MUscle Side-Effects of atorvastatin in coronary patients (MUSE): Follow-up study

Protocol Identification Number: MUSE-follow-up

EudraCT Number: 2019-003959-11

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Title: **Muscle Side-Effects of atorvastatin in coronary patients (MUSE): Follow-up study**

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I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Role	Signature	Date
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Nils Tore Vethe	PhD	Study Co-Chair WP leader, pharmacology	(e-sign)	12.03.20
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Morten Wang Fagerland	PhD	Study statistician	(e-sign)	12.03.20
Trine Lauritzen	MD	PhD candidate	(e-sign)	12.03.20

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Title:	**Muscle Side-Effects of atorvastatin in coronary patients (MUSE): Follow-up study**
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I hereby declare that I will conduct the study in compliance with the Protocol, ICH GCP and the applicable regulatory requirements:

Name	Title	Signature	Date
John Munkhaugen	MD, PhD.	e-sign	05.05.20

PROTOCOL SYNOPSIS

Protocol title: **Muscle Side-Effects of atorvastatin in coronary patients (MUSE): Follow-up study**

Sponsor	Vestre Viken Trust, Drammen Hospital
Phase and study type	Prospective, open, intervention study.
Investigational Medical Product (IMP) (including active comparator and placebo):	The study aims to determine the effect of 7 weeks open treatment with atorvastatin 40 mg/day, followed by 7 weeks open treatment with no lipid lowering treatment, on muscle symptom intensity in patients classified with confirmed statin-associated muscle symptoms (SAMS) (i.e. statin-dependent muscle side-effects) and non-SAMS in the MUscle Side-Effects of atorvastatin in coronary patients (MUSE) randomized double blinded cross-over trial.
Centers:	Two hospitals (Drammen and Vestfold) in Norway
Study Period:	Estimated date of first patient enrolled: 15-AUG-2020 Anticipated recruitment period: 2 weeks Estimated date of last patient completed: 1-DES-2020
Treatment Duration:	Estimated (non) treatment duration per patient: 7 weeks plus one week pharmacological wash-out.
Follow-up:	Subjects will be followed up for 16 weeks for the primary and secondary endpoints .
Objectives	The primary purpose is to provide new patophysiologic knowledge of atorvastatin-dependent muscle side-effects and to develop an accurate diagnostic test that can be used in clinical practice to differentiate patients with muscle side-effects from patients without such side-effects (i.e. muscle symptoms not related to the atorvastatin treatment). The primary objective is to determine the effect of open treatment with atorvastatin 40 mg/day on muscle symptom intensity in patients classified with confirmed SAMS and non-SAMS in the MUSE trial. The key secondary objectives are: 1. To determine the relationship between SAMS and parent drug and the active metabolites in skeletal muscle, and to evaluate the metabolite concentrations in muscle as a diagnostic tool for confirmed SAMS. 2. To determine the relationship between SAMS and parent drug and the active metabolites in blood, and to evaluate the metabolite concentrations in blood as a diagnostic tool for confirmed SAMS. 3. To determine the relationship between SAMS and the atorvastatin to HMGCR ratio in skeletal muscle, and to evaluate the ratio in muscle as a diagnostic tool for confirmed SAMS.

4. To determine the relationship between SAMS and the atorvastatin to HMGCR ratio in blood, and to evaluate the ratio in blood as a diagnostic tool for confirmed SAMS.
5. To determine the relationship between SAMS and inhibition of the mevalonate pathway in skeletal muscle, and to evaluate the concentration of mevalonate pathway intermediates in muscle as a diagnostic tool for confirmed SAMS.
6. To determine the relationship between SAMS and inhibition of the mevalonate pathway in blood, and to evaluate the concentration of mevalonate pathway intermediates in blood as a diagnostic tool for confirmed SAMS.
7. To determine the relationship between SAMS and inhibition of mitochondrial function in skeletal muscle, and to evaluate the use of mitochondrial respiratory enzymes in muscle as a diagnostic tool for confirmed SAMS.
8. To determine the relationship between SAMS and inhibition of mitochondrial function in blood, and to evaluate the use of mitochondrial respiratory enzymes in blood as a diagnostic tool for confirmed SAMS.
9. To determine the relationship between SAMS and the calcium-regulating FKBP1A:RyR1 complex in skeletal muscle, and to evaluate the use of the FKBP1A:RyR1 complex in muscle as a diagnostic tool for confirmed SAMS.
10. To determine the relationship between SAMS and the calcium-regulating FKBP1A:RyR1 complex in blood, and to evaluate the use of the FKBP1A:RyR1 complex in blood as a diagnostic tool for confirmed SAMS.
11. To determine the relationship between SAMS and caspase 3 signaling in skeletal muscle, and to evaluate the use of caspase 3 signaling in muscle as a diagnostic tool for confirmed SAMS.
12. To determine the relationship between SAMS and caspase 3 signaling in blood, and to evaluate the use of the caspase 3 signaling in blood as a diagnostic tool for confirmed SAMS.
13. To determine the relationship between atorvastatin exposure and molecular effects in muscle (inhibition of the mevalonate pathway, mitochondrial function, FKBP1A:RyR1 complexation and caspase 3 signaling).
14. To determine the relationship between atorvastatin exposure and molecular effects in blood (inhibition of the mevalonate pathway, mitochondrial function, FKBP1A:RyR1 complexation and caspase 3 signaling).
15. To study statin adherence between the two study arms.
16. To describe study safety.

Exploratory objectives:

1. To describe the relationship between SAMS and morphology/histology in skeletal muscle, and to explore the morphological/histological findings in muscle as a diagnostic tool for confirmed SAMS.
2. To describe the relationship between morphology/histology in skeletal muscle and atorvastatin-related variables, and molecular effects, in muscle and blood.

3. To identify candidate diagnostic biomarkers for confirmed SAMS in muscle tissue and blood (by explorative analyses of gene expression, epigenetics, lipids, metabolites, peptides and proteins).
4. To identify candidate predisposing factors for confirmed SAMS (by explorative analyses of demographics, physiology, concomitant drugs, genetics, gene expression, epigenetics, lipids, metabolites, peptides and proteins).
5. To determine the relationship between atorvastatin exposure and molecular effects in muscle and blood.
6. To identify factors that are associated with the systemic and local exposure to atorvastatin and metabolites.

Endpoints:

Primary endpoint:
The primary end-point will be the individual mean difference in muscular symptom intensity between treatment periods with statin and no lipid lowering treatment, reported by the patients over the last three weeks of each treatment period measured with aggregated VAS scores.

Secondary endpoints:

1. Correlation between atorvastatin-related variables in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin-related variables in muscle. The ability of atorvastatin-related variables in muscle to diagnose SAMS.
2. Correlation between atorvastatin-related variables in plasma vs. muscle and PBMC vs. muscle. Correlation between atorvastatin-related variables in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin-related variables in blood. The ability of atorvastatin-related variables in blood to diagnose SAMS. The atorvastatin-related variables in blood will additionaly by adjusted for SLC2B1 genetics.
3. Correlation between atorvastatin: HMGCR in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin:HMGCR in muscle. The ability of atorvastatin:HMGCR in muscle to diagnose SAMS.
4. Correlation between atorvastatin:HMGCR in PBMC vs. muscle. Correlation between atorvastatin:HMGCR in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin:HMGCR in blood. The ability of atorvastatin:HMGCR in blood to diagnose SAMS.
5. Correlation between mevalonate pathway intermediates in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mevalonate pathway intermediates in muscle. The ability of mevalonate pathway intermediates in muscle to diagnose SAMS.
6. Correlation between mevalonate pathway intermediates in plasma vs. muscle and PBMC vs. muscle. Correlation between mevalonate pathway intermediates in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mevalonate pathway intermediates in blood. The ability of mevalonate pathway intermediates in blood to diagnose SAMS.
7. Correlation between mitochondrial respiratory enzymes in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mitochondrial respiratory enzymes in

muscle. The ability of mitochondrial respiratory enzymes in muscle to diagnose SAMS.

8. Correlation between mitochondrial respiratory enzymes in PBMC vs. muscle. Correlation between mitochondrial respiratory enzymes in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mitochondrial respiratory enzymes in blood. The ability of mitochondrial respiratory enzymes in blood to diagnose SAMS.
9. Correlation between the FKBP1A:RyR1 ratio in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding the FKBP1A:RyR1 ratio in muscle. The ability of the FKBP1A:RyR1 ratio in muscle to diagnose SAMS.
10. Correlation between the FKBP1A:RyR1 ratio in PBMC vs. muscle. Correlation between the FKBP1A:RyR1 ratio in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding the FKBP1A:RyR1 ratio in blood. The ability of the FKBP1A:RyR1 ratio in blood to diagnose SAMS.
11. Correlation between caspase 3 signaling in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding caspase 3 in muscle. The ability of caspase 3 signaling in muscle to diagnose SAMS.
12. Correlation between caspase 3 signaling in PBMC vs. muscle. Correlation between caspase 3 signaling in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding caspase 3 signaling in blood. The ability of caspase 3 signaling in blood to diagnose SAMS.
13. Difference in muscle response variables between atorvastatin period and non-statin period. Correlation between atorvastatin-related variables and response variables in muscle (i.e. mevalonate pathway intermediates, mitochondrial respiratory enzymes, FKBP1A:RyR1 ratio and caspase 3/pro-caspase 3).
14. Correlation of molecular effects in blood vs. muscle. Difference in blood response variables between atorvastatin period and non-statin period. Correlation between atorvastatin-related variables and response variables in blood (i.e. mevalonate pathway intermediates, mitochondrial respiratory enzymes, FKBP1A:RyR1 ratio and caspase 3/pro-caspase 3).
15. Statin adherence measured with indirect methods and by parent drug and metabolite concentrations in blood
16. New-onset CHD symptoms (e.g. angina, dyspnea). Intolerable muscle symptoms leading to discontinuation from the treatment arm. Creatine kinase (CK) > 10 times upper limit of the normal range or alaninaminotransferase (ALT) > 3 times upper limit of the normal range in blood. Continuous surveillance of serious adverse events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARS).

Exploratory endpoints:

1. Correlation between morphology/histology in muscle and the primary study endpoint. Difference between confirmed SAMS and non-SAMS regarding the morphology/histology in muscle. The ability of morphology/histology in muscle to diagnose SAMS.
2. Correlation between morphology/histology and biomarkers in muscle and blood (atorvastatin and metabolites, mevalonate

	pathway intermediates, mitochondrial respiratory enzymes, gene expression, epigenetics, lipids, metabolites, peptides and proteins). 3. Correlation between candidate biomarkers and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding candidate biomarkers. The ability of candidate biomarkers to diagnose SAMS. 4. Correlation between candidate predisposing factors and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding candidate predisposing factors. The ability of candidate predisposing factors to predict SAMS. 5. Correlation between atorvastatin-related variables and molecular effects in muscle and blood (gene expression, epigenetics, lipids, metabolites, peptides and proteins). 6. Correlation between systemic and local atorvastatin-related variables and exploratory factors (demographics, physiology, concomitant drugs, food, genetics, gene expression, epigenetics, lipids, metabolites, peptides and proteins.
Assessment of primary study end points	The primary study end-points will be measured with aggregated SAMS scores on VAS scales obtained through patient self-report diary at study start, twice weekly during the 7 weeks treatment periods, and at study end. The primary end-point from the MUSE RCT will also be assessed versus biomarkers in the follow-up study.
Assessment of study safety	Study safety data will be collected: - Every 7th days: direct telephone contact with the patient for assessment of intolerable muscle symptoms and symptoms of unstable CHD (i.e. new-onset angina pectoris and/or dyspnea) - Blood samples collected for analyses of ALT and CK at the end of each 7 weeks treatment period or if intolerable muscle symptoms were reported by the patients - Continuous surveillance of serious adverse events (SAEs) obtained through direct weekly telephone contact with the patients and thorugh continuous monitoring of hospital admissions during the study period.
Assessment of secondary end points	The self-report questionnaire and blood samples collected at baseline. The self-report diary, blood samples and muscle biopsies collected at the end of each treatment period.
Study Design:	This is a **prospective, open, intervention study**. A selection of patients classified with confirmed SAMS in the MUSE trial and a selection of patients classified with non-SAMS will receive 7-weeks open-label treatment with atorvastatin 40mg/day in the first period followed by 7-weeks period with no lipid lowering treatment. Both periods will be preceded by a 1-week pharmacokinetic wash-out.
Main Inclusion Criteria:	• Participation in the MUSE trial (Eudract nr. 2018-004261-14) and still fulfilling the study entry criteria listed below (please also refer Appendix J) • First or recurrent diagnosis (myocardial infarction) or treatments (PCI or CABG) for a CHD event 12-42 months prior to study start.
Main Exclusion Criteria	• First or recurrent diagnosis (myocardial infarction) or treatments (PCI or CABG) for a CHD event the a) past 12 months prior to study start in high

risk patients (i.e. at least one of following comorbid conditions: systolic heart failure, >1 previous myocardial infarction, kidney failure, diabetes, and smokers) and b) the past 6 months prior to study start in low risk patients without any of the co-morbid conditions mentioned above and in patients who are not taking a statin at all.

- Patients with symptomatic peripheral artery disease and patients with familial hypercholesterolemia
- Patient has any contraindications for atorvastatin listed in the Summary of Product Characteristics (i.e. known hypersensitivity to the ingredients, acute liver failure/ ALT > 3 times upper limit of the normal range in blood at study start, pregnancy and breastfeeding)
- History of previous rhabdomyolysis, myopathy or liver failure due to statin treatment with CK > 10 times upper limit of the normal range or ALT > 3 times upper limit of the normal range.
- Any condition (e.g. psychiatric illness, dementia) or situation, that in the investigator's opinion could put the subject at significant risk, confound the study results, interfere significantly with the subject participation in the study, or rendering informed consent unfeasible
- Short life expectancy (<12 months) due to other medical conditions
- Not being able to understand Norwegian.
- Women of childbearing potential defined as all premenopausal female.
- Participation in another randomized clinical trial
- Classified with significantly more muscle symptoms on placebo than on atorvastatin in the MUSE trial

Sample Size:	N=30. Patients (n=15) classified with confirmed SAMS in the MUSE trial and patients classified with non-SAMS (n=15) will be included.
Power Calculation	The patients are pre-classified with confirmed SAMS and non-SAMS in the MUSE RCT. The present open follow-up study is performed to reproduce the atorvastatin pharmacodynamics and corresponding presence of muscle symptoms. Pre-classified confirmed SAMS patients not meeting reconfirmation during open atorvastatin treatment will be excluded from data analyses. With respect to the biomarker investigations, we do not have access to data for direct sample size calculations. In the MUSE trial), the 4-OH-atorvastatin acid metabolite demonstrated highest correlation (Spearman rho) with the individual muscle symptom difference between atorvastatin and placebo, although it was not statistically significant. Based on the observed variability in the MUSE data on 4-OH-atorvastatin acid in plasma, obtained from 111 coronary patients on atorvastatin 40 mg, , there is 80% power (P<.05) of detecting a 2.5-fold difference between confirmed SAMS and non-SAMS with n=8+8 patients (mean 0.80 vs. 2.00, SD 0.86). We will include 15 patients with comfirmed SAMS in this follow-up study and a equal group with non-SAMS to account for the uncertainty in the underlying data and potential drop-out during study.
Efficacy Assessments:	Not applicable

Safety Assessments:	Blood samples for analyses of ALT and creatinine kinase will be performed at the end-of each treatment period or if intolerable muscle symptoms are reported by the patients. Participants will be interviewed by phone after a standardized protocol by a specially trained study nurse weekly for the assessment of the other safety endpoints. Due to the relatively low study sample, no safety analysis will be performed.
Type, Dosage and Adherence of statin Treatment	Information will be reported by the patients twice weekly in a diary and by counting pills in returned packages. Statin adherence will also be measured in blood by analyses of statin concentrations by a direct liquid chromatography-tandem mass spectrometry method.
Statistical Analysis	The primary outcome and other continuous outcomes will be estimated with linear regression models. Dichotomous outcomes will be analysed with conditional logistic regression models. Methods for analysis of ROC curves and measures of diagnostic accuracy will be used to identify cut-off values of atorvastatin-related biomarker (i.e. parent drug and metabolites, mevalonate pathway intermediates, mitochondrial respiratory enzymes, FKBP1A:RyR1, caspase 3) levels that can discriminate confirmed SAMS from other muscle symptoms. Differences in variables between groups will be compared with parametric or non-parametric tests, as appropriate according to data distributions. The correlations between variables will be estimated with Spearman correlation coefficients and linear regression analyses. A senior statistician (M Fagerland) at Oslo Centre for Biostatistics and Epidemiology (OCBE) will be responsible for all statistics. A statistical analysis plan (SAP) describing all details in this respect will be produced prior to database lock.
Safety analysis	Due to the low expect number of safety events, no safety analysis are planned, but descriptive data will be presented.
Clinical Endpoint Committee	No end-point commitee will be established for the present study due to the relative small study sample and since the primary and secondary outcomes are based on self-reported data and blood samples.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
CHD	Coronary Heart Disease
CV	Cardiovascular
eCRF	Electronic Case Record Form
IMP	Investigational medicinal product
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL-C	Low Density Lipoprotein Cholesterol
RCT	Randomized Controlled Trial
PROMS	Patient-reported outcome measures (on sociodemographic, clinical and psychosocial factors)
SAMS	Statin Associated Muscle Symptoms
VAS	Visual Analoge Scale

1 INTRODUCTION

1.1 Background

Statins are cornerstone treatment in secondary cardiovascular (CVD) and cerebrovascular disease prevention. In the Norwegian landmark 4S statin trial, statins reduced the risk of all-cause mortality and cardiac death by 30% and 42%, respectively, in coronary heart disease (CHD) patients.[1] Today, statin non-adherence (i.e. patients not taking their prescribed drugs) remains a major public health concern in CVD patients, leading to adverse outcomes in terms of morbidity, mortality and healthcare costs.[2-4] The principal reason for statin non-adherence and discontinuation is statin-associated muscle symptoms (SAMS).[5] In clinical practice, SAMS are challenging to evaluate in patients reporting muscle symptoms as objective diagnostic tools do not exist. The development of diagnostic biomarkers for statin-associated side effects is thus a major need to improve the lipid management and clinical outcomes, as pointed out in the most recent Cochrane review,[3] European guidelines[2] and European consensus statements.[5] The present project aims to address these needs by providing new knowledge and diagnostic biomarkers for SAMS in CHD patients, using novel, highly sensitive biochemical methods. The project has considerable user-involvement, and our strong and interdisciplinary research group has recently developed and validated accurate measurement methods for statins and metabolites.[6] We have recently completed a double-blinded, placebo-controlled, crossover, randomized clinical trial (RCT), MUscle Side-Effects of atorvastatin in coronary patients (MUSE), to identify CHD patients with confirmed SAMS and non-SAMS among those with self-perceived SAMS.[7] A subsample from this RCT will be continued into the present biomarker study where muscle symptoms are registered and skeletal muscle biopsies and blood samples are collected. Clinical data and biological material from both studies will be used in the proposed project. No previous studies have investigated the relevance of drug metabolites and biochemical intermediates directly in skeletal muscle from patients with confirmed SAMS. The results will provide clinically relevant knowledge of mechanistic factors underlying SAMS. We aim to identify diagnostic biomarkers that can be used in clinical practice to differentiate true SAMS from non-SAMS in CHD patients with self-perceived SAMS, thus enabling personalized treatment and follow-up. The long-term results may be better quality of life, improved lipid management, and reduced morbidity, mortality and healthcare costs.

