MUscle Side-Effects of atorvastatin in coronary patients (MUSE) -a randomized controlled trial

Protocol Identification Number: MUSE

EudraCT Number: 2018-004261-14

SPONSOR: **Vestre Viken Trust**

Research Director,

Bjørn Rishovd Rund

Postboks 4956 Nydalen

3004 Drammen

Tel : +47 957 78 094

E-mail: bjørn.r.rund@vestreviken.no

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CONTACT DETAILS

Sponsor:	**Vestre Viken Trust** **Research Director, Bjørn Rishovd Rund** Address Postboks 800, 3004 Drammen Tel : +47 957 78 094 E-mail: bjørn.r.rund@vestreviken.no
Study Chair	**Vestre Viken Trust, Drammen hospital** **MD, PhD. John Munkhaugen** Address Postboks 800, 3004 Drammen Tel: +47 975 24 194 E-mail: johmun@vestreviken.no
Principal investigator at Site 1:	**Vestre Viken Trust, Drammen hospital** **MD, PhD. John Munkhaugen** Address Postboks 800, 3004 Drammen Tel: +47 975 24 194 E-mail: johmun@vestreviken.no
Principal investigator at Site 2	**Sykehuset i Vestfold** **MD, PhD Jan Erik Otterstad** Address Postboks 2168 3103 Tønsberg Tel: + 47 916 62 603 E-mail: jan.erik.otterstad@siv.no
Coordinating monitoring unit:	**Department of research, Vestre Viken Trust** Address: Postboks 800, 3004 Drammen
Sponsor's Medical Officer	John Munkhaugen
Steering Committee	John Munkhaugen (Chair) (Drammen) Oscar Kristiansen (VV) Nils Tore Vethe (co-Chair and WP-leader pharmacology, OUS) Jan Erik Otterstad (Senior Study Chancellor, Tønsberg / SiV) Toril Dammen (WP leader psychosocial factors, UiO) Morten Wang Fagerland (study statistician, OUS)

	Einar Husebye (VV)
Executive Steering Committee	John Munkhaugen (Chair) (Drammen) Nils Tore Vethe (co-Chair, OUS) Jan Erik Otterstad (Senior Study Chancellor, Tønsberg / SiV) Toril Dammen (UiO) Stein Bergan (OUS) Lars Gullestad (UIO/OUS) Oscar Kristiansen (VV) Elise Sverre (VV) Elena Kvan (VV) Morten Lindberg (SiV) Kari Peersen (SiV) Lars Gullestad (UIO/OUS) Erik Gjertsen (VV) Morten Wang Fagerland (OUS) Einar Husebye (VV) Joep Perk, Linneus University, Sweeden

SIGNATURE PAGE

Title: **Muscle Side-Effects of atorvastatin in coronary patients (MUSE).**

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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
John Munkhaugen	MD PhD	Principal Investigator and Study Chair	(e-sign)	10.01.19
Nils Tore Vethe	PhD	Study Co-Chair WP leader, pharmacology	(e-sign)	10.01.19
Jan Erik Otterstad	MD PhD	Senior Study Chancellor	(e-sign)	10.01.19
Einar Husebye	MD PhD	Member of Executive Steering Group	(e-sign)	10.01.19
Oscar Kristiansen	MD	PhD candidate (study physiscan)	(e-sign)	10.01.19
Morten Wang Fagerland	PhD	Study statistician	(e-sign)	10.01.19
Toril Dammen	MD PhD	WP leader, psychosocial factors	(e-sign)	10.01.19

SIGNATURE PAGE, PRINCIPAL INVESTIGATOR / COORDINATING INVESTIGATOR

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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:

John Munkhaugen	MD, PhD.	e-sign	10.01.19

Name	Title	Signature	Date

PROTOCOL SYNOPSIS

Protocol title: **Muscle Side-Effects of atorvastatin in coronary patients (MUSE) -a randomized clinical trial**

