate possible biases this method entails, baseline data (see Section 9.3) for patients for whom endpoint data exist will be tabulated along with baseline data for patients who for some reason drop out or are unable to complete both sets of tests. Any noteworthy differences will be commented on. We will also describe the dropout rate in each treatment arm and comment on any important differences. The extent of missing data will be reported for each endpoint variable.

The impact of missing data for the primary endpoint will be assessed with sensitivity analyses (see Section 10.4).

We expect few missing values on baseline characteristics and will not employ a strategy to impute missing baseline values.

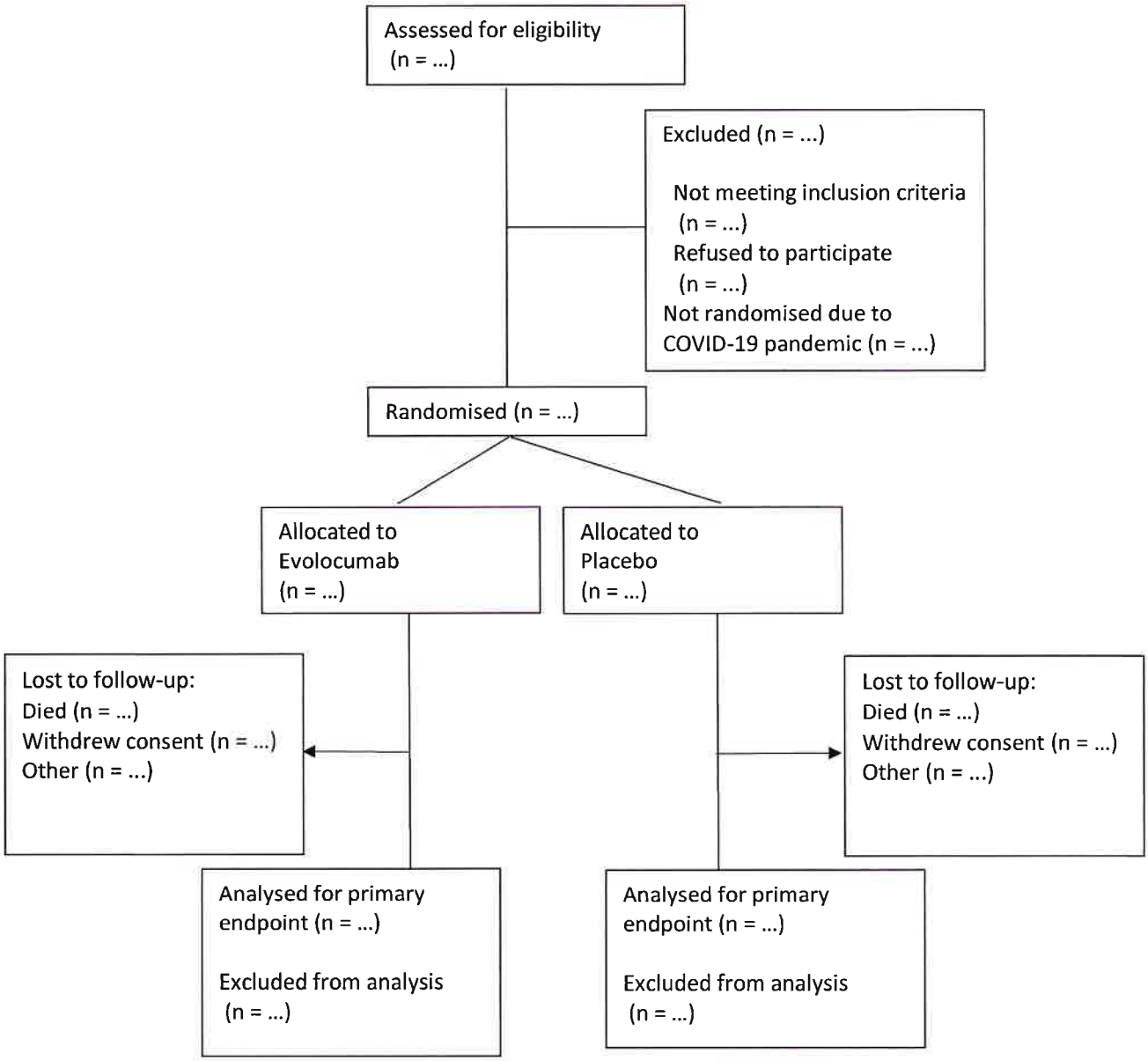
10 Summary of Study Data

We will present the baseline characteristics by columns for each treatment (placebo, evolocumab) on the FAS. All continuous variables will be summarised using the following descriptive statistics: mean ± standard deviation; median (interquartile range). The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures.

10.1 Subject Disposition

We will document how many subjects reached the various stages of the trial (the number screened, randomised, had 12-month follow-up, and could be analysed for the primary endpoint), and how many dropped out and for what reasons (death, withdrew consent, failed to show up) according to the following CONSORT diagram:

10.2 Consort diagram



10.3 Baseline Characteristics

The following baseline variables will be presented.

Demography
Age, years
Male sex
Smoker, current/previous smoker
Body mass index, kg/m^2
Systolic blood pressure, mmHg
Diastolic blood pressure, mmHg
Heart rate, rpm
Time from transplant
Donor age
Cold ischaemia time
Medical history
Cause of heart failure • Ischaemic • Dilated cardiomyopathy • Congenital heart disease • Other
Diabetes
Hypertension
Hypercholesterolemia
Previous stroke or transient ischemic attack
Chronic obstructive pulmonary disease
Medication (No of patients)