Statin treatment and challenges in clinical practice

The beneficial effect of statins on cardiovascular (CV) outcomes is mainly mediated through reduction of the blood levels of the "harmful" low-density lipoprotein cholesterol (LDL-C).[2,8] However, efforts to improve the statin treatment are obviously needed. International[10] and own data from the Norwegian Coronary Prevention (NOR-COR) Study[11] have revealed that 7-12% of the CHD patients did not use statin therapy, and 57-80% on statin therapy still had unfavorably elevated LDL-C. Moreover, 40% had subclinical inflammation.[12] Why is lipid management with statins suboptimal or failing in that many patients, and how do we achieve the benefits of statins documented in the randomized landmark statin trials like 4S in today's clinical practice? We recently found that low self-reported statin adherence and self-perceived statin muscle symptoms were the major factors associated with elevated LDL-C,[11] and inflammation[12] after a coronary event. The in-depth interviews with the patients' primary physicians also revealed insufficient knowledge about how to deal with muscle symptoms assumed to be statin-related.[13] Therefore, we developed and validated a sensitive liquid chromatography mass spectrometry (LC-MS/MS) method for quantification of atorvastatin and its major metabolites in clinical samples.[6] With this gold-standard technology, we are able to study the *in vivo* atorvastatin exposure in relation to muscle symptoms and adherence.

Statin associated muscle symptoms –prevalence and clinical implications

Serious statin side-effects, including liver failure, rhabdomyolysis, or myositis with elevated creatine kinase (CK) levels in blood, are very rare.[14] In contrast, SAMS is a prevalent challenge in clinical practice,[5] amounting to 70% of all statin adverse events.[15] Registries and observational studies indicate that the real-life prevalence of SAMS ranges from 7% to 29%.[5] SAMS comprise a heterogeneous group of muscle symptoms including pain/aching, stiffness, tenderness or cramps, usually with normal or minimally elevated CK levels.[5] Importantly, there is a link between SAMS and statin non-adherence/discontinuation. A large US survey demonstrated that 60% of those who had discontinued the statin therapy claimed to have SAMS.[16] In line

with this, the European Atherosclerosis Society Consensus Panel stated that **"SAMS is one of the principal reasons for statin non-adherence and/or discontinuation, contributing to adverse cardiovascular outcomes"**.[5] The mortality is higher (24% vs. 16%) in CVD patients with low adherence to statin therapy[5] and 'not taking statins' was the strongest predictor for recurrent CV events in our 4-year follow-up of the NOR-COR population.[17] A major limitation of observational studies of SAMS is the absence of blinding. Patients on statins may expect side-effects, and therefore report a higher percentage than in a comparable population not on statins, the so-called 'nocebo' effect. Only one previous study, in subjects without CVD, has tested whether self-reported SAMS was actually related to the statin therapy; In a randomized, double-blinded crossover study that included patients complaining of SAMS, 36% experienced that their muscle symptoms persisted during treatment with simvastatin 20 mg and disappeared during placebo treatment.[18] In our ongoing RCT, we expect at least a similar proportion to be classified with confirmed SAMS, since a more potent statin (atorvastatin 40 mg) is used in an elderly CHD population.

Statin-associated muscle symptoms –pathophysiology and mechanistic basis

The clinical presentation of SAMS usually occurs within one month of initiation of statin therapy or dose increase.[15] The muscle symptoms can occur at rest or shortly after exercise, and they usually appear symmetrically in the lower extremities.[15] Some of the reported risk factors for SAMS include: Using a lipophilic statin (simvastatin, atorvastatin) at high dose, high age, female sex, low body mass index, comorbidities, history of CK elevations, history of muscle/joint pain, drug-drug interactions, drug transporter genetics, and excess alcohol consumption.[5] **It remains unclear how statins produce muscle symptoms, and reliable biomarkers for the prediction or diagnosis of true SAMS are lacking.** The suggested mechanisms are mainly deduced from *in vitro* studies, and to some degree supported with biomarkers in clinical studies. However, the clinical studies have major limitations (e.g. non-blinded, non-randomized, few cases).

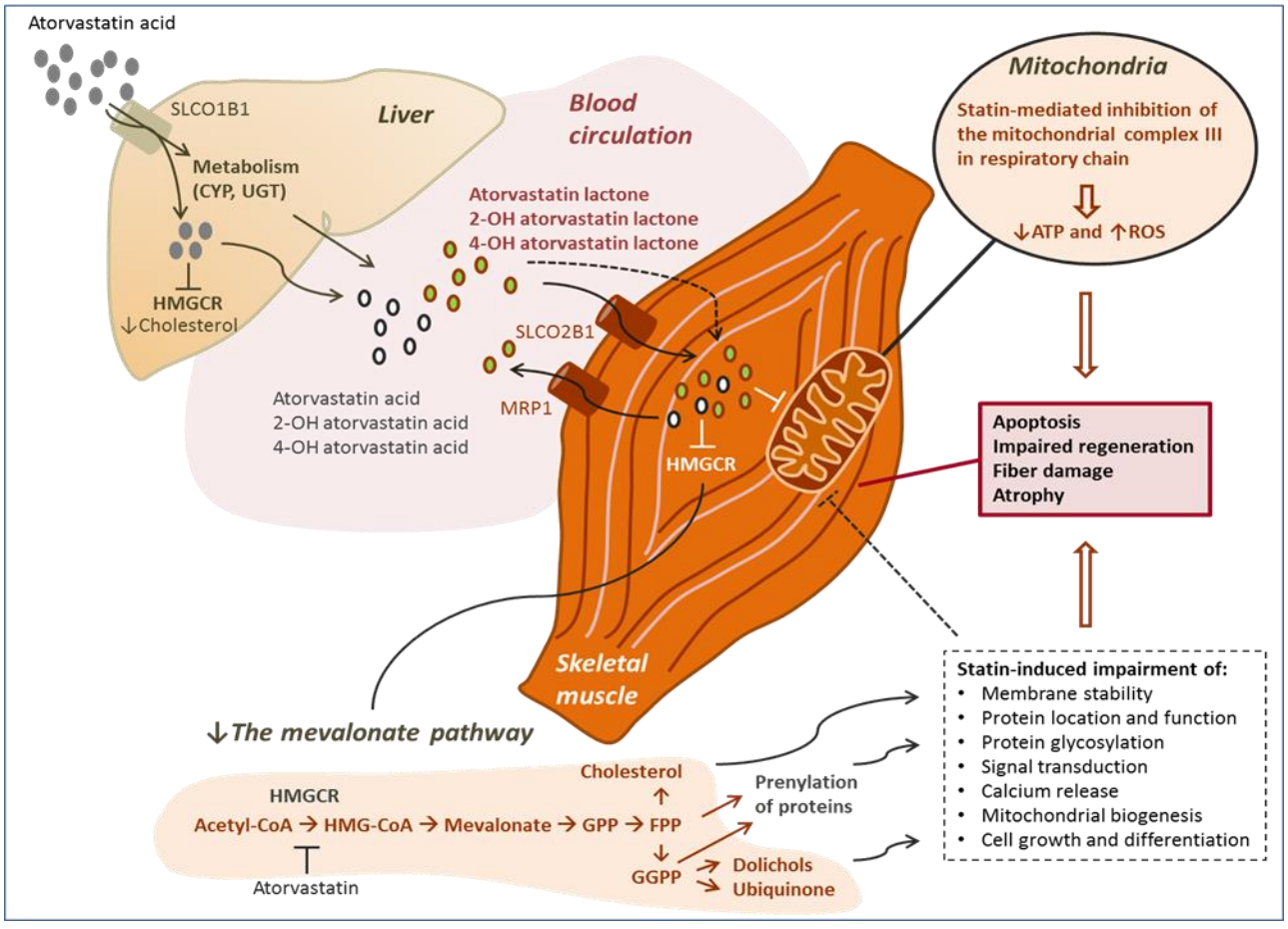


Figure 1 (previous page). Hypothetical mechanisms for the development of statin-associated muscle symptoms. Atorvastatin is taken up in the liver via the transporter SLCO1B1 and inhibits HMG-coenzyme A reductase (HMGCR), thereby mediating its systemic cholesterol-lowering effect. The drug is extensively metabolized in liver to both acid and lactone metabolites which enter the blood circulation. Suggested distribution to skeletal muscle: The parent drug and metabolites are distributed to skeletal muscle via the

SLCO2B1 transporter and by passive diffusion. The efflux transporter MRP1 pumps the drug and metabolites back to the blood. Suggested effects in skeletal muscle: HMGCR in skeletal muscle is inhibited, causing decreased synthesis of intermediates in the mevalonate pathway. A range of cellular functions are impaired due to the HMGCR inhibition, especially due to reduced prenylation of proteins (i.e. prenylation through farnsyl pyrophosphate [FPP] and geranylgeranyl pyrophosphate [GGPP]). The lactone metabolites are direct inhibitors of the mitochondrial complex III, causing reduced ATP production and increased levels of reactive oxygen species (ROS). The molecular effects lead to apoptosis and fiber damage in the skeletal muscle.

Based on the literature, we point out three direct drug-related characteristics in skeletal muscle which appear as substantiated factors underlying SAMS (i.e. local statin exposure, inhibition of the mevalonate pathway, and inhibition of the mitochondrial function) However, their clinical impact on the development of SAMS is not known. The three factors are elaborated below, and an overview is given in **Figure 1** on the previous page.

Local statin exposure in skeletal muscle: The risk of experiencing SAMS is associated with high statin doses.[19] A genetic variant in the hepatic uptake transporter SLCO1B1 and concomitant use of drugs that inhibit the liver enzyme CYP3A4 are both factors that increase the statin levels in blood and the risk of SAMS,[19] thus supporting a relationship between SAMS and high systemic statin exposure. The statin lactone metabolites demonstrate superior ability to induce myotoxic effects *in vitro*,[20,21] and an elevated atorvastatin lactone:acid ratio in blood plasma has been associated with probable SAMS in a clinical non-blinded study.[22] Even if there is an association between high systemic statin exposure and SAMS, it is not likely that statin blood concentrations entirely predict the adverse events. The drug metabolites have to distribute into skeletal muscle cells to produce the toxic effects. Interestingly, proteins that transport atorvastatin in and out of cells (SLCO2B1 and the multidrug-resistance associated protein 1 [MRP1], respectively) are expressed in human skeletal muscle.[23] A human *in vitro* model of skeletal muscle cells also demonstrated that the atorvastatin-induced toxicity was promoted in relation to the expression level of *SLCO2B1* and prevented with co-expression of *MRP1*.[23] Therefore, it is hypothesized that the *in vivo* activity of SLCO2B1 and MRP1 in skeletal muscle modulate the risk of developing SAMS, though with dependency on the systemic statin exposure (**Figure 1**).The *SLCO2B1* gene variant rs12422149 (c.935G>**A)** causes impaired protein function.[38] In a non-blinded case-control clinical study, the *SLC02B1* genotype status was significantly associated with SAMS.[24] Interestingly, the atorvastatin transport protein MRP1 is also expressed in peripheral blood mononuclear cells (PBMC).[25] Thus, the atorvastatin levels in PBMC may potentially reflect the atorvastatin exposure in skeletal muscle. Indeed, we have pilot data indicating that the toxic atorvastatin lactone metabolites are accumulated in PBMC to a 3-fold higher level than the acid metabolites. In the present project, **we will be the first to investigate the relationship between *in vivo* atorvastatin metabolite levels in skeletal muscle, blood and confirmed SAMS**. Furthermore, we will investigate whether the non-invasive principle of genotyping *SLC02B1* in combination with measurement of atorvastatin metabolites in blood plasma can be used to predict the local drug exposure in muscle tissue.

Inhibiton of the mevalonate pathway in skeletal muscle: The enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) is expressed in all tissues in the body[26] and catalyzes the conversion of HMG-coenzyme A to mevalonate as the rate-limiting step in the mevalonate pathway (**Figure 1**). The down-stream biochemical intermediates play important roles in gene expression, post-translational modification of proteins, cell signaling, cytoskeletal assembly, endocytotic/exocytotic transport, membrane fluidity, cell differentiation and proliferation.[27] Not surprisingly, inhibition of HMGCR results in a range of biochemical and cellular effects in diverse tissue. Inhibition of HMGCR in the liver is the primary mechanism of action of the statins, responsible for the systemic effect on LDL-C.[28]

The most plausible mechanism of SAMS arises from local inhibition of HMGCR in muscle tissue at high statin exposure, resulting in a wide range of biochemical consequences and subsequent toxic effects.[15,28] The heterogeneous clinical presentations of SAMS may be attributable to the highly diverse molecular and cellular effects caused by inhibition of HMGCR (**Figure 1**). Several *in vitro* studies indirectly suggest that reduced levels of mevalonate pathway intermediates are linked to the myotoxic statin effects, since the statin-induced myotoxicity *in vitro* is prevented when muscle cells simultaneously are supplemented with excess mevalonate, farnesyl pyrophosphate (farnesyl-PP) or geranylgeranyl pyrophosphate (geranylgeranyl-PP).[28-32] Farnesyl-PP and geranylgeranyl-PP are present in very low concentrations naturally, thus *in vivo* quantifications have been challenging. In the present project we will apply recently published mass spectrometry methods which are capable of the sensitive quantification of the *in vivo* levels of mevalonate, farnesyl-PP and geranylgeranyl-PP.[33,34] Hereby, **we will be the first to investigate the relevance of these**

biochemical intermediates directly in skeletal muscle from patients with confirmed SAMS. In parallel, we will explore the potential of measuring these biochemical intermediates in blood, in order to develop non-invasive diagnostic biomarkers of SAMS.

Inhibition of mitochondrial function in skeletal muscle: Decreased mitochondrial respiration in muscle cells has been demonstrated during exposure to lipophilic statins in several *in vitro* studies, and also reported in some pre-clinical and *in vivo* studies.[15,28] Furthermore, it has been reported that statins increase the production of mitochondrial reactive oxygen species (ROS) with subsequent initiation of apoptotic cascades in skeletal muscle *in vitro*.[28] It was recently revealed that the mitochondrial complex III in the respiratory chain is a direct inhibitory target of statin lactones, and its enzymatic activity was decreased in muscle biopsies from patients with probable SAMS.[20] Although there are limitations to these data, it is worth noting that inhibition of complex III is mechanistically related to increased ROS production with toxic cellular consequences.[28] **We will be the first to investigate the relevance of the mitochondrial respiratory enzymes directly in skeletal muscle and blood cells from patients with confirmed SAMS**.

Modulation of the sarcoplasmic reticulum calcium release channel, ryanodine receptor 1 (RyR1): It has been demonstrated that statins cause dissociation of the stabilizing protein FK506 binding protein (FKBP12, synonymous with FKBP1A) from RyR1 in the sarcoplasmic reticulum in skeletal muscle. The statin-mediated modulation of the calcium release channel lead to spontaneous calcium sparks, and the calcium leak was associated with reactive nitrogen/oxygen species and pro-apoptotic signaling through caspase 3.[44] In this study, we will perform quantitative measurements of the FKBP1A to RyR1 ratio in their protein complex, and the caspase 3 to pro-caspase 3 ratio be investigated as an apoptotic marker. **We will be the first to investigate the relevance of the FKBP1A:RyR1 complex directly in skeletal muscle and blood cells from patients with confirmed SAMS.**

Some muscle conditions related to statins demonstrate morphological alterations. In self-limited toxic statin myopathy with CK elevations, necrosis and regenerating muscle fibers may be observed in muscle biopsies. In immune-mediated necrotizing myopathy with anti-HMGCR antibodies, muscle biopsies usually show necrosis with regeneration of muscle fibers and scarce inflammation.[45] The pattern of potential morphological and histological alterations in patients with confirmed SAMS (without CK elevations) are yet to be described. In the present study, we will explore the muscle pathology in SAMS patients by using morphological and histochemical techniques. Furthermore, the relationship with the exposure to atorvastatin and its metabolites, and with statin-mediated molecular effects, will be explored.