Sponsor	Vestre Viken Trust, Drammen Hospital
Phase and study type	Prospective, randomized double-blinded placebo controlled cross-over phase 4 study.
Investigational Medical Product (IMP) (including active comparator and placebo):	The study aims to compare muscle symptoms during treatment with atorvastatin 40 mg x1 and matched placebo in coronary heart disease (CHD) patients with subjective statin associated muscle symptoms (SAMS).
Centers:	Two hospitals (Drammen and Vestfold) in Norway
Study Period:	Estimated date of first patient enrolled: 1-MAR-2019 Anticipated recruitment period: 6 months Estimated date of last patient completed: 31-DES-2019
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 of the study is to identify, and confirm pharmacologically, true SAMS (definition: at least a 25% higher muscle symptom intensity during the treatment period of atorvastatin than placebo) in CHD patients. The primary objective is to estimate the effect of atorvastatin on muscular symptom intensity in coronary patients with subjective SAMS. The key secondary objectives are: 1. To determine the proportion of patients who report muscle symptoms on atorvastatin treatment compared with on placebo (dichotomous SAMS classification) 2. To determine the relationship between muscle symptom intensity and blood concentrations of parent drug and the active metabolites of atorvastatin 3. To determine the diagnostic properties of blood concentrations of parent drug and the active metabolites of atorvastatin for classification of true SAMS (dichotomous SAMS) 4. To determine the likelihood of statin discontinuation within and between the treatment periods 5. To study statin adherence between the two study arms 6. To compare blood concentrations of parent drug and the active metabolites of atorvastatin between patients with failing placebo-

test for connecting SAMS to atorvastatin and the control group without muscle symptoms.
7. To assess study safety

Explorative objectives:
1. To compare patients muscle symptom charcteristics between the two study arms
2. To study sociodemographic, clinical, and psychosocial characteristics (PROMS and clinical data) between the two study arms

Endpoints:

Primary endpoint:
The primary end-point will be the individual mean difference in muscular symptom intensity between treatment periods with statin and placebo, reported by the patients over the last three weeks (i.e. week 4-7) measured with aggregated VAS scores.

Secondary endpoints:
1. The proportion of patients who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS classification)
2. The correlation between individual mean difference in muscular symptom intensity between treatment periods with statin and placebo, reported by the patients over the last three weeks (i.e. week 4-7) measured with aggregated VAS scores, and levels of atorvastatin and its metabolites in blood plasma and white blood cells.
3. Sensitivity, specificity, and area under the curve of blood concentrations of parent drug and the active metabolites of atorvastatin for the classification of true SAMS
4. Individual mean difference in likelihood of statin discontinuation between treatment periods with statin and placebo, reported by the patients over the last three weeks (i.e. week 4-7) measured with aggregated scores on a 1-10 Likert scale.
5. Statin adherence measured with indirect (self-reported questionnaires and pill counts of returned packages) and direct (liquid chromatography-tandem mass spectrometry method) methods
6. Levels of atorvastatin and its metabolites in blood plasma and white blood cells at study end
7. Safety endpoints:
   - New-onset CHD symptoms (e.g. angina, dyspnea)
   - Intolerable muscle symptoms reported by the patient 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

Explorative endpoints:
1. Features of SAMS characterized by McGill Pain Questionnaire (SF-MPQ) and Brief Pain Inventory (BPI-SF)
2. Sociodemographic, clinical, and psychosocial factors ascertained through self-reported questionnaires, clinical examinations, and blood samples