Tacrolimus
Cyclosporine
Everolimus
MMF
Prednisone
Statin
Ezetimibe
Anticoagulant
Platelet inhibitor
Beta blocker
Angiotensin converting enzyme inhibitor or angiotensin receptor blocker
Calcium channel blocker
Diuretic
Biochemistry
Haemoglobin, g/dL
N-terminal pro-B-type natriuretic peptide (NT-proBNP), ng/L
P-troponin T, ng/L
C-reactive protein (CRP), mg/L
Creatinine, µmol/L
Estimated glomerular filtration rate (eGFR), mL/min
Total cholesterol mmol/L

LDL cholesterol, mmol/L
HDL cholesterol, mmol/L
Triglycerides, mmol/L
ALT (Units/L)

10.4 Treatment Compliance

Study drug injections are made on-site at 0, 1, 2, 3, 6, and 9 months, whereas patients self-inject on months 4, 5, 7, 8, 10, and 11. The patients deliver empty boxes for the estimation of drug compliance after self-administration. Treatment compliance (in percent) for each patient is calculated as 100 times the number of study drug injections (observed and estimated based on the delivery of empty boxes) divided by 12 (max number of injections). We will consider a patient with compliance > 80% as a treatment complier to be included in the PPS. Patients who die during follow-up, withdraw from the trial, or who demonstrate contraindications to the study drug will be considered non-compliers. We will report the average and SD of treatment compliance and the number and percentage of treatment compliers and non-compliers by each treatment arm.

11 Statistical analyses of primary and secondary endpoints

11.1 Statistical framework

This trial was designed and powered to detect a single primary endpoint. The hypothesis setup for the primary endpoint is:

Null hypothesis (H_0): The baseline-adjusted maximal intimal thickness after 12 months follow-up differ between the placebo and Evolocumab treatment arms.

Alternative hypothesis (H_A): The baseline-adjusted maximal intimal thickness after 12 months follow-up is either greater in the placebo group than the Evolocumab group or greater in the Evolocumab group than in the placebo group.