Our ambition is to develop diagnostic tests, preferentially non-invasive, that can be used to identify patients with true SAMS among patients with self-perceived SAMS. Our strategy is primarily to examine biomarkers that are correlated to the direct effects of statins in muscle tissue. We will be the first to examine these biomarkers in relation to confirmed SAMS, and indeed in a relevant high-risk CHD population. The utmost strength will be that SAMS is confirmed in two subsequent double-blinded, placebo-controlled, crossover RCTs.

The overall objective is to provide new pathophysiologic knowledge of SAMS and develop an accurate diagnostic test that can be used in clinical practice to differentiate confirmed (i.e. real) SAMS and non-SAMS (i.e. muscle symptoms not related to the statin treatment) among CHD patients with self-perceived SAMS, thereby allowing efficient diagnostics and actions to prevent future cardiovascular events.

1.2 Study rationale and implications for patients, healthcare providers and the society

Our current knowledge of the mechanistic basis for SAMS is based on *in vitro* experiments and limited observational clinical studies. This is the first direct *in vivo* study designed to determine molecular factors of SAMS in a population that is confirmed to suffer from SAMS versus a population confirmed to be without SAMS, thus providing clinically relevant knowledge. In today's clinical practice, no objective diagnostic test for SAMS exist[15] and the assessment of SAMS in the individual patient is time-consuming and prone to bias as it involves intermittent statin discontinuation and re-challenge accompanied with subjective, non-blinded

assessments. An objective diagnostic test that can be used to identify patients with true SAMS among those with perceived SAMS, will be efficient both to the patient and health care system, and it will help healthcare providers to identify patients in need of altered cholesterol-lowering therapy due to intolerable side-effects. A recent study documented that negative statin-related stories in media led to statin discontinuation and subsequently increased CVD risk.[35] Biomarkers may represent an important tool in the communication with these patients misattributing their muscle symptoms to statins. In turn, such a tool may prevent statin discontinuation, facilitate change of drug when indicated, and improve adherence. The benefit for the patients is primarily less muscle side-effects, improved statin adherence and LDL-C control and thereby prevention of CVD with reduced mortality and morbidity. Diagnostic testing based on a minimally invasive biopsy may be justified in patients with high CV risk and with complicated self-perception of symptoms. However, we will attempt to develop a non-invasive test which will be preferable in the general CHD population. Fewer re-hospitalizations for CV events and lower healthcare costs are societal long-term benefits of optimized statin treatment and high adherence.[36] Also, the study results may be transferable to primary prevention populations. In 2018, there were 560 000 Norwegian statin users (59% on atorvastatin) with a cost of NOK 277 million.[37] Sufficient doses and adequate adherence are thus of major importance. New, expensive drugs to lower lipids increases the relevance of this study. Costs of novel lipid-lowering drugs (PCSK9 inhibitors) are substantially higher than statins; 64 500 NOK per patient/year versus 1 860 NOK (statins) or 6 600 NOK (statins combined with ezetimib). Therefore, the project may be of importance for the healthcare system, by optimizing treatment with cost-effective statins.[4] Furthermore, a reliable diagnostic test for SAMS may facilitate the development of innovative treatments/drugs that are suitable for statin-intolerant patients.

Risk/Benefit

A potential risk in the present study is the risk of adverse cardiovascular events during the 8 week period without statin treatment and the risk of serious side-effects (e.g. acute liver failure, rhabdomyolysis, myopathy) during treatment with atorvastatin. The investigating medical product (atorvastatin) has a strong scientific documentation (level 1A evidence) for CHD patients and a well-documented safety profile. Dispite this, statin therapy is frequently discontinued for a longer period or permanently in the high-risk CHD sub-population with muscle symptoms that will be included in the present study. To our best knowledge, only two previous randomized studies that have investigated the risk associated with a short time statin withdrawl. Heeschen and colleagues[40] reported a 3-fold increase in the risk of death and nonfatal MI when statins therapy was withdrawn after an admission for an acute coronary syndrome. The same group subsequently reassessed their analysis and found only a trend toward greater cardiac risk with abrupt statin discontinuation[41]. In contrast, a large randomized study including more than 15 000 stable CHD patients, 6 weeks statin discontinuation did not lead to increased risk of subsequent cardiovascular events and mortality[42]. Swedish nationwide real world data in post-myocardial infarction patients have documented that the risk of subsequent cardiovascular events are highest during the first 12 months following the index event[43]. They also demonstrated that patients with diabetes, previous myocardial infarction, no index myocardial infarction revascularisation, periferial artery disease, systolic heart failure and and kidney failure were at highest risk of subsequent events.

Since our study population comprises patients who presently are not taking statins at all due to muscle symptoms or who report muscle symptoms that put them at significantly increased risk of statin discontinuation and thus subsequent cardiovascular events compared to a general CHD population, (6, 7) it is crucial to gain new clinical and pathophysiologic knowledge about SAMS in these patients. A short-term discontinuation of statin therapy of maximum 8 weeks (i.e. 1-week wash-out plus seven weeks during the non statin treatment period) required for the implementation of the study is regarded safe and sound in patients fulfilling the strict study entry criteria (*See Section 4.3 and 4.4.*). To minimize the risk of study participation, atorvastatin will be discontinued after the patients have been in a stable phase (without symptoms of angina/dyspnea) for at least 12 months following the index event in high risk patients (i.e. patients with at least one of following comorbid conditions: systolic heart failure, kidney failure, diabetes, , and smokers), whereas low risk patients without any of these co-morbid conditions and patients who are not taking a statin at all may be included 6 months after the coronary index event. To further reduce the risk of

study participation, patients with familial hypercholesterolemia, symptomatic perpherial artery disease and/or patients with untreated significant stenoses on the main left coronary artery will be excluded from the study.

Patients who have previously experienced rhabdomyolysis or myopathy will also be excluded from the study, based on information from their hospital medical records. Patients with blood levels of ALT exceeding >3 times upper limit of the normal range or creatinine kinase > 10 times upper limit of the normal range at study start or at the end of each 7-weeks treatment period will be withdrawn (*Table 2*). If new-onset CHD symptoms (i.e. angina pectoris and/or dyspnea) were revealed through the telephone interview or at the study visits, patients will be examined by the study cardiologists at the hospital outpatient clinics within two days. In addition, all Serious Adverse Events (SAEs) will be continuously monitored by the study cardiologists. The sponsors medical officer will review all SAEs and evaluate whether the event is expected according to the reference safety information (RSI). The Summary of Product Characteristics will be used as RSI in this trial. All SUSARs will be reported to the Norwegian Medical Agency within 7/15 days by the medical officer.

One patient died, most likely due to a primary arrhythmia, and 2 patients were hospitalized with suspected unstable coronary syndrome in the MUSE RCT in 2019. Importantly, emergency un-blinding revealed that all these patients all received atorvastatin therapy at the time of the adverse event. Three other patients developed chest pain or new-onset dyspnea during the trial. These patients were evaluated by the study cardiologists and allowed to continue. One patient was un-blinded due to a significant elevation of alanine aminotransferase (>10 x upper normal limit) at the end of the atorvastatin treatment period, which resolved rapidly when atorvastatin was discontinued.

1 out of ten people are treated with a statin in Norway and in Europe. Our unpublished data from the MUSE trial revealed that 10% of these patients report SAMS during statin treatment (Kristiansen et al, under review in Ciculation). Thus, the greatest benefit from the present follow-up study will be to provide new pathophysiologic knowledge of SAMS and develop an accurate diagnostic test that can be used in clinical practice to differentiate confirmed (i.e. real) SAMS and non-SAMS (i.e. muscle symptoms not related to the statin treatment) among CHD patients with self-perceived SAMS, thereby allowing efficient diagnostics and actions to prevent future cardiovascular events

1.3 Study Hypotheses

The overall hypothesis is that it is possible to develop an accurate diagnostic test that can be used in clinical practice to differentiate confirmed SAMS and non-SAMS (i.e. muscle symptoms not related to the statin treatment) among coronary heart disease patients with self-perceived SAMS, thereby allowing efficient diagnostics and actions to prevent future cardiovascular events.

Secondary hypotheses:

- The concentration of atorvastatin and/or its metabolites in muscle is significantly higher in patients with confirmed SAMS compared to those with non-SAMS. A concentration cut-off in muscle can discriminate these two groups with diagnostic sensitivity and specificity above 80%. Secondary hypothesis: Atorvastatin and/or its metabolites concentrations in blood plasma, combined with a genotype-dependent muscle/plasma distribution ratio, can be used to estimate the exposure in muscle. There is a positive correlation between atorvastatin and/or its metabolite levels in peripheral blood mononuclear cells (PBMC) and muscle. The blood-based biomarkers can discriminate confirmed SAMS and non-SAMS with sensitivity and specificity above 80%.

- The concentration of mevalonate pathway intermediates in muscle is more decreased in patients with confirmed SAMS compared to those with non-SAMS. A mevalonate pathway biomarker cut-off in muscle can discriminate confirmed SAMS and non-SAMS with diagnostic sensitivity and specificity above 80%. Secondary hypothesis: There is a positive correlation between mevalonate pathway biomarkers in PBMC vs. muscle, and

in blood plasma vs. muscle. The blood-based biomarkers can discriminate confirmed SAMS and non-SAMS with sensitivity and specificity above 80%.

- The functional activity and/or expression of mitochondrial respiratory enzymes in muscle is lower in patients with confirmed SAMS compared to those with non-SAMS. A mitochondrial enzyme cut-off in muscle can discriminate confirmed SAMS and non-SAMS with diagnostic sensitivity and specificity above 80%. Secondary hypothesis: There is a positive correlation between mitochondrial enzyme biomarkers in PBMC and muscle. The blood-based biomarkers can discriminate confirmed SAMS and non-SAMS with sensitivity and specificity above 80%.

- The ratio between FKBP1A and RyR1 within their protein complex in muscle is lower in patients with confirmed SAMS compared to those with non-SAMS. A FKBP1A:RyR1 cut-off in muscle can discriminate confirmed SAMS and non-SAMS with diagnostic sensitivity and specificity above 80%. Secondary hypothesis: There is a positive correlation between FKBP1A:RyR1 in PBMC and muscle. The blood-based biomarker can discriminate confirmed SAMS and non-SAMS with sensitivity and specificity above 80%.The caspase 3 level (or caspase 3 to pro-caspase 3 ratio) in muscle is lower in patients with confirmed SAMS compared to those with non-SAMS. A caspase 3-related cut-off in muscle can discriminate confirmed SAMS and non-SAMS with diagnostic sensitivity and specificity above 80%. Secondary hypothesis: There is a positive correlation between caspase 3 (or caspase 3 to pro-caspase 3 ratio) in PBMC and muscle. The blood-based biomarker can discriminate confirmed SAMS and non-SAMS with sensitivity and specificity above 80%.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

	Objectives	Endpoints	Assessments
Primary	To determine the effect of open treatment with atorvastatin 40 mg/day on muscle symptom intensity in patients classified with confirmed SAMS and non-SAMS.	The individual mean difference in muscular symptom intensity between treatment periods with statin and no lipid lowering treatment, reported by the patients over the last three weeks of each treatment period.	Obtained through patient self-report measured with aggregated scores on a VAS scale administred at study start, weekly during the treatment periods and at study end .
Secondary	To determine the relationship between SAMS and parent drug and the active metabolites in skeletal muscle, and to evaluate the metabolite concentrations in muscle as a diagnostic tool for confirmed SAMS.	Correlation between atorvastatin-related variables in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin-related variables in muscle. The ability of atorvastatin-related variables in muscle to diagnose SAMS.	Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites in muscle biopsies.
	To determine the relationship between SAMS and parent drug and the active metabolites in blood, and to evaluate the metabolite concentrations in blood as a diagnostic tool for confirmed SAMS.	Correlation between atorvastatin-related variables in plasma vs. muscle and PBMC vs. muscle. Correlation between atorvastatin-related variables in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin-related variables in blood. The ability of atorvastatin-related variables in blood to diagnose SAMS. The atorvastatin-related variables in blood	Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites in blood plasma and PBMC. Genotyping of the *SLCO2B1* gene variant rs12422149 (c.935 G>A)..

	Objectives	Endpoints	Assessments
		will additionaly by adjusted for *SLC2B1* genetics.	
	To determine the relationship between SAMS and the atorvastatin to HMGCR ratio in skeletal muscle, and to evaluate the ratio in muscle as a diagnostic tool for confirmed SAMS	Correlation between atorvastatin: HMGCR in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin:HMGCR in muscle. The ability of atorvastatin:HMGCR in muscle to diagnose SAMS.	Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites, and by measurement of HMGCR, in muscle biopsies. .
	To determine the relationship between SAMS and the atorvastatin to HMGCR ratio in blood, and to evaluate the ratio in blood as a diagnostic tool for confirmed SAMS.	Correlation between atorvastatin:HMGCR in PBMC vs. muscle. Correlation between atorvastatin:HMGCR in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding atorvastatin:HMGCR in blood. The ability of atorvastatin:HMGCR in blood to diagnose SAMS.	Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites, and by measurement of HMGCR, in PBMC..
	To determine the relationship between SAMS and inhibition of the mevalonate pathway in skeletal muscle, and to evaluate the concentration of mevalonate pathway intermediates in muscle as a diagnostic tool for confirmed SAMS.	Correlation between mevalonate pathway intermediates in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mevalonate pathway intermediates in muscle. The ability of mevalonate pathway intermediates in muscle to diagnose SAMS.	Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of mevalonate, farnesyl-PP and geranylgeranyl-PP in muscle biopsies.

	Objectives	Endpoints	Assessments
	To determine the relationship between SAMS and inhibition of the mevalonate pathway in blood, and to evaluate the concentration of mevalonate pathway intermediates in blood as a diagnostic tool for confirmed SAMS.	Correlation between mevalonate pathway intermediates in plasma vs. muscle and PBMC vs. muscle. Correlation between mevalonate pathway intermediates in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mevalonate pathway intermediates in blood. The ability of mevalonate pathway intermediates in blood to diagnose SAMS.	Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of mevalonate, farnesyl-PP and geranylgeranyl-PP in blood plasma and PBMC.
	To determine the relationship between SAMS and inhibition of mitochondrial function in skeletal muscle, and to evaluate the use of mitochondrial respiratory enzymes in muscle as a diagnostic tool for confirmed SAMS.	Correlation between mitochondrial respiratory enzymes in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mitochondrial respiratory enzymes in muscle. The ability of mitochondrial respiratory enzymes in muscle to diagnose SAMS.	Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantification of mitochondrial respiratory enzymes (expression and activity) in muscle biopsies.
	To determine the relationship between SAMS and inhibition of mitochondrial function in blood, and to evaluate the use of mitochondrial respiratory enzymes in blood as a diagnostic tool for confirmed SAMS.	Correlation between mitochondrial respiratory enzymes in PBMC vs. muscle. Correlation between mitochondrial respiratory enzymes in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding mitochondrial respiratory enzymes in blood. The ability of mitochondrial respiratory enzymes in blood to diagnose SAMS.	Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantification of mitochondrial respiratory enzymes (expression and activity) in PBMC.

	Objectives	Endpoints	Assessments
	To determine the relationship between SAMS and the calcium-regulating FKBP1A:RyR1 complex in skeletal muscle, and to evaluate the use of the FKBP1A:RyR1 complex in muscle as a diagnostic tool for confirmed SAMS.	Correlation between the FKBP1A:RyR1 ratio in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding the FKBP1A:RyR1 ratio in muscle. The ability of the FKBP1A:RyR1 ratio in muscle to diagnose SAMS.	Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Immunoprecipitation of the sarcoplasmatic reticulum RyR1 in muscle biopsies and quantification of FKBP1A (FKBP12) and RyR1 in their protein complex.
	To determine the relationship between SAMS and the calcium-regulating FKBP1A:RyR1 complex in blood, and to evaluate the use of the FKBP1A:RyR1 complex in blood as a diagnostic tool for confirmed SAMS.	Correlation between the FKBP1A:RyR1 ratio in PBMC vs. muscle. Correlation between the FKBP1A:RyR1 ratio in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding the FKBP1A:RyR1 ratio in blood. The ability of the FKBP1A:RyR1 ratio in blood to diagnose SAMS.	Obtained by collection of blood samples in the end of the atorvastatin treatment period. Immunoprecipitation of the sarcoplasmatic reticulum RyR1 in PBMC and quantification of FKBP1A (FKBP12) and RyR1 in their protein complex.
	To determine the relationship between SAMS and caspase 3 signaling in skeletal muscle, and to evaluate the use of caspase 3 signaling in muscle as a diagnostic tool for confirmed SAMS.	Correlation between caspase 3 signaling in muscle and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding caspase 3 in muscle. The ability of caspase 3 signaling in muscle to diagnose SAMS.	Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantification of caspase 3 and pro-caspase 3 in muscle biopsies, and calculation of the ratio between caspase 3 (active) and pro-caspase 3 (inactive).
	To determine the relationship between SAMS and caspase 3 signaling in blood, and to evaluate the use of the caspase 3 signaling in blood as a diagnostic tool for confirmed SAMS.	Correlation between caspase 3 signaling in PBMC vs. muscle. Correlation between caspase 3 signaling in blood and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding caspase 3 signaling in blood. The ability of caspase 3 signaling in blood to diagnose SAMS.	Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantification of caspase 3 and pro-caspase 3 in PBMC, and calculation of the ratio between caspase 3 (active) and pro-caspase 3 (inactive).