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 questionnaires administred at study start, weekly during the 7 weeks treatment periods, and at study end
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	Self-report questionnaires, a brief clinical examination, and blood samples collected at baseline, during the treatment periods, and at study-end.
Study Design:	This is a **prospective, randomized placebo-controlled double-blinded, cross-over study**. CHD patients will be randomized to atorvastatin 40mg/day in the first period and matched placebo in the second period, or placebo in the first period and atorvastatin in the second period. Both periods consist of 7-weeks of treatment with a preceding 1-week pharmacokinetic wash-out. A control group of coronary patients on atorvastatin without a history of perceived SAMS and without other muscle symptoms will be included to study secondary objective number 6. The patients in the control group will undergo an open 7 weeks treatment period taking an atorvastatin dose similar to that used in the cross-over arms to patients with SAMS.
Main Inclusion Criteria:	• 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. • Self-reported muscle complaints (i.e. pain, weakness, tenderness, stiffness or cramp to the body of any intensity) that they attribute to atorvastatin therapy at study inclusion • Self-reported muscle complaints that has led to atorvastatin discontinuation prior to study inclusion.
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
Main entry criteria for the control group	• Entry criteria for the control group are equal to those described above except for bullet point number 2 and 3 described under the inclusion criteria. A prerequisite for participation in the control group is no history of muscle symptoms.
Sample Size:	80 patients for the randomized cross-over study, plus an additional 40 patients in a control group t that will be used to study secondary objective number 6 only
Power Calculation	Power calculations are based on our being able to detect a 1 cm difference in the VAS symptom score between the treatment periods on atorvastatin and placebo since the smallest change in VAS symptom score corresponding to 'a little more' or 'a little less' symptoms was 1.3 cm, with a lower limit of the CI at 1 cm in a previous study.(23) Gallagher et al. (23) report a standard deviation (SD) of 1.7 for a difference of 1.0 between two VAS symptom scores. Because of the differences in both populations and specific VAS scale between that study in this one, we use SD=2.5 to account for a much larger variation in this study. With n=68, we shall will have 90% power to detect a difference of 1.0, using a one-sample T test. With n=68, we will also have 80% power to detect a difference of 40% SAMS under statins vs. 15% SAMS under placebo, using the McNemar test for paired probabilities. To account for some missing information data due to drop-outs or and protocol deviations, we plan to include (40x2) 80 patients.
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 patinets. 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 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 all other continuous outcomes will be estimated with linear regression models with the stratification factors in the randomization (i.e. centre and previous statin discontinuation) as covariates.

	Dichotomous outcomes will be analysed with conditional logistic regression models with treatment, centre, and previous statin discontinuation as covariates. Methods for analysis of ROC curves and measures of diagnostic accuracy will be used to identify cut-off values of metabolite concentrations that can discriminate between confirmed SAMS from other muscle symptoms. The correlations between individual mean difference in muscular symptom intensity between treatment periods with statin and placebo and levels of atorvastatin and its metabolites in blood plasma and white blood cells will be estimated with Spearman correlation coefficients and linear regression analyses. Oslo Centre for Biostatistics and Epidemiology (OCBE) is responsible for all statistics. A statistical analysis plan (SAP) describing all details in this respect will be produced prior to database lock.
Safety analysis	Deue 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.

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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
LCMS-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

5 INTRODUCTION

5.4 Background

Statins are the cornerstone drug treatment to reduce low-density lipoprotein cholesterol (LDL-C) with improvement of cardiac outcomes in coronary heart disease (CHD) patients. (1, 2) Statins are cost-effective (3) and recommended with the highest level of evidence in international guidelines. (1, 2) Statin treatment in CHD patients is, however, far from optimal in clinical practice. Both international (4) and our own data from the NORwegian-CORonary Prevention Study (5) have revealed that 7-12% of the CHD patients did not use statin therapy at all, whereas 57-80% of those on statin therapy still have elevated LDL-C levels above the recommended target level of 1.8 mmol/L. Statin side-effects, mainly statin-associated muscle symptoms (SAMS), low statin adherence, and low statin doses have been reported as major independent determinants of unfavourably elevated LDL-C.(5) SAMS is one of the principal reasons for statin non-adherence and discontinuation leading to adverse cardiac outcomes.(6, 7), influence the patient's quality of life, and may adversely affect health-related variables such as physical activity, muscle strength and ability to perform activities of daily living. (6, 7)