Decision rule

- If the two-sided P-value for H_0 is less than 0.05 and the estimated coefficient for Evolocumab vs placebo (see Section 10.2) is less than 0, superiority of Evolocumab is claimed
- If the two-sided P-value for H_0 is less than 0.05 and the estimated coefficient for Evolocumab vs placebo (see Section 10.2) is greater than 0, superiority of placebo is claimed
- If the two-sided P-value for H_0 is greater than or equal to 0.05, no superiority is claimed and no statements of treatment efficacy will be made

No other hypotheses will be tested in this trial. All secondary endpoints will be estimated with 95% confidence intervals (CIs), and the results will be considered supportive of the results of the primary endpoint or exploratory. No statements regarding treatment effects or other definitive conclusions will be made from the results. The CIs will not be adjusted for multiplicity, and they will not be interpreted in place of hypothesis tests.

11.2 Continuous endpoints measured at two points in time

Continuous variables measured at baseline and 12 months' follow-up only, including the primary endpoint, percent atheroma volume, and cardiac allograft vasculopathy, will be performed as analysis of covariance (ANCOVA) in the full analysis set. The model will be a linear regression with

the 12 months' follow-up measurement as the outcome (dependent) variable and treatment allocation (0=placebo, 1 = Evolocumab), baseline value, and centre (stratification factor in the randomisation) as explanatory (independent) variables. The effect measure will be the beta-coefficient for treatment allocation (the between-group difference), estimated with a 95% confidence interval. For the primary endpoint only, we will also report the two-sided p-value for the null hypothesis of a zero-treatment effect.

The observed data and the estimated between-group difference from the ANCOVA analyses will be illustrated with the regression lines for placebo and Evolocumab superimposed on a scatter plot of the baseline measurements (x-axis) and the 12-months follow-up measurements (y-axis).

11.3 Continuous endpoints measured at more than two points in time

A linear mixed model will be fitted to all continuous endpoints with more than two measurements (LDL, NT-proBNP, TnT). Treatment, visit, treatment x visit interaction, and centre (stratification factor in the randomisation) will be fixed factors. A random intercept will be used. Based on the fitted model, we will estimate treatment group means with 95% confidence intervals for baseline, end of treatment time points, and changes from baseline to end of treatment. We will also estimate (with a 95% CI) the between-group difference in changes from baseline to end of treatment.

The observed values of LDL for each measured time point will be plotted as a connected line plot with error bars (showing the SD) for each treatment arm.

11.4 Sensitivity analyses

To determine the robustness of the analysis of the primary endpoint, we will perform sensitivity analyses with imputations for missing data. While we do not expect the trial intervention to affect dropouts, it is unreasonable to assume that dropouts will occur completely at random, and dropouts may therefore bias the results. We therefore aim to do best-case, worst-case, no-change scenario imputations for missing data:

- Scenario 1 (best-case): missing data in the intervention arm are imputed such that the change from baseline to 12 months is mean change - 1 standard deviation (SD), whereas missing data in the placebo arm are imputed such that the change from baseline to 12 months is equal to the mean change. The mean change and SD are based on all observed values from both the intervention and placebo arms.
- Scenario 2 (worst-case): missing data in the intervention arm are imputed such that the change from baseline to 12 months is mean change + 1 SD, whereas missing data in the placebo arm are imputed such that the change from baseline to 12 months is equal to the mean change. The mean change and SD are based on all observed values from both the intervention and placebo arms.
- Scenario 3 (no-change): all missing data in intervention and placebo arms are imputed as the overall (i.e., both treatment arms combined) mean observed value at each time point

12 Safety Analyses and Adverse Events

Safety analyses will include tabulation of type and frequency of all adverse events. Any value of safety laboratory parameters outside normal ranges will be identified. The final report will include the absolute number of adverse and severe adverse events in each group. The results will be reported for the SS only.

Adverse events include

- Injection site reactions
- Infections
- Any event leading to discontinuation of study medicine
- Death
- Any rejection
- Treated rejections
- Renal event
- Cardiovascular events

Safety laboratory parameters include

- Creatinine > 3 times above upper limit of normal
- Total leucocyte count < $2.0x10^9$/L
- Creatinine kinase > 10 times above upper limit of normal
- ALT > 3 times upper limit of normal

Serious adverse events and adverse events of special interest (pregnancies) will be reported with comprehensive narratives.

13 References

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