	Objectives	Endpoints	Assessments
	To determine the relationship between atorvastatin exposure and molecular effects in muscle (inhibition of the mevalonate pathway, mitochondrial function, FKBP1A:RyR1 complexation and caspase 3 signaling).	Difference in muscle response variables between atorvastatin period and non-statin period. Correlation between atorvastatin-related variables and response variables in muscle (i.e. mevalonate pathway intermediates, mitochondrial respiratory enzymes, FKBP1A:RyR1 ratio and caspase 3/pro-caspase 3).	Obtained by collection of muscle biopsies on and off atorvastatin. Quantitative LC-MS/MS analyses of atorvastatin and its hydroxy and lactone metabolites, as well as mevalonate, farnesyl-PP and geranylgeranyl-PP. Quantification of mitochondrial respiratory enzymes (expression and activity), the FKBP1A:RyR1 ratio in their sarcoplasmatic reticulum protein complex, caspase 3, and the ratio between caspase 3 and pro-caspase 3.
	To determine the relationship between atorvastatin exposure and molecular effects in blood (inhibition of the mevalonate pathway, mitochondrial function, FKBP1A:RyR1 complexation and caspase 3 signaling)	Correlation of molecular effects in blood vs. muscle. Difference in blood response variables between atorvastatin period and non-statin period. Correlation between atorvastatin-related variables and response variables in blood (i.e. mevalonate pathway intermediates, mitochondrial respiratory enzymes, FKBP1A:RyR1 ratio and caspase 3/pro-caspase 3).	Obtained by collection of blood samples on and off atorvastatin. Quantitative LC-MS/MS analyses of atorvastatin and its hydroxy and lactone metabolites, as well as mevalonate, farnesyl-PP and geranylgeranyl-PP. Quantification of mitochondrial respiratory enzymes (expression and activity), the FKBP1A:RyR1 ratio in their sarcoplasmatic reticulum protein complex, caspase 3, and the ratio between caspase 3 and pro-caspase 3.
	To study statin adherence between the two study arms.	Statin adherence measured with indirect methods and by parent drug and metabolite concentrations in blood	Obtained through pill counts of returned packages, and from analyses of atortastatin level in blood determined by liquid chromatography-tandem mass spectrometry method at the end of the atorvastatin treatment period
	To describe study safety	-New-onset CHD symptoms (e.g. angina, dyspnea) - Intolerable muscle symptoms leading to discontinuation from the treatment arm	- Obtained every 7th days through direct telephone contact with the patient - Obtained every 7th days through direct telephone contact with the patient. - Obtained thorugh blood samples collected at the end of each 7 weeks treatment period or if

	Objectives	Endpoints	Assessments
		- Creatine kinase (CK) > 10 times upper limit of the normal range or alaninaminotransferase (ALT) > 3 times upper limit of the normal range in blood - Continuous surveillance of serious adverse events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARS)	intolerable muscle symptoms were reported by the patients - Obtained through direct telephone contact with the patient and through monitoring of hospital admissions throughout the study period
Exploratory	To describe the relationship between SAMS and morphology/histology in skeletal muscle, and to explore the morphological/histological findings in muscle as a diagnostic tool for confirmed SAMS.	Correlation between morphology/histology in muscle and the primary study endpoint. Difference between confirmed SAMS and non-SAMS regarding the morphology/histology in muscle. The ability of morphology/histology in muscle to diagnose SAMS.	Obtained by collection of muscle biopsies in the end of the atorvastatin and non-statin treatment periods. Assessment of morphology and histology by pathologist.
	To describe the relationship between morphology/histology in skeletal muscle and atorvastatin-related variables, and molecular effects, in muscle and blood (.	Correlation between morphology/histology and biomarkers in muscle and blood (atorvastatin and metabolites, mevalonate pathway intermediates, mitochondrial respiratory enzymes, gene expression, epigenetics, lipids, metabolites, peptides and proteins).	Obtained by collection of muscle biopsies in the end of the atorvastatin and non-statin treatment periods. Assessment of morphology and histology by pathologist. Molecular analyses with appropriate methods.
	To identify candidate diagnostic biomarkers for confirmed SAMS in muscle tissue and blood (by explorative analyses of gene expression, epigenetics, lipids, metabolites, peptides and proteins)	Correlation between candidate biomarkers and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding candidate biomarkers. The ability of candidate biomarkers to diagnose SAMS.	Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.

	Objectives	Endpoints	Assessments
	To identify candidate predisposing factors for confirmed SAMS (by explorative analyses of demographics, physiology, concomitant drugs, genetics, gene expression, epigenetics, lipids, metabolites, peptides and proteins).	Correlation between candidate predisposing factors and the primary study endpoint. The difference between confirmed SAMS and non-SAMS regarding candidate predisposing factors. The ability of candidate predisposing factors to predict SAMS.	Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.
	To determine the relationship between atorvastatin exposure and molecular effects in muscle and blood.	Correlation between atorvastatin-related variables and molecular effects in muscle and blood (gene expression, epigenetics, lipids, metabolites, peptides and proteins).	Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.
	To identify factors that are associated with the systemic and local exposure to atorvastatin and metabolites (.	Correlation between systemic and local atorvastatin-related variables and exploratory factors (demographics, physiology, concomitant drugs, food, genetics, gene expression, epigenetics, lipids, metabolites, peptides and proteins.	Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.

3 OVERALL STUDY DESIGN

This is a prospective, open, multi-center, intervention study in Norway that aims include 30 CHD patients classified with confirmed SAMS (i.e. statin dependent muscle side-effects) and non-SAMS in the MUscle Side-Effects of atorvastatin in coronary patients (MUSE) randomized double blinded cross-over trial. The patients will receive 7-weeks open treatment with atorvastatin 40mg/day in the first period followed by 7 weeks open treatment with no lipid lowering treatment in the second period. Each study period is preceeded by a 1 week pharmacological wash-out period (i.e. no statin). The study flow chart is shown in Figure 1.

3.1 Recruitment Plan

All patients classified with confirmed SAMS (n=20) and non-SAMS (n=39, no significant difference between atorvastatin and placebo treatment periods) in the MUSE trial are potentially eligible for study participation as long as they still fulfill the study entry criteria listed below. Patients will be pre-screened in a telephone interview and invited to the baseline evaluation. The telephone interview is already scheduled in May 2020 as a part of the post-trial care of MUSE. We expect that at least 75% classified with confirmed SAMS and at atleast 60% classified with non-SAMS are willing to participate and still fulfill the study entry criteria. Hence, a conservative estimate is that 15 patients with confirmed SAMS and 15 patients with non-SAMS may be enrolled during May 2020. Confirmed SAMS patients will be asked to participate, starting at the high end of muscle symptom difference between atorvastatin vs. placebo and then consecutively performing recruitment according to decreasing muscle symptom difference until inclusion of 15 patients. Non-SAMS patients will be asked to participate, starting at the low end of muscle symptom difference between atorvastatin vs. placebo and placebo vs. atorvastatin (i.e. regardless of direction), and then consecutive recruitment according to increasing muscle symptom difference until inclusion of 15 patients.

Patient enrolment for all study participants are scheduled in August 2020. With mean follow-up time of 16 weeks, the results of primary endpoint are expected in December 2020. Results of the secondary endpoints are expected in 2021 and 2022.

Study Period	Estimated date of first patient enrolled: 15-Aug-2020
	Anticipated recruitment period: 2 weeks (all participants are already identified as a part of MUSE)
	Estimated date of last patient completed: 1-Dec-2020
Treatment Duration:	Until end of study period (16 weeks after study start)
Follow-up:	Patients will be followed for 16 weeks after study start.
End of study	Last patient last visit
Post-trial follow-up	Telephone contact with a study cardiologist 3 months after the last visit

4 STUDY POPULATION

4.1 Selection of Study Population

All participants in the study will recruited from the MUSE trial (EudraCT Number: 2018-004261-14). All study entry criteria and safety end-points will be identical. MUSE was conducted at two representative Norwegian hospitals (Drammen and Vestfold) with a total catchment area of 380,000 inhabitants, corresponding to 7.4%

of the Norwegian population. In MUSE, consecutive patients aged 18-80 years undergoing a first or recurrent coronary event or treatment (i.e. acute myocardial infarction (ICD-10; I21), coronary artery bypass graft operation, or elective or emergency percutaneous coronary intervention) were identified from hospital patient discharge lists by searching chronologically after last admission for the index event during the past 6-36 months (2016-18).

Screening for study participation in the present follow-up study will be performed by two study physicians through the 6 months telephone follow-up of MUSE. Patients who still fulfill the study entry criteria through the telephone interview and who are willing to participate, will be invited to the hospital's outpatient clinics for a comprehensive baseline screening and study eligibility evaluation. A prerequisite for participation in the study is no coronary events in the past 6-12 months (dependent on risk profile, see Section 4.3 and 4.4) and no history of rhabdomyolysis/ or myopathy or significantly elevated levels of liver and muscle enzymes in blood at study start.

4.2 Number of Patients

30 CHD patients who previously participated in MUSE will be included in this follow-up study.

4.3 Inclusion Criteria for participation in the study

To be eligible for inclusion in the study, subjects must fulfill the following criteria at inclusion:

- Participation in the MUSE -trial (Eudract nr. 2018-004261-14) and still fulfilling the study entry criteria listed below (inclusion criteria in the previous MUSE -trial (Eudract nr. 2018-004261-14) are listed in Appendix J).
- First or recurrent diagnosis (myocardial infarction) or treatments (PCI or CABG) for a CHD event 12-42 months prior to study start.
- Signed informed consent and expected cooperation of the patient according to ICH/GCP and national/local regulations

4.4 Exclusion Criteria for participation in the study

Study subjects must not meet any of the following criteria:

- First or recurrent diagnosis (myocardial infarction) or treatments (PCI or CABG) for a CHD event the a) past 12 months prior to study start in high risk patients (i.e. at least one of following comorbid conditions: systolic heart failure, >1 previous myocardial infarction, kidney failure, diabetes, and smokers) and b) the past 6 months prior to study start in low risk patients without any of the co-morbid conditions mentioned above and in patients who are not taking a statin at all
- Patients with symptomatic peripheral artery disease and patients with familial hypercholesterolemia
- Patient has any contraindications for atorvastatin listed in the Summary of Product Characteristics (i.e. known hypersensitivity to the ingredients or peanuts or soybean, acute liver failure/ ALT > 3 times upper limit of the normal range in blood at study start, pregnancy and breastfeeding, concomitant use of glekaprevir/pibrentasvir)
- History of previous rhabdomyolysis, myopathy or liver failure due to statin treatment with CK > 10 times upper limit of the normal range or ALT > 3 times upper limit of the normal range.
- Any condition (e.g. psychiatric illness, dementia) or situation, that in the investigator's opinion could put the subject at significant risk, confound the study results, interfere significantly with the subject participation in the study, or rendering informed consent unfeasible
- Short life expectancy (<12 months) due to other medical conditions
- Not being able to understand Norwegian.
- Women of childbearing potential defined as all premenopausal female.
  (A postmenopausal state is defined as no menses for 12 months without an alternative medical cause)
- Participation in another randomized clinical trial

- Classified with significantly more muscle symptoms on placebo than on atorvastatin in the MUSE trial

5 TREATMENT

If all eligibility criteria are met and written informed consent is provided, patients will receive 7-weeks open treatment with atorvastatin in the first period followed by 7 weeks open treatment with no lipid lowering treatment in the second period. Each study period is preceeded by a 1 week pharmacological wash-out period.

A standard dose of 40 mg per day will be used. The study medication should be taken between 08:00 and 11:00 AM. Patients will not have breakfast or other food until the last blood sampling has been performed 3 hours after dose (t_3). Patients with ongoing lipid lowering treatment at baseline will undergo a 1-week pharmacological wash-out period before study start (Figure 1). All participants will then be treated for 7 weeks or until muscle symptoms are intolerable in the first treatment period. Patients will then be informed to not take any lipid lowering treatment for the subsequent 8-weeks (i.e. one week wash-out of atorvastatin treatment plus the 7 weeks period without lipid lowering treatment) . In total, study participation comprises 3 clinical visits with blood sampling per patient. At the end of each 7-weeks treatment periods, we will also collect muscle biopsies from all participants. Patients will be encouraged to continue the treatment period with atorvastatin for 7 weeks or until intolerable muscle symptoms persist for one week. Previous data from two observational studies using atorvastatin, indicate that 7-week treatment length is sufficient for muscle symptoms to appear and disappear in 100% and 80% of these patients, respectively. (19, 20)

All study patients will receive an information letter (ID-card size) stating that they participate in a clinical study, containing information about the sponsor and contact information to the principal investigators (PI) and the study nurses. Contraindicated foods and drugs that interact strongly with atorvastatin are also listed in the ID chard (See Section 5.2). Patients will be instructed to wear the ID-card in case of medical contact or primary care visits that may influence adherence to treatment.

5.1 Drug Identity, Supply and Storage

Atorvastatin are the Investigation Medicinal Product (IMP). In this trial we will use atorvastatin mylan® 40 mg (No 100) fabricated by Mylan (Mylan AB, Box 23033, 104 35 Stockholm, Sverige). The products have a marketing authorization, are routinely ordered by the pharmacy and will be dispensed from the pharmacy's own stock. The study drugs will be stored and supplied by the hospital pharmacy as specified on the package leaflet from the manufacturer

At the end of the baseline visit, all patients will receive a standard reimbursed prescription electronically (so-called “blåresept”) of atorvastatin mylan by the research cardiologists. The prescriptions will be labelled with the following additional information: “MUSE oppfølgingsstudien. Til klinisk utprøvning v/ Dr. John Munkhaugen, Drammen sykehus, tlf 97524194. ID nummmer:”. The study medication will be labelled by the pharmacies at the hospitals of Drammen and Vestfold. The study medication will be also delivered to patients from these pharmacies. The signed written agreement with the pharmacies are shown in (Appendix E). Study nurses will follow all patients to the pharmacy and count all tablets delivered to ensure that each participant receives exactly 50 tablettes (i.e. treatment for 7 weeks + one extra tablet). Participants will be asked to return all empty or unused pills at the follow-up visit at the end of the 7 weeks treatment period. The study nurses will be responsible for the medicines accounting and for registering the batch number for the drug provided to each patient. This information will be documented in a seprate list.

5.2 Dosage and Drug Administration

Atorvastatin tablets are administered orally once daily during the first 7 weeks treatment period. The recommened and most frequently used dose of atorvastatin for in CHD patients, tablets of 40 mg, is chosen.

5.3 Concomitant Medication

All concomitant medication will be registered at baseline and at study end. The following contraindicated foods and drugs that interact strongly with atorvastatin and thus influence the study results are listed in the ID chard:

Atazanavir
Barbiturates and derivates
Cyclosporine
Fucidinic acid
Glekaprevir
Pibrentasvir
Kobicistat
Letermovir
Lopinavir/ritonavir
Rifampicin, rifampin
Ritonavir
Sofosbuvir and ledipasvir
Elbasivir/grazoprevir
Telaprevir
Tipranavir
Indinavir
Boceprevir
Darunavir
Sakinavir
Fosamprenavir
Nelfinavir
Efavirenz
Carbamazepin
Fenytoin
Clarithromycin
Telitromycin
Delavirdine
Stiripentol
Ketokonazol, vorikonazol, itrakonazol, posakonazol

Fibrates (Lopid, Fenofibrat, Lipantil og Lipanthyl) are also contraindicated since they increase the risk of SAMS.

Grapefruitjuice and Johanneswort (prikkperikum, hypericum perforatum) are contraindicated since their influence on the atorvastatin pharmacokinetics is unpredictable and may be variable in the individual patient (i.e. dependent on consumed amount and variable content of interacting substances).

Drugs with moderate pharmacokinetic interaction potentials are contraindicated if they are intended to be used occasionally during the atorvastatin study period. However, they will be allowed if used continuously throughout the atorvastatin study period in both the present follow-up study and the previous MUSE main study:

Amiodaron
Diltiazem
Verapamil
Amlodipin
Erthromycin
Kolestipol

Antacids with magnesium and aluminium
Flukonazol

5.4 Subject Compliance

Study participants will report adherence to study treatment weekly in a diary. In addition, remaining pills in the returned package will be counted (participants will be asked to return any empty or unused pill packets at the end of the first 7 weeks follow-up visit). Statin adherence will also be measured directly by spot measurements of parent drug and metabolite concentrations in blood, analyzed by a LC-MC/MS method (ref). Statin measurements will also be performed at the end of the 7 weeks treatment period with no lipid lowering therapy to confirm that no drugs are are present in blood.