Serious statin adverse-effects, including liver failure or myopathy with significantly elevated levels of creatine kinase in blood, are rare. (6, 7) Furthermore, side-effects are only reported in a minority (i.e. 1-5%) of CHD patients participating in randomized placebo-controlled statin trials.(8) SAMS, however, comprises a heterogeneous group of muscle symptoms including pain, aching, stiffness, tenderness or cramps, usually with normal or minimally elevated creatine kinase levels, amounts to 20-30% in observational studies (9). Strict entry criteria in the randomized trials, excluding patients with potentially polypharmacy, multiple comorbidities, elderly, females and low body weight, all factors that predispose to musculoskeletal symptoms, may in part explain variations in frequency of SAMS among these populations. (6, 7) A major limitation of observational studies is the lack of blinding. Patients on statins may expect side-effects, and therefore report a higher percentage of SAMS than untreated patients, the so-called 'nocebo' effect. In a population-based randomized, double-blinded cross-over study of patients complaining of SAMS at study start, only 36% experienced that their muscle symptoms persisted during treatment with simvastatin 20 mg and disappeared during placebo treatment.(10) Accordingly, SAMS was confirmed to be related to the statin treatment (i.e. true SAMS) in only one-third of the patients. The prevalence of confirmed SAMS in a CHD population, treated with potent statins according to the guidelines, (1, 2) remains unknown. (6)

Patients with psychosocial distress may be at increased risk of misattributing their symptoms to statins or being hypervigilant to true adverse effects of statins such as muscle pain.(11) In a randomized placebo-controlled atorvastatin trial in patients without cardiovascular disease and depression, depression scores within normal range did not predict changes in muscle pain severity between the atorvastatin and placebo group after 6 months follow-up. (12) Anxiety symptoms have been associated with non-adherence to statin therapy and with increased pain perception, in general.(13) Type D personality is associated with pain perception, pain inference, and musculoskeletal pain.(14) The relationship between these psychosocial factors and SAMS remains to be investigated.

It remains unclear how statins may produce muscle symptoms. Individual variations in statin pharmacokinetics, mitochondrial dysfunction, and vitamin D or coenzyme Q10 deficiency are suggested mechanisms for SAMS. (15) Reliable diagnostic biomarkers for the prediction or diagnosis of SAMS are not yet available. (6, 7) A few studies indicate that pharmacokinetic alterations in statin metabolites may contribute to SAMS. (16-18) The lactone metabolites of statins seem to be more potent in inducing myotoxic effects compared to the corresponding acid metabolites. Plasma concentrations of atorvastatin lactones have been associated with clinical muscle symptoms.(17, 18) Accordingly, the lactones inhibit the mitochondrial complex III enzyme activity, thereby reducing the respiratory capacity in muscle cells.(19). We have recently developed and validated a fast, sensitive, and reliable LC-MS/MS method for precise quantification of atorvastatin and its major lactone and acid metabolites in blood.(20) We have also included the acyl glucuronide of atorvastatin as acyl glucuronide metabolites of drugs in general are associated with

toxicity.(21) Atorvastatin or metabolite levels have previously not been investigated as diagnostic markers of SAMS, under randomized, controlled conditions.

The overall objective is to provide new clinical and pathophysiologic knowledge of SAMS in CHD patients that enables reliable detection of statin related SAMS and SAMS unrelated to statins. A novel LC-MS/MS method for quantification of atorvastatin and its major lactone and acid metabolites in blood (20) will be applied. Distinction of true SAMS in clinical practice may improve the management of CHD by personalized statin treatment and monitoring and subsequently improved lipid control compared to current practice.

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

New knowledge of SAMS and the identification of diagnostic biomarkers are raised as major needs to improve lipid management in European and US guidelines (1, 2) and in Consensus documents. (6, 7) The study will address the major criticisms in previous evidence in studies of SAMS. The study is double-blinded and placebo-controlled and will thus confirm whether the patients muscle symptoms are truly related to the statin therapy or not. Additionally, the within-patient comparisons of muscle symptoms experienced while on placebo versus statin along with measurement of statin- and metabolite levels, will enable us to determine the relationship between these blood levels and muscle symptoms in patients with versus without true statin side-effects.

This is the first randomized study to test the reproducibility of SAMS with assessment of objective pharmacological markers. The LC-MS/MS method developed for quantifications of atorvastatin and metabolites demonstrated to be accurate and precise over wide concentration ranges, and the lactone instability was controlled during the pre-analytical and analytical phases.(13) In addition, the study provides new knowledge about the clinical and psychosocial characteristics of patients with and without true SAMS. Our pilot data (Section 6.1.4) demonstrate that blood levels of atorvastatin metabolites are significantly higher in patients with subjective SAMS compared to those without SAMS. The present randomized placebo-controlled study, enables us to determine the relationship between atorvastatin metabolite levels and muscle symptom intensity in patients with and without confirmed SAMS, and potentially pave the way for diagnostic testing of confirmed SAMS. In turn, this will identify patients in need of altered statin therapy or doses reduction due to intolerable side-effects and thus contribute to individualize statin treatment. Pharmacological data will facilitate to communicate to patients the role that statin drugs play for their muscle symptoms. Thus, alternative explanations for the patents complains may be elucidated. In turn, such a tool may prevent statin discontinuation, facilitate change of drug when indicated, and improve adherence. By adding a control group without muscle symptoms, we can also reveal whether atorvastatin and metabolites concentrations in study participants without confirmed SAMS are in line with blood concentrations in patients without muscle symptoms. The latter is of importance for the external validity of the study results.

In 2014, Norwegian patients and health welfare spent 263.3 million NOK on statin therapy (14). Sufficient doses and adequate adherence are thus of major importance. The recent introduction of new, expensive drugs to target subclinical inflammation (e.g. canacinumab) (15) and to lower lipids (e.g. PSCK-9 inhibitors) (16), increases the relevance of this study. Costs of PSCK-9 inhibitors are substantially higher than currently used statins. Therefore, optimizing treatment and adherence with cost-effective (3) statins is of outmost importance for the healthcare system. The study results are likely to translate to statin therapy in primary prevention. The potential impact on public health care is thus substantial

5.6 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 (1, 2) 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. (22) To our best knowledge, only two previous randomized studies that have investigated the risk associated with a short time statin withdrawl. Heeschen and colleagues (23) 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(24). 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.(25) 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.(26) 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 curical 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 placebo 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 signifificant 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.

The greatest benefit will be to answer to what extent SAMS are caused by atorvastatin or not in CHD patients. Furthermore, if objective diagnostic markers of SAMS caused by statins are identified, treatment and monitoring for the most prescribed drug worldwide will be significantly improved.

5.7 Study Hypotheses

Based on evidence from a previous randomized double-blinded study in a primary preventive population (10), the primary hypothesis is that 30-40% of the patients will report SAMS during treatment with atorvastatin compared to placebo (definition: at least a 25% higher muscle symptom intensity).

The secondary hypothesis is that patients with confirmed SAMS will have higher levels of the parent drug (atorvastatin) and/or its metabolites than their counterparts without placebo-controlled SAMS, and that patients with confirmed SAMS can be identified with high sensitivity and specificity. We also hypothesize that

the parent drug atorvastatin and its metabolite levels will neither relate to SAMS in the control group without muscle symptoms, nor in patients with failing placebo-test for connecting SAMS to atorvastatin.

6 STUDY OBJECTIVES AND RELATED ENDPOINTS

	Objectives	Endpoints	Assessments
Primary	To estimate the effect of atorvastatin on muscular symptom intensity in coronary patients with subjective SAMS.	The individual mean difference in muscular symptom intensity over the last three weeks (i.e. week 4-7) between treatment periods with atorvastatin and placebo.	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 proportion of patients who report muscle symptoms on atorvastatin treatment compared with on placebo (dichotomous SAMS classification)	The proportion of patients who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS classification)	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.
	To determine the relationship between muscular symptom intensity and blood concentrations of parent drug and the active metabolites of atorvastatin	The correlation between individual mean difference in muscular symptom intensity over the last three weeks (i.e. week 4-7) between treatment periods with atorvastatin and placebo and levels of atorvastin and its metabolites in blood plasma and white blood cells	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. Drug and metabolites in blood measured with liquid chromatography-tandem mass spectrometry