5.5 Drug Accountability

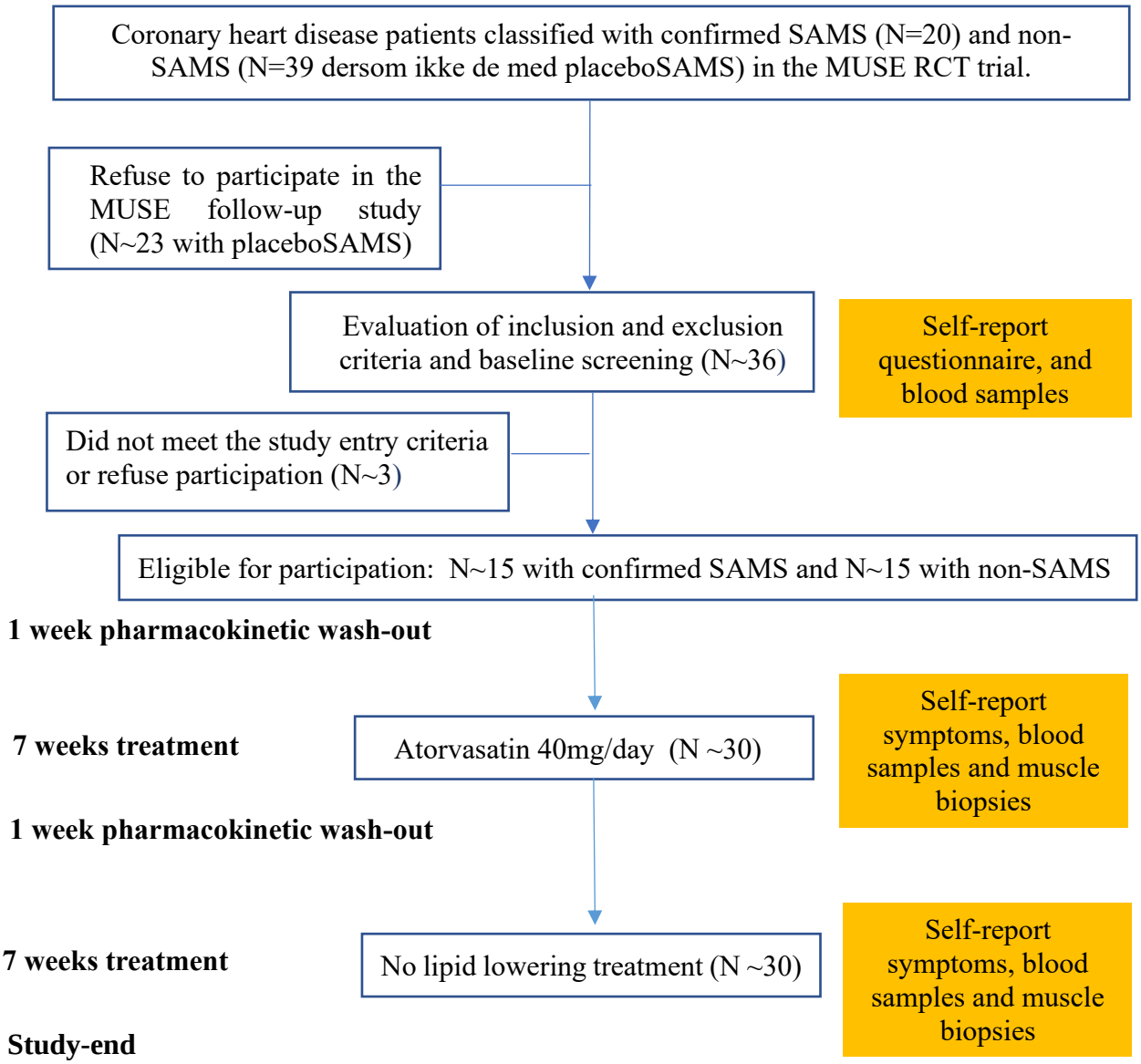
Drug accountability will be performed by local study nurses

5.6 Subject Numbering

Each subject is identified in the study by a unique subject number (similar number as used in the MUSE trial), which is assigned after the subject has signed the Informed Consent Form. Once assigned the subject number cannot be re-used for any other subject.

6 STUDY PROCEDURES

6.1 Figure 1. Study Flow Chart



- **Primary end-point:** Mean difference in muscle symptoms measured with VAS

Secondary end-points:

- Relationship between confirmed SAMS and levels of i. atorvastatin metabolites, ii. atorvastatin to HMG-CoA reductase ratio, iii, mevalonate pathway intermediates, iv. mitochondrial respiratory enzymes, v. FKBP1A:RyR1 complex, vi. caspase 3 signaling in muscle tissue and blood, and to evaluate the these biomarkers as a diagnostic tool
- Adherence to the treatment
- Study safety

Table 1. Schedule of activities

Table 2 Study data collection

	Baseline screening (n=71)	**Baseline evaluation/ inclusion (n~36)**	**Visit after first 7 weeks treatment period**	**Visit after second 7 weeks treatment period (Study end)**	**With drawal visits**
	Day-60 to -50	**Day 1**	**Week 8**	**Week 16**	
Inclusion and exclusion evaluation[1)]	X	X			
Informed consent [2)]		X			
Prescription of the IMP		X			
Collection of relevant hospital record data[3)]		X			
Self-reported questionnaires (PROMs)[4)]		X			
Collection of blood samples[5)]		X	X	X	X
Collection of muscle biopsies[6)]			X	X	X
Safety assessment obtained from blood samples[7)]			X	X	
Safety assessment obtained **weekly** from patient self-report[8)]			X	X	

1. Inclusion/exclusion evaluation will be performed during the telephone interview (See Appendix A) and at the baseline visit by the study physicians.
2. Inclusion and collection of informed consent will be performed at baseline visit by the study physician.
3. Relevant hospital record data will be registered at baseline in an eCRF by specially trained study nurses. The following variables will be recorded: Recurrent cardiac events since participation in the MUSE trial (NSTEMI, STEMI, stable or unstable angina) and eventually related angiographic findings, coronary treatment (PCI with or without stent implantation, thrombolysis) and prescribed medical treatment.
4. A self-report questionnaire comprises current lipid lowering treatment, muscle symptoms (i.e. pain/aching, stiffness, tenderness or cramps) measured on 1-10 Visual Analogue Scales and on 1-10 Numeric rating scales, muscle symptom characteristics and location (short-form McGill Pain Questionnaire and Brief Pain Inventory). In addition, muscle symptoms (i.e. pain/aching, stiffness, tenderness or cramps) and likelihood of statin discontinuation will be measured on 1-10 Visual Analogue Scales reported in a diary by the patients twice weekly during the treatment periods.

5. Blood sample collection at baseline (t_0) and at the end of the 7-weeks atorvastatin treatment period (t_0, t_1, t_2 and t_3) and the non-statin period (t_0) will be performed by the local study nurse or a bioengineer. The following tests will be included: hemoglobin, leucocytes, hs-CRP, eGFR, cystatin C, creatinine, CK, myoglobin, AST, ALT, total protein, albumin, non-fasting lipid profile (total cholesterol, HDL cholesterol, LDL-cholesterol) and concentrations of atorvastatin and metabolites (e.g. atorvastatin acid, atorvastatin lactone, atorvastatin 4-hydroxy [OH] lactone and acid, and atorvastatin 2-hydroxy [OH] lactone and acid), mevalonate, farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP), HMG-CoA reductase (HMGCR) protein expression, SLCO2B1 gene variant rs12422149 (c.935 G>A), mitochondrial complex I, II, III, IV and IV activity and protein expression, FKBP1A:RyR1 association, apoptosis biomarker panel (including caspase-3, Bad, Bak, Bax, Bax/Bcl-2 dimer, Bcl-xL, Bcl-xL/Bak dimer, Smac), calpain activity (mediator of apoptosis).
6. Muscle biopsies collected pre-dose in the morning (8-11 a.m.) from the thigh (vastus lateralis muscle) according to the hospital's standardized routine procedure. The following tests will be performed**:** Atorvastatin and metabolites (e.g. atorvastatin acid, atorvastatin lactone, atorvastatin 4-hydroxy [OH] lactone and acid, and atorvastatin 2-hydroxy [OH] lactone and acid), mevalonate, farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP), HMG-CoA reductase (HMGCR) protein expression, SLCO2B1 gene variant rs12422149 (c.935 G>A), mitochondrial complex I, II, III, IV and IV activity and protein expression, FKBP1A:RyR1 complex, apoptosis biomarker panel (including caspase-3, Bad, Bak, Bax, Bax/Bcl-2 dimer, Bcl-xL, Bcl-xL/Bak dimer, Smac), calpain activity (mediator of apoptosis). Morphological and histochemical characteristics.
7. Safety data during the treatment will be collected from blood samples at baseline and at the end of each treatment period and from weekly telephone interviews. Patients with blood levels of ALAT exceeding >3 times upper limit of the normal range or creatinine kinase > 10 times upper limit of the normal range will be withdrawn from the study. All Serious Adverse Events (SAEs) will be continuously monitored by the study Medical Advisor. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be limited to symptoms and signs not listed in the Summary of Product Characteristics.

6.1.1 Informed Consent

Informed written consent must have been given voluntarily by each subject before any study specific procedures are initiated.

A subject who has signed the informed consent form and has been assigned a subject identification number (i.e. similar identification number as used in the MUSE trial) is considered included.

All subjects will receive a study specific ID card stating that they participate in a clinical trial, containing information about the sponsor and contact information to the local PI/study nurse as well as the treatment allocation.

6.1.2 Data registered from the hospital medical records

Most hospital record data are already registered in the MUSE trial database. The following relevant hospital record data will be registered in an eCRF in this follow-up study by specially trained study nurses.

- Recurrent cardiac events since participation in the MUSE trial (NSTEMI, STEMI, stable or unstable angina) and eventually related angiographic findings, coronary treatment (PCI with or without stent implantation, thrombolysis) and prescribed medical treatment.

6.1.3 Patient self-report using commonly used and mainly validated questionnaires (See Appendix C)

- Statin treatment,
    - Current lipid lowering treatment including type and doses

- Muscle symptoms
    - Pain, aching, stiffness, tenderness or cramps will be measured on Visual Analogue Scales and on 1-10 Numeric rating scales
    - Characteristics will be measured with the short-form McGill Pain Questionnaire and Brief Pain Inventory

The local study nurse will overview all self-reported questionnaires obtained at baseline to ensure that the risk of missing data is reduced. Multiple imputation tecniques will be used to replace missing data.

6.1.4 Laboratory evaluations and biobanking

Blood sample collection at baseline and at the end of each 7-weeks treatment period will be performed by the local study nurse or a bioengineer. All blood samples will be sent to the laboratory at Drammen hospital for analyses of standard blood samples, pharmacological analyses and biobanking. Details on the collections, shipment of samples and reporting of results will be prepared in a laboratory manual.

Clinical chemistry:
The following tests are included in the chemistry: hemoglobin, leucocytes, hs-CRP, eGFR, cystatin C, creatinine, CK, myoglobin, AST, ALT, total protein, albumin

Non fasting lipid profile:
The following tests are included in the non-fasting lipid profile: total cholesterol, HDL cholesterol, LDL-cholesterol

6.1.5 Clinical data

Muscle symptoms, blood samples and muscle biopsies will be assessed during the follow-up period from study inclusion until study-end.

- **Muscle symptoms** will be assessed twice weekly in a diary by the patients on a VAS Likert scale and a 1-10 Numeric Ratin Scale (NRS).

- **Blood samples** for concentration measurements of atorvastatin its metabolites (incl. reactive acylglucuronide) in plasma and in white blood cells (i.e. lymphocytes) will be collected in the end of the first wash-out period (to confirm statin naivity before entering the treatment period) and in the end of each 7 weeks treatment period. Patients who experience intolerable muscle symptoms will have blood samples collected in the morning as soon as possible to prevent discontinuation before blood sampling. In the end of the atorvastatin treatment period, blood samples will be collected immediately before the morning dose and 1, 2 and 3 hours after observed tablet intake. This sampling scheme will allow both the trough and peak exposure of the drug to be investigated as diagnostic markers of SAMS. Covariates that potentially may explain diversity in the pharmacokinetics of atorvastatin and its metabolites will be assessed from the MUSE trial database: Age, gender, weight, renal and liver function, concomitant medication and pharmacogenetic variants in SLCO1B1 and CYP3A. (6, 7) In the end of the non-statin treatment period, blood samples will be collected as corresponding to a t_0 sample.

Following biomarkers will be assessed: Mevalonate, farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP), HMG-CoA reductase (HMGCR) protein expression, SLCO2B1 gene variant rs12422149 (c.935 G>A), mitochondrial complex I, II, III, IV and IV activity and protein expression, FKBP1A:RyR1 association, apoptosis biomarker panel (including caspase-3, Bad, Bak, Bax, Bax/Bcl-2 dimer, Bcl-xL, Bcl-xL/Bak dimer, Smac), calpain activity (mediator of apoptosis).

- **Muscle biopsies** collected pre-dose in the morning (8-11 a.m.) from the thigh (vastus lateralis muscle) according to a standardized procedure (attachment *MUSE-FUp Muskelbiopsi_Ous patologi 20200308*). The following tests will be performed: Mevalonate, farnesyl pyrophosphate (FPP), geranylgeranyl pyrophosphate (GGPP), HMG-CoA reductase (HMGCR) protein expression, mitochondrial complex I, II, III, IV and IV activity and protein expression, FKBP1A:RyR1 association, apoptosis biomarker panel (including caspase-3, Bad, Bak, Bax, Bax/Bcl-2 dimer, Bcl-xL, Bcl-xL/Bak dimer, Smac), calpain activity (mediator of apoptosis).

In general, biomarkers in muscle and blood cells will be normalized to total protein amount and/or citrate synthase activity.

6.1.6 Safety data

The Steering Committee has chosen the following events considered important for safety reasons:
- Intolerable muscle symptoms reported by the patients during the atorvastatin treatment period will result in discontinuation from the treatment arm and blood sample and muscle biopsy collections within 48 hours. The patient can then continue to the other treatment arm after the 1 week wash-out period.
- Patients reporting new-onset symptoms of angina pectoris and/or dyspnea during the telephone interview or at the clinical visits will be withdrawn from the study
- Patients with blood levels of ALT exceeding >3 times upper limit of the normal range or creatinine kinase > 10 times upper limit of the normal range will be withdrawn from the study. However, none of these patients had significant elevations in these enzymes in the MUSE trial.
- All Serious Adverse Events (SAEs) will be continuously monitored by the study Medical Advisor
- Unexpected Serious Adverse Reactions (SUSARs) will be limited to symptoms and signs not listed in the Summary of Product Characteristics (i.e."Preparatomtalen").

In addition, patients in need of treatment with any of the drugs listed in Section 5 interacting strongly with atorvastatin will be withdrawn from the study.

6.2 Withdrawals and Procedures for Stopping Data Collection

Once included in the study, all patients will be assessed until study closure unless informed consent is withdrawn for study participation. Patients can withdraw their consent to participate at any time during follow-up without prejudice to further treatment. Data collection will stop at the time of withdrawal.

All included patients will comprise the study population. Patients who withdraw or are withdrawn from the study after randomization will not be replaced.

6.3 Procedures for Discontinuation

6.3.1 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 by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.

- Safety reason as judged by the Principal Investigator including:
    - Blood levels of ALT exceed >3 times upper limit of the normal range or creatinine kinase > 10 times upper limit of the normal range during the treatment periods
    - Symptoms of symptomatic CHD (i.e. new-onset angina pectoris and/or dyspnea)
    - Occurrence of SAEs/SUSARS
- Major protocol deviation
- Patient's non-compliance to study treatment and/or procedures

6.3.2 Trial Discontinuation

The whole trial may be discontinued at the discretion of the PI 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

The sponsor and principal investigator(s) 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.

6.4 End of Study and post-trial care

The study period ends the day after the last treatment day has been completed (i.e. 16 weeks after study start). This will be considered as the end of study for participants, and recommendations for further lipid management will be continued as recommended after participation in MUSE RCT. Three months after completion of the study, all patients will receive a phone call from the study PI to evaluate their experiences with study participation. In addition, hospitalizations for SAEs during this period will be registered.

7. Assessments

7.1 Assessment of the Primary and Secondary Endpoint

Assessment of the primary and secondary end-points will be obtained by patient self-report measured with aggregated scores on a VAS Likert scale and a 1-10 numeric rating scale administered at study start, twice weekly during the treatment periods and at study end. The primary end-point from the MUSE RCT will also be assessed versus end-points in the follow-up study.

Assessment of secondary end-points:

1. Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites in muscle biopsies.
2. Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites in blood plasma and PBMC. Genotyping of the SLCO2B1 gene variant rs12422149 (c.935 G>A).
3. Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites, and by measurement of HMGCR, in muscle biopsies. .

4. Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of atorvastatin and its major hydroxy and lactone metabolites, and by measurement of HMGCR, in PBMC.
5. Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of mevalonate, farnesyl-PP and geranylgeranyl-PP in muscle biopsies.
6. Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantitative LC-MS/MS analysis of mevalonate, farnesyl-PP and geranylgeranyl-PP in blood plasma and PBMC.
7. Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantification of mitochondrial respiratory enzymes (expression and activity) in muscle biopsies.
8. Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantification of mitochondrial respiratory enzymes (expression and activity) in PBMC.
9. Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Immunoprecipitation of the sarcoplasmatic reticulum RyR1 in muscle biopsies and quantification of FKBP1A (FKBP12) and RyR1 in their protein complex.
10. Obtained by collection of blood samples in the end of the atorvastatin treatment period. Immunoprecipitation of the sarcoplasmatic reticulum RyR1 in PBMC and quantification of FKBP1A (FKBP12) and RyR1 in their protein complex.
11. Obtained by collection of muscle biopsies in the end of the atorvastatin treatment period. Quantification of caspase 3 and pro-caspase 3 in muscle biopsies, and calculation of the ratio between caspase 3 (active) and pro-caspase 3 (inactive).
12. Obtained by collection of blood samples in the end of the atorvastatin treatment period. Quantification of caspase 3 and pro-caspase 3 in PBMC, and calculation of the ratio between caspase 3 (active) and pro-caspase 3 (inactive).
13. Obtained by collection of muscle biopsies on and off atorvastatin. Quantitative LC-MS/MS analyses of atorvastatin and its hydroxy and lactone metabolites, as well as mevalonate, farnesyl-PP and geranylgeranyl-PP. Quantification of mitochondrial respiratory enzymes (expression and activity), the FKBP1A:RyR1 ratio in their sarcoplasmatic reticulum protein complex, caspase 3, and the ratio between caspase 3 and pro-caspase 3.
14. Obtained by collection of blood samples on and off atorvastatin. Quantitative LC-MS/MS analyses of atorvastatin and its hydroxy and lactone metabolites, as well as mevalonate, farnesyl-PP and geranylgeranyl-PP. Quantification of mitochondrial respiratory enzymes (expression and activity), the FKBP1A:RyR1 ratio in their sarcoplasmatic reticulum protein complex, caspase 3, and the ratio between caspase 3 and pro-caspase 3.
15. Obtained through pill counts of returned packages, and from analyses of atortastatin level in blood determined by liquid chromatography-tandem mass spectrometry method at the end of the atorvastatin treatment period.
16. Obtained every 7th days through direct telephone contact with the patient . Obtained thorugh blood samples collected at the end of each 7 weeks treatment period or if intolerable muscle symptoms were reported by the patients. Obtained through direct telephone contact with the patient and through monitoring of hospital admissions throughout the study period.

Assessment of exploratory endpoints:

1. Obtained by collection of muscle biopsies in the end of the atorvastatin and non-statin treatment periods. Assessment of morphology and histology by pathologist.
2. Obtained by collection of muscle biopsies in the end of the atorvastatin and non-statin treatment periods. Assessment of morphology and histology by pathologist. Molecular analyses with appropriate methods.
3. Obtained by MRI of thighs in the end of the atorvastatin and non-statin treatment periods. Assessment of MRI characteristics (edema and fatty muscle changes) by radiologist.

4. Obtained by MRI of thighs in the end of the atorvastatin and non-statin treatment periods. Assessment of MRI characteristics (edema and fatty muscle changes) by radiologist. Molecular analyses with appropriate methods.
5. Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.
6. Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.
7. Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.
8. Obtained by collection of muscle biopsies and blood samples in the end of the atorvastatin and non-statin treatment periods. Molecular analyses with appropriate methods.

7.2. Safety Assessments

Safety endpoints will be under the responsibility of the primary investigators at the participating centers and will be collected:

- Every 7th days: direct telephone contact with the patient for assessment of intolerable muscle symptoms and symptoms of unstable CHD (i.e. new-onset angina pectoris and/or dyspnea) after a standardized protocol by a specially trained study nurse.

- Blood samples collected for analyses of ALAT and CK at the end of each 7 weeks treatment period or if intolerable muscle symptoms were reported by the patients

- Continuous surveillance of serious adverse events (SAEs) obtained through direct weekly telephone contact with the patients and thorugh continuous monitoring of hospital admissions during the study period.

Due to the relatively low study sample, no safety analysis will be performed in this study, but descriptive data will be presented.

7.3 Adherence Assessments

Information about adherence to the study medication will be reported by counting pills in returned packages. Statin adherence will also be measured in blood by analyses of statin concentrations by a direct liquid chromatography-tandem mass spectrometry method.

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.

The methods for collection of safety data are described below.

8.1. Adverse Events

Suspected Unexpected Serious Adverse Reactions (SUSARS) will be reported to NoMA by using CIOMS forms.

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 unfavorable 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 is associated with clinical signs and symptoms, the clinical 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.

8.2. If an abnormal laboratory value is not associated with clinical signs and symptoms, the laboratory result should itself be reported as an AE.Serious Adverse Events (SAEs)

A Serious Adverse Event is defined as any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is an important medical event that may jeopardize 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 hospitalization, but may jeopardize 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. Hospitalization 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 hospitalization.

A pre-planned hospitalization admission (ie, elective or scheduled surgery arranged prior to the start of treatment) for pre-existing condition is not considered to be a serious adverse event.

8.3. Suspected Unexpected Serioud Adverse Reactions (SUSARs)

The Sponsor's Medical Officer will review all SAEs and evaluate relationship with study drug and whether the event is expected according to the Reference Safety Information (RSI). The SPC (section 4.8 «Bivirkninger») of the IMPs is used as Reference Safety Information (RSI) in this trial. SAEs that are considred related by the treating investigator or by the sponsors medical officer and that are considered unexpected will be defined as SUSAR.

SUSARs will be reported to the Competent Authority according to national regulation.

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 Competent Authorities 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.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

Two independent study SAE evaluators at each site will consider whether a SAE is an adverse reaction/serious adverse reaction or not based on the temporal relationship between the treatment periods and the event. For example acute liver failure with elevated liver enzymes will only conisderes as an AR/SAR during the treatment period with atorvastatin (as this is a rare side effect of statins).

SUSARs will be reported using the CIOMS form.

8.4. Safety and Reporting

Safety assessments will be continuously monitored throughout the study. Please see previously were this is described in detail.

8.4.1. Annual Safety Report

The study is planned to be completed within 6 months and therefore an annual safety report will not be needed. If the study is to continue for more than a year, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements.

8.4.2. 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

Emergency procedures will be initiated when either *statin treatment* may have caused the emergency situation (i.e. acute liver failure, myopathy or rabdomyolysis) or when *no lipid lowering treatment* may have caused the emergency situation (i.e. new-onset acute coronary syndrome). In case of hospitalization for acute liver failure, myopathy or rabdomyolysis, all drugs used by the patient (including the study intervention) will be temporary stopped according to routine clinical practice. In case of hospitalization for acute coronary syndrome, high-dose atorvastatin (i.e. 80 mg x1) treatment will be routinely prescribed to all patients regardless of participation in the present study or not. In these situations, the study patiens will be withdrawn from the study. Potentially, the need for treatment initination with any of the drugs listed in 5.3 (that interact with atorvastatin) may also require study withdrawel. However, none of these drugs will be initiated within 24 hours following acute hospitalizations.

9. DATA MANAGEMENT AND MONITORING

Study monitoring will be performed by an independent study monitor from the Clinical Trial Unit .

A risk assessment of the study will be performed by the study monitor prior to study start. Based on the risk assessment, a monitor plan will be developed.

9.1. Case Report Forms

The designated investigator staff will enter the data required by the protocol into the Case report forms (CRF). The Principal Investigator is responsible for assuring that data entered into the CRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each CRF. If any assessments are omitted, the reason for such omissions will be noted on the CRFs. Corrections, with the reason for the corrections will also be recorded. After database lock, the paper copies of the subject data will be filed at the investigational site. We will use paper CRF in the first place and look into the possibility of transferring data registration to eCRF in time.

9.2. Source Data

Source data are all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

The medical records for each patient should contain information which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least that the patient is participating in the study, e.g. by including the enrollment number and the study code or other study identification;

- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent;
- Results of all assessments confirming a patient's eligibility for the study;
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- Treatments given, 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;
- Additional information according to local regulations and practice.

Specify and provide details if any source data will be recorded directly into the Case Report Form (meaning that for the defined parameters, CRF is source data and not the hospital records).

A source data list will be agreed upon for each site specifying the source at a module or a variable level.

9.3. Study Monitoring

Study monitoring will be based on the risk assessment and will be described in a monitor plan that will be prepared prior to study start. Study monitoring will be performed by one research cardiologists that are otherwice not involved in the study.

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 25 years after study closure). All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9.5. Database management

An electronic database will be generated and stored in a dedicated project folder at Vestre Viken secure research server with access for authorized personnel only. The research server is provided with continuous back-up to prevent loss of data. All data management will be according to Vestre Viken standard operating procedures with regard to storage of research data. Data quality will be assured by random sample check by the monitor.

9.6. Determination of Sample Size and Power Calculation

9.6.1. Sample Size

N=30. Patients (n=15) classified with confirmed SAMS in the MUSE trial and patients classified with non-SAMS (n=15) will be included.

The patients are pre-classified with confirmed SAMS and non-SAMS in the MUSE RCT. The present open follow-up study is performed to reproduce the atorvastatin pharmacodynamics and corresponding presence of muscle symptoms. Pre-classified confirmed SAMS patients not meeting reconfirmation during open atorvastatin treatment will be excluded from data analyses.

With respect to the biomarker investigations, we do not have access to data for direct sample size calculations. In the MUSE trial), the 4-OH-atorvastatin acid metabolite demonstrated highest correlation (Spearman rho) with the individual muscle symptom difference between atorvastatin and placebo, although it was not statistically significant. Based on the observed variability in the MUSE data on 4-OH-atorvastatin acid in plasma, obtained from 111 coronary patients on atorvastatin 40 mg, , there is 80% power (P<.05) of detecting a 2.5-fold difference between confirmed SAMS and non-SAMS with n=8+8 patients (mean 0.80 vs. 2.00, SD 0.86). We will include 15 patients with comfirmed SAMS in this follow-up study and a equal group with non-SAMS to account for the uncertainty in the underlying data and potential drop-out during study.

9.7. Planned analyses

The main statistical analysis is planned when all patients have been followed for 16 weeks, all data have been entered, verified and validated, and the database has been locked.

Oslo Centre for Biostatistics and Epidemiology (OCBE) will be responsible for the statistical quality of the trial. Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. A

statistical analysis plan (SAP) describing all the statistical methods will be produced prior to database lock. The treatment allocation will be revealed after the database lock and used in the statistical analysis.

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

9.8. Statistical Analysis

The primary outcome and other continuous outcomes will be estimated with linear regression models. Dichotomous outcomes will be analysed with conditional logistic regression models. Methods for analysis of ROC curves and measures of diagnostic accuracy will be used to identify cut-off values of atorvastatin-related biomarker (i.e. parent drug and metabolites, mevalonate pathway intermediates, mitochondrial respiratory enzymes, FKBP1A:RyR1, caspase 3) levels that can discriminate confirmed SAMS from other muscle symptoms. Differences in variables between groups will be compared with parametric or non-parametric tests, as appropriate according to data distributions. The correlations between variables will be estimated with Spearman correlation coefficients and linear regression analyses. A senior statistician (M Fagerland) at Oslo Centre for Biostatistics and Epidemiology (OCBE) will be responsible for all statistics. A statistical analysis plan (SAP) describing all details in this respect will be produced prior to database lock.

9.8.1. Safety analyses

Due to the low number of patients, no safety analyses are planned for this study, but descriptive data will be presented.

10. STUDY MANAGEMENT

10.1. 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.

10.2. 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).

10.3. 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.

10.4. Audit and Inspections

Authorized representatives of a Competent Authority and Ethics Committee may visit the study centers to perform inspections, including source data verification. Likewise the representatives from sponsor may visit the center 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, analyzed, 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.

11. 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/Good Clinical Practice and applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

11.1. 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 before enrolment of any patients into the study.

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

11.2. Other Regulatory Approvals

The protocol will be submitted and approved by the applicable competent authorities before commencement of the study.

The protocol will also be registered in www.clinicaltrials.gov and the European Clinical Trials Database (EudraCT) as before inclusion of the first patient.

11.3. Informed Consent Procedure

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

It will be emphasized that the 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. Documented informed consent must be obtained for all patients included in the study before they are registered 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 will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder.

11.4. 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 CRFs by patient number, initials and date of birth (define as applicable).

11.5. User involvement

The NOR-COR study user-group comprising user-group representatives from the Norwegian Health Association (n=1), "Landsforeningen for Hjerte og Lungesyke" in Buskerud and Vestfold (n=2), general practitioners (GPs) (n=5), cardiac nurses (n=3), and clinical cardiologists (n=2) from the hospitals of Drammen and Vestfold have provided feedback in the study design, the self-reported study questions, patient information letters, and the data collection tools. The group will also play an important role in disseminating the study results.

12. TRIAL SPONSORSHIP AND FINANCING

Vestre Viken Trust is financing the trial, which is funded by grants from Vestre Viken Trust and Department of Pharmacology, OUH. Further applications for funding and researchers have been submitted. Other than mediating financial support, the financial sponsors are not involved in the conduction of this study.

13. TRIAL INSURANCE

The Principal investigator will provide insurance coverage for this study through membership of the Drug Liability Association before study start (see http://www.laf.no for more details).

14. PUBLICATION POLICY

Upon study completion and finalization 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.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee 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.

15. APPENDICES

15.1. APPENDIX A – Informed consent letter main study

FORESPØRSEL OM DELTAGELSE I FORSKNINGSPROSJEKT

MUSE oppfølgingsstudien -biomarkører for statin-avhengige muskelbivirkninger

Kjære MUSE deltager

Dette er en forespørsel til deg om å delta i forskningsprosjektet, *Biomarkører for statin-avhengige muskelbivirkninger*, som har til hensikt å fremskaffe ny kunnskap om årsakene til muskelbivirkninger ved bruk av kolesterolmedisinen atorvastatin og utvikle en blod test som korrekt kan identifisere disse pasientene. Studien er en oppfølging av den randomiserte studien, MUSE, som du deltok i ved sykehusene i Drammen og Vestfold i 2019.

HVA INNEBÆRER DELTAGELSE I DENNE DELSTUDIEN?

Alle pasienter som hadde statin-avhengige muskelbivirkninger i MUSE og et utvalg av inntil 20 pasienter som ikke hadde forskjell i muskelplager mellom atorvastatin og placebo, vil bli forespurt om å delta i denne oppfølgingsstudien. Aktuelle pasienter blir kontaktet i forbindelse med en avsluttende samtale for MUSE ila. våren 2020. En forutsetning for å delta er at du fortsatt oppfyller kriteriene for deltagelse. Dersom du vurderes å være kandidat for å delta, vil du som sist, få behandling med atorvastatin 40 mg/dag i 7 uker eller inntil muskelsymptomene kommer tilbake. Du skal deretter gå 7 uker uten å ta kolesterolmedisiner og du får ingen behandling med placbo slik som sist. I motsetning til forrige gang vil det heller ikke bli trukket lodd om rekkefølgen på behandlingen. Tilsvarende som i MUSE studien skal du ikke ta dine faste kolesterolmedisiner (verken statin eller andre kolesterolsenkende medisiner) siste uke før studiestart eller under studiens forløp. Du skal ta inntil 4 blodprøver fastende ved oppstart og ved studieslutten av hver behandlingsperiode og rapportere muskelsymptomer ukentlig i en dagbok under studiens forløp. Denne gangen blir du også bedt om å avgi en vevsprøve fra muskelen på slutten av hver behandlingsperiode. Vevs-prøven tas fra en muskel på ditt høyre lår og er på størrelse med en sukkerbit. Prøven tas av personell med stor erfaring og det er ikke mer ubehag enn å ta en blodprøve. For at vi skal kunne trekke konklusjoner fra denne studien er det avgjørende viktig at vi også tar muskelprøve fra deg som opplevde muskelsymptomer som ikke var forårsaket av atorvastatin.

Hvis du takker nei til deltagelse vil det ikke ha noe konsekvens for annen behandling eller oppfølging som er planlagt på sykehuset.

HENSIKTEN MED STUDIEN

1 av 10 personer i Norge og Europa bruker statiner. Selv om 10% av disse personene opplever muskelbivirkninger så vet vi ikke årsaken. Formålet med studien er å undersøke om nivåer av atorvastatin og/eller tilhørende biomarkører (metabolitter, fettstoffer, proteiner, arvestoff) i muskel kan brukes til å identifisere pasientene som har muskelbivirkninger. Vi vil også undersøke muskelprøvene i mikroskop for å avklare om det finnes forandringer i strukturen til muskelcellene eller det omkringliggende vev.

Det er ofte krevende både for pasienten og legen å vite om pasientens muskelplager skyldes kolesterolmedisinen eller ikke. Denne studien gir helt ny kunnskap om mekanismene bak muskelbivirkninger og kan potensielt bidra til utvikling av en blod- eller muskeltest som kan avklare om muskelbivirkningene skyldes medisinen eller ikke. Resultatet vil kunne gi ny og skreddersydd diagnostikk og bedre behandling med statiner til et stort antall mennesker.

MULIGE FORDELER, ULEMPER OG ALVORLIGE BIVIRKNINGER

Tilsvarende som i MUSE studien, er den potensielle risikoen forbundet med å gå 7 uker uten statiner. Data fra over 15000 hjerteinfarktpasienter viste ingen økt risiko for nye hjerte-kar hendelser hos pasienter som kutter ut statiner noen uker når det gjøres i forbindelse med en studie. Det var ingen pasienter som hadde alvorlige hjerte-kar hendelser under 7 ukers behandling med placebo medisin i MUSE studien. Som i MUSE studien vil du få nøye oppfølging av studiepersonell ukentlig i studieperioden. Risikoen ved å få behandling med kolesterolmedisin er legemiddelets kjente bivirkninger som du kjenner svært godt til. Noen pasienter kan kjenne et lett ubehag i forbindelse med prøvetaking fra muskel, men dette er ikke mer enn ved en blodprøvetaking og du får lokal bedøvelse i huden. Risikoen for å få blødning og infeksjon i forbindelse med prøvetaking er minimal. For å redusere denne risikoen ytterligere skal du ikke ta dine blodfortynnende medisiner de siste 3 dagene på forhånd.