	Objectives	Endpoints	Assessments
	To determine the diagnostic properties of blood concentrations of parent drug and the active metabolites of atorvastatin for classification of true SAMS	Sensitivity, specificity, and area under the curve of blood concentrations of parent drug and the active metabolites of atorvastin for the classification of true SAMS	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. Drug and metabolites in blood measured with liquid chromatography-tandem mass spectrometry
	To determine the likelihood of statin discontinuation within and between the treatment periods	Individual mean difference in likelihood of statin discontinuation over the last three weeks (i.e. week 4-7) between treatment periods with statin and placebo.	Obtained through patient self-report measured with aggregated scores on a 1-10 Likert scale administred at study start, weekly during the treatment periods and at study end
	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 self-reported questionnaires , 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 each treatment period
	To compare blood concentrations of parent drug and the active metabolites of atorvastatin between patients with failing placebo-test for connecting SAMS to atorvastatin and the control group without muscle symptoms.	Levels of atorvastatin and its metabolites in blood plasma and white blood cells	Drug and metabolites in blood measured with liquid chromatography-tandem mass spectrometry
	To descrive study safety	-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	- 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
		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
Explorative	To compare patients with and without confirmed SAMS regarding muscle symptom charcteristics	The proportion of patients who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS classification)	Features of SAMS obtained through patient self-report measured with McGill Pain Questionnaire (SF-MPQ) and Brief Pain Inventory (BPI-SF) administred at study start and at study end
	To study sociodemographic, clinical, and psychosocial characteristics (PROMS and clinical data) between the two study arms	The proportion of patients who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS classification)	Obtained through patient self-report measured with Hospitality Anxiety and Depression Scale, Patient Health Questionnaire-2, Penn State Worry Questionnaire, DS-14, Bergen Insomnia scale, Believes in Medicine questionnaire, and Short Form -12 and questionnaires covering education and lifestyle behavior administred at study start and at study end

7 OVERALL STUDY DESIGN

This is a randomized, double-blinded, multi-center, cross-over study in Norway that will include 80 CHD patients with subjective SAMS during atorvastatin therapy who report i) ongoing SAMS or ii) atorvastatin discontinuation because of SAMS. The patients will be randomized to either atorvastatin in the first period and placebo in the second period or placebo in the first period and atorvastatin in the second period, in an AB/BA cross-over design. The study flow chart is shown in Figure 1. In addition, 40 coronary patients without SAMS on atorvastatin will be included at random and undergo an open 7 weeks treatment period with atorvastatin in a similar dose as in those with SAMS.

7.4 Recruitment Plan

Based on evidence from the NOR-COR 1 study, (5) we expect to identify about 850 patients with a CHD event by searching hospital medical records at the participating hospitals the past 2-36 months prior to study start. Among these, at least 200 patients will report subjective SAMS or statin discontinuation due to SAMS during a telephone screening interview. Based on the study entry criteria and significant non-participation rate, a conservative estimate is that 40% of these patients (n=80) along with the control group of n=40 may be enrolled over a 3 months period.

Patient enrolment will start in March 2019. With mean follow-up time at end of inclusion of 3 months, the total study duration will be no more than 6 months. The results of primary endpoint are expected during fall 2019 whereas results of the secondary endpoints are expected in 2020.

Study Period	Estimated date of first patient enrolled: 1--Mar-2019
	Anticipated recruitment period: 2 months (due to hospital medical record screening)
	Estimated date of last patient completed: 1-Sept-2019
Treatment Duration:	Until end of study period (16 weeks after randomization)
Follow-up:	Patients will be followed for 16 weeks after randomization.
End of study	Last patient last visit
Post-trial follow-up	Telephone contact with a study cardiologist 3 months after the last visit

8 STUDY POPULATION

8.4 Selection of Study Population

The study will be 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. 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) will be 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 will be performed by two study physicians through a standardized telephone interview. Patients reporting muscle complaints (defined as pain, weakness, tenderness, stiffness or cramps) perceived as related to atorvastatin through the telephone interview or discontinuation of atorvastatin due to muscle

complaints will be invited to the hospital's outpatient clinics for a comprehensive baseline screening and study eligibility evaluation. A prerequisite for participation in the randomized 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. A random selected control group without a history of muscle symptoms will aslo be reqruited based on the telephone interview.