Ved å delta i studien bidrar du også med helt ny kunnskap som potensielt endrer måten vi stiller diagnose, behandler og følger pasienter som opplever muskelplager når de tar statiner. Resultatet kan bli mer skreddersydd og korrekt kolesterolbehandling og færre bivirkninger for et stort antall mennesker i hele verden.

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Listen som kan koble ditt navn til koden vil bli oppbevart på sykehuset og bare personell med ansvar for studien har tilgang til denne. Deltakelse innebærer at opplysninger om din helsetilstand og behandling registreres og benyttes i forskningsøyemed. Det blir registrert opplysninger om behandlingen og din hjertesykdom ved start av studien og gjennom behandlingsperiodene på til sammen 16 uker. Opplysningene blir samlet fra flere kilder:

- Relevante opplysninger om din hjertesykdom blir registrert fra din pasientjournal og din kjernejournal på sykehuset
- Opplysninger du gir i det korte spørreskjemaet som er vedlagt og dagboken som du fyller ut ukentlig gjennom studien
- Undersøkelser av blodprøver og muskelprøver tatt av deg ved i løpet av studien

Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Utlevering av materiale og opplysninger til andre
Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at avidentifiserte opplysninger utleveres til våre samarbeidspartnere. Våre viktigste samarbeidspartnere er Universitet i Oslo og Oslo Universitetssykehus.

Innsynsrett og oppbevaring av materiale
Hvis du takker ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Opplysningene vil da ikke brukes videre i studien.

BLODPRØVER TIL BIOBANK

Tilsvarende som i MUSE studien, ber vi deg ta stilling til om vi kan ta blod og muskelprøver av deg for lagring i en forskningsbiobank (NOR-COR Biobank) lokalisert på Drammen sykehus. Senere analyser av disse blodprøvene med andre metoder enn de som eksisterer i dag, vil kunne gi oss nye markører til å studere legemiddelnivåer, virkningsmekanismer og bivirkninger ved kolesterolmedisiner samt andre hjerte/kar-medisiner.

Avdelingssjef ved Medisinsk avdeling, Drammen sykehus er ansvarshavende for NOR-COR Biobank. Biobanken opphører 25 år etter studieslutt, det vil si i 2047. Studiespesifikke prøver blir destruert og slettet etter interne retningslinjer når alle planlagte analyser er gjort. Det biologiske materialet kan bare bli anvendt til medisinske formål jf, Bioteknologiloven (§5) og kan kun brukes videre etter godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK).

Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger også kan oppbevares, analyseres og behandles ved Klinikk for laboratoriemedisin ved Oslo Universitetssykehus.

GENETISKE UNDERSØKELSER

Tilsvarende som i MUSE studien ber vi også om tillatelse til å gjennomføre genetiske undersøkelser (gensekvenser og sammensetning i arvestoffet DNA, genuttrykk målt som RNA, proteiner, peptider, lipider og metabolitter) av blod- og muskelprøvene som er samlet inn. Studiens analyser er begrenset til genetiske markører som enten har eller som kan ha betydning for legemiddelomsetning, effekt eller bivirkninger ved behandling med kolesterolmedisiner og andre hjertemedisiner. Det vil også kunne bli utført analyser flere år frem i tid og svar på disse undersøkelsene kan derfor ikke gis til studiedeltagerne, med mindre fremtidig forskning avdekker at slike funn bør følges opp.

- Dersom det i forbindelse med studien eller i fremtiden påvises funn av genvarianter som har betydning for pasientenes prognose eller aktuell behandling med kolesterolmedisin eller andre hjertemedisiner, vil deltagere få tilbakemelding av studiens hjerteleger og ved behov bli tilbudt genetisk veiledning ved Avdeling for Medisinsk genetikk på Rikshospitalet.
- Mulig reidentifisering: Selv om navn og personnummer fjernes, er genomsekvensen så unik at den i teorien ikke kan sies å være anonym.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning [saksnr. hos REK 54041]. Studien er også godkjent av Statens legemiddelverk (SLV) (nr. 20/04280-10).

Etter ny personopplysningslov har behandlingsansvarlig [Vestre Viken HF- Drammen sykehus] og prosjektleder [John Munkhaugen] et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6a. Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

FORSIKRING

Ordinær pasientskadeerstatning er gjeldende. Du er også forsikret i henhold til Lov om produktansvar i Legemiddelforsikringen.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er helt frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til deltagelse i studien. Dette vil ikke få konsekvenser for din videre behandling. Du undertegner samtykkeerklæringen dersom du ønsker å delta. Dersom du senere ønsker å trekke deg eller har spørsmål om studien kan du kontakte prosjektleder PhD John Munkhaugen på tlf. 975 24 194 eller spesialfysioterapeut/forsker Kari Peersen på Telefon: 99267726 .

Du kan ta kontakt med institusjonens personvernombud dersom du har spørsmål om behandlingen av dine personopplysninger i prosjektet. Drammen sykehus: Henriette Henriksen, tlf +47 41764786, epost: Henriette.Henriksen@vestreviken.no. Sykehuset i Vestfold: Ida Mollerud, tlf. +47 33 34 33 86, epost: PVO@siv.no

ØKONOMI

Studien er finansiert gjennom forskningsmidler fra Nasjonalforeningen for folkehelsen og de deltagende sykehusene; Sykehuset i Drammen, Vestre Viken og Sykehuset i Vestfold. Disse har ingen økonomiske interesser i forskningsresultatene.
Alle pasienter vil få en økonomisk kompensasjon på kr 5000 for tiden de må avsette for deltagelse og til å dekke reiseutgifter.

SAMTYKKE TIL DELTAGELSE

Jeg er villig til å delta i studien

Sted og dato

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Deltakers signatur Deltakers navn med BLOKKBOKSTAVER

Jeg er villig til å gi materialet til biobank (blod- og muskelprøve)

Sted og dato ---------- ----------

Deltakers signatur Deltakers navn med BLOKKBOKSTAVER

Jeg er villig til at det kan utføres genetiske analyser

Sted og dato ---------- ----------

Deltakers signatur Deltakers navn med BLOKKBOKSTAVER

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato Sted og dato ---------- ----------

Signatur Rolle i prosjektet

Informed consent for long-term storage in NORCOR biobank

FORESPØRSEL OM LAGRING AV BIOLOGISK MATERIALE I NORCOR BIOBANK

Kjære MUSE deltager

Dette er en forespørsel til deg om å gi tillatelse til at det innsamlede biologiske materiale fra blod og muskelveve kan lagres i den generelle biobanken, NORCOR-biobank lokalisert på Drammen sykehus. Senere analyser av disse blodprøvene med andre metoder enn de som eksisterer i dag, vil kunne gi oss nye markører til å studere legemiddelnivåer, virkningsmekanismer og bivirkninger ved kolesterolmedisiner samt andre hjerte/kar-medisiner.

Avdelingssjef ved Medisinsk avdeling, Drammen sykehus er ansvarshavende for NOR-COR Biobank. Biobanken opphører 25 år etter studieslutt, det vil si i 2047. Studiespesifikke prøver blir destruert og slettet etter interne retningslinjer når alle planlagte analyser er gjort. Det biologiske materialet kan bare bli anvendt til medisinske formål jf, Bioteknologiloven (§5) og kan kun brukes videre etter godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK).

Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at prøver og avidentifiserte opplysninger også kan oppbevares, analyseres og behandles ved Klinikk for laboratoriemedisin ved Oslo Universitetssykehus.

Informasjonen som registreres i biobanken skal kun brukes etter godkjenning fra Regional Etisk komite. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Listen som kan koble ditt navn til koden vil bli oppbevart på sykehuset og bare personell med ansvar for studien har tilgang til denne. Deltakelse innebærer at opplysninger om din helsetilstand og behandling registreres og benyttes i forskningsøyemed.

SAMTYKKE TIL LAGRING AV DATA I NORCOR BIOBANK

Jeg er villig at mitt biologiske materiale (blod- og muskelprøve) kan lagres i NORCOR biobank

Sted og dato ---------- ----------

Deltakers signatur Deltakers navn med BLOKKBOKSTAVER

Jeg bekrefter å ha gitt informasjon om lagring i biobank

Sted og dato Sted og dato ---------- ----------

Signatur Rolle i prosjektet

15.2. APPENDIX B – Baseline questionnaire

Spørreskjema

Kjære NOR-COR MUSE deltager. Tusen takk for at du vil svare på et nytt spørreskjema. Vi håper du vil svare på alle spørsmålene nedenfor så nøye som mulig. De fleste vil bruke ca. 5 minutter på å svare.

MEDISINBRUK

Bruker du kolesterolsenkende medisiner av typen statin (Simvastatin, Zocor, Atorvastatin, Lipitor, Lescol, Pravachol, Pravastatin, Lovastatin, Rosuvastatin, Crestor) ?

Ja…… Nei……..

Hvis ja, vennligst oppgi navn og styrke på alle dine kolesterolmedisiner:

Navn: …….. Dose: ……. mg

Navn: …….. Dose: ……. mg

Bruker du kolesterolmedisin av typen PCSK-9 hemmer?
Ja…… Nei……..

Opplever du bivirkninger når du tar dine kolesterolmedisiner i dag?

Nei…… Ja ……

I så fall kan du beskrive hvilke bivirkninger? ……

……

MUSKEL SYMPTOMER OG PLAGER

Har du vært plaget med symptomer (smerter, ømhet, svakhet, stivhet, kramper) fra muskler den siste måneden?

Generelle symptomer i hele kroppen? (sett ring rundt det tallet som beskriver dine plager best)

Ingen symptomer 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Symptomer fra hofte og lår? (sett ring rundt det tallet som beskriver dine plager best)

Ingen symptomer 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Symptomer fra leggene? (sett ring rundt det tallet som beskriver dine plager best)

Ingen symptomer 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Symptomer fra skuldre og nakke? (sett ring rundt det tallet som beskriver dine plager best)

Ingen symptomer 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Symptomer fra rygg? (sett ring rundt det tallet som beskriver dine plager best)

Ingen symptomer 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig

Vennligst sett ring rundt det tallet som best beskriver de sterkeste muskelplagene du har hatt i løpet av de siste 24 timer:

Ingen smerter 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelig smerter

Hvilken behandling eller medisiner får du for å lindre smertene dine?

……..

……

……

I hvor stor grad har behandling eller medisiner lindret smertene dine de siste 24 timene?

Vennligst sett en ring rundt det prosenttallet som best viser hvor stor smertelindring du har fått:

Ingen lindring 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Fullstendig lindring

Vennligst beskriv smertene dine i løpet av siste uke

Sett ett kryss i en rute på hver linje

	Ingen	Mild	Moderat	Sterk
1. Pulserende	0 ☐	1 ☐	2 ☐	3 ☐
2. Ilende	0 ☐	1 ☐	2 ☐	3 ☐
3. Stikkende	0 ☐	1 ☐	2 ☐	3 ☐
4. Skarp	0 ☐	1 ☐	2 ☐	3 ☐
5. Krampelignende	0 ☐	1 ☐	2 ☐	3 ☐
6. Gnagende	0 ☐	1 ☐	2 ☐	3 ☐
7. Varm/brennende	0 ☐	1 ☐	2 ☐	3 ☐
8. Verkende	0 ☐	1 ☐	2 ☐	3 ☐
9. Tyngende	0 ☐	1 ☐	2 ☐	3 ☐
10. Øm	0 ☐	1 ☐	2 ☐	3 ☐
11. Sprengende	0 ☐	1 ☐	2 ☐	3 ☐
12. Trettende/utmattende	0 ☐	1 ☐	2 ☐	3 ☐
13. Kvalmende	0 ☐	1 ☐	2 ☐	3 ☐
14. Skremmende	0 ☐	1 ☐	2 ☐	3 ☐
15. Uutholdelig	0 ☐	1 ☐	2 ☐	3 ☐

Vurder dine muskelsymptomer i løpet av siste uke

Den følgende linja står for smerte av økende intensitet fra ”ingen symptomer” til ”verst tenkelige symptomer”. Sett en strek (|) tvers over linja som beskriver smerten din i løpet av siste uke.

Ingen symptomer — Verst tenkelig symptomer

Medisiner

Bruker du lette smertestillende medisiner av typen paracet eller ibux?

ja, hver dag ☐ ja, av og til ☐ nei ☐

Bruker du sterke smertestillende medisiner (tramadol, paralgin forte, morfin)?

ja, hver dag ☐ ja, av og til ☐ nei ☐

Tusen takk for at du tok deg tid til å svare på disse spørsmålene

15.3. APPENDIX C – Patient diary with self-reported questionnaire to be completed during the treatment periodes

Please refer to the attached document.

15.4. APPENDIX D – Phone guide to patients for weekly safety assessment

Følgende spørsmål skal stilles til alle pasienter når disse kontaktes av lokal studiesykepleier ukentlig etter randomisering

1. Har du tatt alle dine studiemedisiner som foreskrevet?
2. Er dine muskelplager så sterke at du ikke ønsker å fortsette i studien?
3. Har du merket hjertesymtpomer slik som brystsmerter eller tung pust?

15.5. APPENDIX E – Drug label IMP and signed agreements with the pharmacies

The regular labelling for atorvastatin mylan 40 mg (No 100) will used. In addition, the following text will be applied to the front of each packet "MUSE oppfølgingsstudien. Til klinisk utprøvning v/ Dr. John Munkhaugen, Drammen sykehus, tlf 97524194 ID nummer..». Below the drug labeling proposal is shown:

Etikettforslag MUSE oppfølging Studiekode: 2019-003959-11

TIL KLINISK UTPRØVING
ID nummer
v/ Dr. John Munkhaugen
Drammen sykehus
Tlf. 97524194

100 filmdrasjerte tabletter Varenummer: 403512
Atorvastatin Mylan 40 mg
Pasient ID…….
Boks 1 av 1
Utlevert dato……..
BRUKSANVISNING
1 tablett daglig
Tas mellom kl 0700 og 1000
Oppbevares tørt og beskyttes mot lys i utleveringsembalasjen og ved temp. mellom +15-25 grader Celsius
Oppbevares utilgjenglig for barn

The signed agreements with the pharmacies at Drammen and Vestfold are shown below:¨

A signed agreement with the pharmacies at the hospitals in Drammen and Vestfold will made prior to study start.

15.6. APPENDIX F – Biobank procedure

RR HF

Instruction to the users: This template is a guide

Generell informasjon

- Studieoppfølging av pasienter i MUSE RCT 2019. Inklusjon av pasienter som er klassifisert med SAMS v/atorvastatin 40 mg og pasienter klassifisert med non-SAMS (ikke signifikant forskjell mellom atorvastatin 40 mg og placebo).

- Blodprøver tas ved tre visitter:
    - Visitt 1, baseline
        - T0 Blodprøver til medisinsk-biokjemisk analyse
        - T0 Blodprøver til biobank
    - Visitt 2, uke 8 (med atorvastatin)
        - T0 Prøver til medisinsk-biokjemisk analyse
        - T0 Muskebiopsi til patologisk undersøkelse og biobank
        - *T0, T1, T2 Blodprøver til biobank
    - Visitt 3, uke 16 (uten atorvastatin)
        - T0 Prøver til medisinsk-biokjemisk analyse
        - T0 Muskelbiopsi til patologisk undersøkelse og biobank
        - *T0, T1, T2 Blodprøver til biobank

    - Dersom pasienter ønsker å slutte ila. studien skal det tilstrebes å gjennomføre en fremskyndet visitt med standardisert prøvetaking
      = visitt 2 (T0, T1, T2, T3) eller visitt 3 (T0)

- Visitt 1, 2 og 3: Pasientene skal møte medikamentfastende (dvs. uten å ha tatt morgendosene av medisiner) slik at T0-biopsi og blodprøve kan tas i tidsrommet kl 8-11.
  T0-blodprøve tas tettest mulig opp til tidspunkt for biopsi på visitt 2 og 3.
  NB: Pasientene skal møte uten å ha spist på morgenen. De skal faste inntil siste prøve er tatt (ved visitt 2 innebærer det at pasientene skal vente med å spise til T3-prøve er tatt). De kan drikke vann.

- Visitt 2 og 3: T1, T2 og T3-prøve tas 1, time 2 timer og 3 timer (±10 min) etter dose
    - Registrere nøyaktig tidspunkt for dose dagen før, dose på visittdagen, samt tidspunkter for biopsi (tt:mm)

- Praktisk ifb. prøvehåndtering
    - Man kan bruke den type prøvetakingsglass som er standard på de respektive steder.
    - Alikvotering i cryo-rør med tilpasset volum (fortrinnsvis 0.5 mL eller 2 mL polypropylen)
    - Bruk separate esker for hver type materiale (eks. EDTA-blod, plasma, serum, celler)
    - Alt alikvotert materiale til biobank fryses i ultrafryser (**- 80 °C**)

Visitt 1 (uke 0) Baseline	Visitt 2 (uke 8)	Visitt 3 (uke 16)
T0: Medisinsk biokjemi	T0: Medisinsk biokjemi	T0: Medisinsk biokjemi
T0: Biobanking (blod)	T0: Patologi og biobanking (muskel, blod)	T0: Patologi og biobanking (muskel, blod)
	T1, T2, T3: Biobanking (blod)	

Medisindose tas i tidsrommet kl 8-11. Pasientene møter fastende (mht. medisin og mat).
Medisinsk biokjemi: HbA1C, hemoglobin, hs-CRP, kreatinin, eGFR, CK, ALAT, ASAT, LD, total protein, albumin, INR, lipid profil (total kolesterol, HDL-kolesterol, LDL-kolesterol), leukocytter
Patologi: Morfologi og histologi i muskelvev.
Biobank: Legemiddelanalyser, biomarkører (DNA, RNA, proteiner, peptider, lipider, metabolitter).

- NB: Prosedyren som følger nedenfor gjelder kun blodprøver til biobanking (dvs. ikke T0-prøver til medisinsk-biokjemiske analyser som spesifisert i tabellen ovenfor.
    - Medisinsk-biokjemiske analyser utføres fortløpende ved lokalt sykehuslaboratorium
    - Muskelbiopsier og videre håndtering av disse følger separat prosedyre.

Merking og sporing av prøver som skal lagres i biobank

- Sykehus kode
    - D = Drammen, V = Vestfold
- Pasientnr (XXX)
- Visitt nr X
    - (X=1 ved baseline, X=2 ved visitt 2 osv.)
- Type materiale
        - EDTA-fullblod (EDTA-B), lilla farge
        - EDTA-plasma (EDTA-P), lilla farge
        - Serum, rød farge
        - PAX RNA, grå farge

        - Celler pellet (PBMC)
        - Celler suspensjon (PBMC-PBS)
        - Celler RNA-stabilisert (PBMC-RNA)

        - Merking med farge brukes dersom det er mer praktisk enn å bruke tekst

- **Merking av <u>esker</u>** (fortrinnsvis 10x10 esker)
    - MUSE
    - Sykehus kode: D eller V
    - Visitt: 1, 2 eller 3

- Materiale: EDTA-B, EDTA-P, serum eller celler

- ~~o~~ Eksempel på merking av eske:
  MUSE
  EDTA-P
  D
  Visitt 3

- **Merking av alikvoterte rør:**

*Eksempel A: Pasientnr. 12, **visitt 1**, T0, Drammen sykehus, EDTA-plasma*

- Alternativ 1
  Studie; sykehus - pasient – visitt – tidspunkt mht. dose; materiale
  - MUSE
  - D-12-1-T0
  - EDTA-P (evt. lilla farge, tilsvarende rød og blå)

- Alternativ 2
  - MUSE
  - Sykehus: D
  - Pasient: 12
  - Visitt: 1
  - Tidspunkt: T0
  - EDTA-P (evt. lilla farge)

*Eksempel B: Pasientnr. 12, **visitt 2**, **T2**, Drammen sykehus, celler*

- Alternativ 1
  Studie ; sykehus – pasient - visitt – tidspunkt mht. dose; materiale
  - MUSE
  - D12-2-T2
  - Celler (evt. blå farge)

- Alternativ 2
  - MUSE
  - Sykehus: D
  - Pasient: 12
  - Visitt: 2
  - Tidspunkt: T2
  - Celler (evt. blå farge)

- **Prøvetakingsliste** (eget Excel-ark: MUSE-biobank_Prøvetakingsliste_Sykehusnavn.xls)

Prøvehåndtering og alikvotering

Tabellene angir hvilke prøveglass som skal tas, samt hvordan prøvene skal prosesseres. Alt alikvotert materiale lagres i ultrafryser (-70/80 °C). Ikke bruk rør som er større enn 2 mL til alikvotering (rørene fylles maks ca. 80% ved alikvotering).

- Fullblod homogeniseres (vendes) før eventuell alikvotering.
- Celler isoleres og alikvoteres etter egen prosedyre (på Rikshospitalet)
- Prøve til plasma (samt avpipettert plasma) holdes kjølig hele tiden og det tilstrebes å fryse innen 1 time etter prøvetaking
- Serum fryses så snart som mulig, det tilstrebes innen 2 timer etter prøvetaking
- PAX-rør skal stå vertikalt ved romtemperatur i 2 timer, deretter fryses de direkte

Blodprøver til biobank

Visitt 1: Uke 0, baseline

Tid	Prøveglass	Type	Farge	Temp.	Sentrifugering	Fordeling
T0 Biobank	1 x 5mL	EDTA u/gel	Lilla	RT	Ingen	Fullblod: x 2 aliq (DNA/genetikk)
	1 x 5mL	EDTA u/gel	Lilla	På is	Kjøl *(2500 rct, 15 - 20 min)*	Plasma: x 4 aliq (minst 250 uL per alikvot)
	1 x 5mL	Uten tilsetning, u/gel	Rød	RT	Henstand ca. 30 min, vanlig *(2000 rct 10-15 min)*	Serum: x 4 aliq (minst 250 uL per alikvot)

- *T0: I tillegg kommer standard prøveglass til medisinsk-biokjemiske analyser som rekvireres og analyseres som vanlige prøver.*

Visitt 2: Uke 8 (med atorvastatin)

Tid	Prøveglass	Type	Farge	Temp.	Sentrifugering	Fordeling
T0, T1, T2, T3 Biobank	1 x 5mL	EDTA u/gel	Lilla	Kjøl	Ingen. Leveres til RH (transporteres i kjølebag)	RH: Celler: x 4 aliq (+1 aliq RNA-stabilisert)
	1 x 5mL	EDTA u/gel	Lilla	På is	Kjøl *(2500 rct, 15 - 20 min)*	Plasma: x 4 aliq (minst 250 uL per alikvot)
Ekstra ved T0 Biobank	1 x 5mL	Uten tilsetning, u/gel	Rød	RT	Henstand ca. 30 min, vanlig *(2000 rct 10-15 min)*	Serum: x 4 aliq (minst 250 uL per alikvot)
	1 x 2-3 mL	EDTA u/gel	Lilla	RT	Ingen	Fullblod: x 2 aliq (epigenetikk)
	1 x 3mL	PAX RNA	Grå	RT	Ingen (2 timer henstand v/RT)	Ingen, fryses direkte (RNA)

- *T0: I tillegg kommer standard prøveglass til medisinsk-biokjemiske analyser som rekvireres og analyseres som vanlige prøver.*

Visitt 3: Uke 16 (uten atorvastatin)						
Tid	Prøveglass	Type	Farge	Temp.	Sentrifugering	Fordeling
T0 Biobank	1 x 5mL	EDTA u/gel	Lilla	Kjøl	Ingen. Leveres til RH (transporteres i kjølebag)	RH: Celler: x 4 aliq (+1 aliq RNA-stabilisert)
	1 x 5mL	EDTA u/gel	Lilla	På is	Kjøl *(2500 rct, 15 - 20 min)*	Plasma: x 4 aliq (minst 250 uL per alikvot)
T0 Biobank	1 x 5mL	Uten tilsetning, u/gel	Rød	RT	Henstand ca. 30 min, vanlig *(2000 rct 10-15 min)*	Serum: x 4 aliq (minst 250 uL per alikvot)
	1 x 2-3 mL	EDTA u/gel	Lilla	RT	Ingen	Fullblod: x 2 aliq (epigenetikk)
	1 x 3mL	PAX RNA	Grå	RT	Ingen (2 timer henstand v/RT)	Ingen, fryses direkte (RNA)
• *T0: I tillegg kommer standard prøveglass til medisinsk-biokjemiske analyser som rekvireres og analyseres som vanlige prøver.*						

Dersom pasienter ønsker å slutte ila. studien skal det tilstrebes å gjennomføre en fremskyndet visitt med standardisert prøvetaking tilsvarende visitt 2 (T0, T1, T2, T3) eller visitt 3 (T0) før de avslutter. Da inkluderes også prøver til medisinsk-biokjemiske analyser.

Analyser som rekvireres i DIPS

- Prøver til medisinsk biokjemi tas ved T0 på alle visitter (baseline, uke 8 og uke 16).
  Prøver fra Vestfold som skal til Medisinsk-biokjemi i Drammen, fryses og sendes i batch.

Analyse	Kommentar	Lab
HbA1C	Fortløpende analyse	Vestfold, Drammen
Hemoglobin		
Leukocytt-telling		
CK	Fortløpende analyse (safety)	
ALAT		
hs-CRP	Sendes fra Vestfold til Drammen	Drammen
Kreatinin		
eGFR		
ASAT		
LD		
Albumin		
INR		
Total protein		
Ikke-fastende lipid profil:		
Total kolesterol	Sendes fra Vestfold til Drammen	Drammen
HDL-kolesterol		
LDL-kolesterol		

15.7. APPENDIX G – Pharmaceutical and chemical documentation atorvastatin

Please see the SPC at https://www.felleskatalogen.no/ir/medisin/spc-atorvastatin-mylan-612079

15.8. APPENDIX I – LAF -patient insurance

LEGEMIDDELANSVARSFORENINGEN

Sekretariat: Advokat Gunnar Sørlie
Advokatfirmaet BAHR AS
Postboks 1524 Vika, NO-0117 Oslo
Tlf: + 47 21 00 00 50
Organisasjonsnummer: 979 218 141
www.laf.no
Epost: unedv@bahr.no

John Munkhaugen
Medisinsk avdeling
Drammen sykehus

Kun sendt per epost: johmun@vestreviken.no

Oslo, 14. april 2020

Vår ref: #9207103/1

BEKREFTELSE AV MEDLEMSKAP FOR KALENDERÅRET 2020

Vi bekrefter med dette at De har tegnet medlemskap i Legemiddelansvarsforeningen ved å betale premietilskudd for kalenderåret 2020 i forbindelse med klinisk legemiddelforsøk.

De har opplyst å stå bak et forsøk benevnt "*MUscle Side-Effects of atorvastatin in coronary patients (MUSE) -a randomized controlled trial.*"

Medlemskapet er tegnet til å gjelde klinisk legemiddelforsøk på 50 pasienter (minste-kontingenten) kalenderåret 2020. Dersom forsøket går utover det kalenderår medlemskapet gjelder for, må medlemskap fornyes.

Medlemskapet innebærer at det kliniske legemiddelforsøk, som gjennomføres av Dem eller av andre i Deres regi, omfattes av den obligatoriske forsikringsordning i henhold til kapittel 3 i produktansvarsloven av 23.12.88 nr 104.

Med vennlig hilsen
for LEGEMIDDELANSVARSFORENINGEN

Unni Edvardsen /s/

15.9. **Appendix J – Inclusion criteria in the previous MUSE -trial (Eudract nr. 2018-004261-14)**

18 years or older

First or recurrent diagnosis (myocardial infarction) or treatments (PCI or CABG) for a CHD event 6-36 months prior to study start and prescribed atorvastatin (irrespective of dose)

Reporting muscle complaints (i.e. pain, weakness, tenderness, stiffness or cramp) that they attribute to atorvastatin therapy or atorvastatin discontinuation due to muscle complains

Signed informed consent and expected cooperation of the patient according to ICH/GCP and national/local regulations

15.10. APPENDIX K – Approval Regional Committee of Ethics

REK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst A	Tove Irene Klokk	22845522	25.05.2020	54041
			Deres referanse:	

John Munkhaugen

54041 Muskelbivirkninger ved bruk av atorvastatin hos koronarpasienter

Forskningsansvarlig: Vestre Viken HF

Søker: John Munkhaugen

Søkers beskrivelse av formål:

Formålet er å fremskaffe ny patofysiologisk kunnskap om muskelbivirkninger ved statinbruk og utvikle en diagnostisk test som kan identifisere pasienter med reelle bivirkninger. Pasienter med koronarsykdom med og uten reelle muskelbivirkninger i den randomiserte kontrollerte MUSE studien blir invitert til denne observasjonelle oppfølgingsstudien. Studiedata registreres fra en pasientdagbok, fra blodprøver og muskelbiopsier. Data skal analyseres med velkjente statistiske metoder. Muskelbivirkninger er den viktigste enkeltårsaken til at koronarpasinter avslutter statinbehandlingen midlertidig eller permanent. Dette har betydelige kliniske og helseøkonomiske konsekvenser. En test som identifiserer reelle muskelbivirkninger vil potensielt gi klinikere ett nytt verktøy til å skreddersy statinbehandling til pasientenes individuelle farmakoklogiske profil. Studien vil også gi helt ny patofysiologisk kunnskap om muskelbivirkninger ved bruk av statiner.

REKs vurdering

Kristine K. Sahlberg ble erklært inhabil og deltok ikke i behandlingen av saken.

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt (EudraCT. no. 2019-003959-11). Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst A) i møtet 30.04.2020. Vurderingen er gjort med hjemmel i helseforskningslovens § 10.

Formålet med prosjektet er å framskaffe ny kunnskap om årsaker til muskelbivirkninger ved bruk av statiner, samt å utvikle en biologisk diagnostisk test for å påvise muskelbivirkninger.

Personer med koronarsykdom behandles ofte med statiner, og bruk av statiner reduserer risikoen for alvorlig sykdom og død i denne pasientgruppen. En av ti som behandles med statiner opplever muskelbivirkninger, og slike bivirkninger er den viktigste årsaken til at pasienter slurver eller slutter helt å ta statiner. Det er derfor viktig å fremskaffe mer kunnskap om muskelbivirkninger ved bruk av statiner, og å kunne identifisere de pasientene med muskelbivirkninger.

på grunn av atorvastatin, og inntil 20 pasienter hvor muskelbivirkninger ble avkreftet i en tidligere RCT, kalt MUSE (REK 2018/2302). Disse pasientene skal undersøkes på nytt med klinisk undersøkelse, blodprøver og muskelbiopsier etter inntil 7 ukers behandling med atorvastatin, etterfulgt av 7 uker uten slik behandling. Blodprøver tas ved prosjektstart og deretter to ganger, mens muskelbiopsi (fra lårmuskel) tas to ganger. Prøvene skal analyseres for ulike proteiner, og i tillegg skal det gjøres DNA og RNA analyser som er relatert til legemiddelomsetning av artovastatin og muskelbivirkninger.

Deltakerne blir i tillegg bedt om å avgi blod og muskelvev til den generelle forskningsbiobanken NOR-COR (REK 2013/2193).

Komiteen mener dette er et nyttig prosjekt som kan være til fordel for pasientgruppen. Ulempen med å delta er blodprøvetaking og spesielt muskelbiopsi som kan gi smerter. Deltakerne får god informasjon om dette, og komiteen mener studien er forsvarlig å gjennomføre. Det opplyses om at biologisk materiale som samles inn skal lagres i den generelle biobanken NOR-COR, og i informasjonsskrivet er det separat avkrysning for om man samtykker til slik lagring av prøver. Dette er en generell biobank basert på et bredt samtykke til fremtidig forskning på ubestemt tid. Komiteen mener derfor at deltakerne skal forelegges et eget samtykke for NOR-COR biobanken, i tillegg til samtykke for prosjektet, slik at det fremgår tydelig at dette er to separate formål. Deltakerne kan da samtykke til lagring i biobank uavhengig av deltakelse i studien.

Komiteen godkjenner derfor prosjektet på vilkår om at deltakerne forelegges et separat samtykke for lagring av biologisk materiale i den generelle biobanken NOR-COR, og at dette ikke er en forutsetning for deltakelse i denne studien.

Vedtak

Godkjent med vilkår

REK har gjort en helhetlig forskningsetisk vurdering av alle prosjektets sider. Prosjektet godkjennes med hjemmel i helseforskningsloven § 10, under forutsetning av at ovennevnte vilkår er oppfylt.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Godkjenningen gjelder til 20.12.2024.
Komiteens avgjørelse var enstemmig.

Av dokumentasjonshensyn skal opplysningene oppbevares i 15 år etter prosjektslutt. Opplysningene skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres.

15.11.APPENDIX L – Approval the National Medical Agency

Vestre Viken HF
Sykehuset Buskerud
3004 DRAMMEN

John Munkhaugen

Unntatt offentlighet jf.
Offl §13 første ledd, jf. fvl. §13 første ledd nr2, jf. lml. §30

Deres ref.:	Dato:	Vår ref.:	Saksbehandler:
	05.05.2020	20/04280-10	Beate Rindal

KLINISK STUDIE – ATORVASTATIN (MYLAN®) – EUDRACT NR. 2019-003959-11

Vi viser til korrespondanse i ovenfor nevnte sak, senest vårt brev, datert 2020-04-17 og deres brev, datert 2020-05-04.

Vurdering av studien er gjort med hjemmel i § 1-4 og kapittel 4 i *Forskrift om klinisk utprøving av legemidler til mennesker av 30 oktober 2009*.

Våre spørsmål er tilfredsstillende besvart og vi har ingen ytterligere kommentarer.

Konklusjon: Studien er godkjent.

Vi ønsker lykke til med prosjektet og ser frem til å motta årsrapport og/eller sluttrapport når disse foreligger.

Vi gjør oppmerksom på at godkjennelsen ikke omfatter eventuelle tillatelser til tilvirkning og/eller innførsel til Norge.

Legemiddelverkets vedtak kan påklages, jf. forvaltningsloven § 28. En eventuell klage sendes til Legemiddelverket. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29. Mer informasjon om klageadgang, samt skjema finnes her.

Vennlig hilsen
Statens legemiddelverk

Anna Randby, MD, PhD
Seniorrådgiver/klinikkutreder

Beate Rindal, MSc
Forsker, koordinator

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