8.5 Number of Patients

Eighty CHD patients with ongoing atorvastatin therapy or previous muscle symptoms that led to discontinuation of atorvastatin will be included in the randomized study. Forty CHD patients without a history of muscle symptoms will be included in the study as controls.

8.6 Inclusion Criteria for participation in the randomized study

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

- 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

8.7 Exclusion Criteria for participation in the randomized 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, 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

8.8 Inclusion and Exclusion Criteria for the control group

The study entry criteria for the control group are similar to those described above except for the inlcusion criterion described in bullet point 3 under 4.3 (i.e. reporting muscle complaints). A prerequisite for participation in the control group is no history of muscle symptoms.

9 TREATMENT

If all eligibility criteria are met and written informed consent is provided, patients will be randomized by the study physicians to double-blinded prescription of atorvastatin or a matched placebo tablet in a 1:1 ratio using the electronic randomisation system (Viedoc™) of the clinical trials unit (CTU) at OUH. Block randomization with block size 4 and 6 in random order, stratified according to centre (Drammen Hospital and Hospital of Vestfold) and previous statin discontinuation (yes/no), will be used.

A standard dose of 40 mg will be used in all RCT and control patients. The study medication should be taken between 08:00 and 10:00 AM. Patients with ongoing statin treatment at baseline will undergo a 1-week pharmacological wash-out period before randomization (Figure 1). All RCT participants will then be treated for 7 weeks or until muscle symptoms are intolerable. After a second 1-week wash-out period patients will be switched from atorvastatin to placebo or vice versa for a subsequent 7-weeks period. In total, study participation comprises 3 clinical visits with blood sampling per patient. Control patients will have 2 visits, one before and after wash-out and one after 7 weeks treatment with atorvastatin 40 mg. Patients will be encouraged to continue the prescribed medication until the end of the study 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). Finally, is specifically mentioned that measurements of blood lipids (i.e. LDL- C, HDL-C and/or total cholesterol) are not allowed during the study period to prevent unblinding. Patients will be instructed to wear the ID-card in case of medical contact or primary care visits that may influence adherence to treatment.

9.4 Drug Identity, Supply and Storage

Atorvastatin 40 mg and placebo are the Investigation Medicinal Product (IMP)s. Atorvastatin and placebo pills will be fabricated and labelled at Kragerø Tablettproduksjon AS (Fabrication number 9101). Study drugs and codes will be stored in closed envelopes and sent directly to the study sites (not via the Pharmacy). The study medication will be stored in lockable cabitens at the Section for cardiology at the participating hospitals. The study codes will be stored in a separate cabinets at the hospital departments and only the principal investigators (Otterstad and Munkhaugen) and two research cardiologist (one at each hospital who are not participating in the trial will have access to the codes. The research cardiologists will be responsible for emergency unblinding (see also Section 8.5). This will minimize the risk of unblinding during the treatment periods.

Study medication for each 7 –weeks treatment period will be provided to the study patients by dedicated research nurses at the baseline visit and at the visit before cross-over. Specific labelling of trial drugs will be performed by batch number registration. Participants will be asked to return all empty or unused pill packets at the next follow-up visit. The study nurses will be responsible for the medicines accounting. The drug label is shown in Appenix E.

9.5 Dosage and Drug Administration

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

9.6 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:

Grapefruitjuice
Johanneswort (prikkperikum, hypericum perforatum)
Barbiturates and derivates
Ciklosporine
Fucidinacid
Glekaprevir
Pibrentasvir
Kobicistat
Letermovir
Rifampicin
Ritonavir
Sofosbuvir og ledipasvir
Telaprevir
Tipranavir
Karbamazepin
Fenytoin
Claritromycin

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

9.7 Subject Compliance

Study participants will report adherence to study treatment weekly in a diary. In addition, remaining pills in returned packages will be counted (participants will be asked to return any empty or unused pill packets at the follow-up visits). 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.

9.8 Drug Accountability

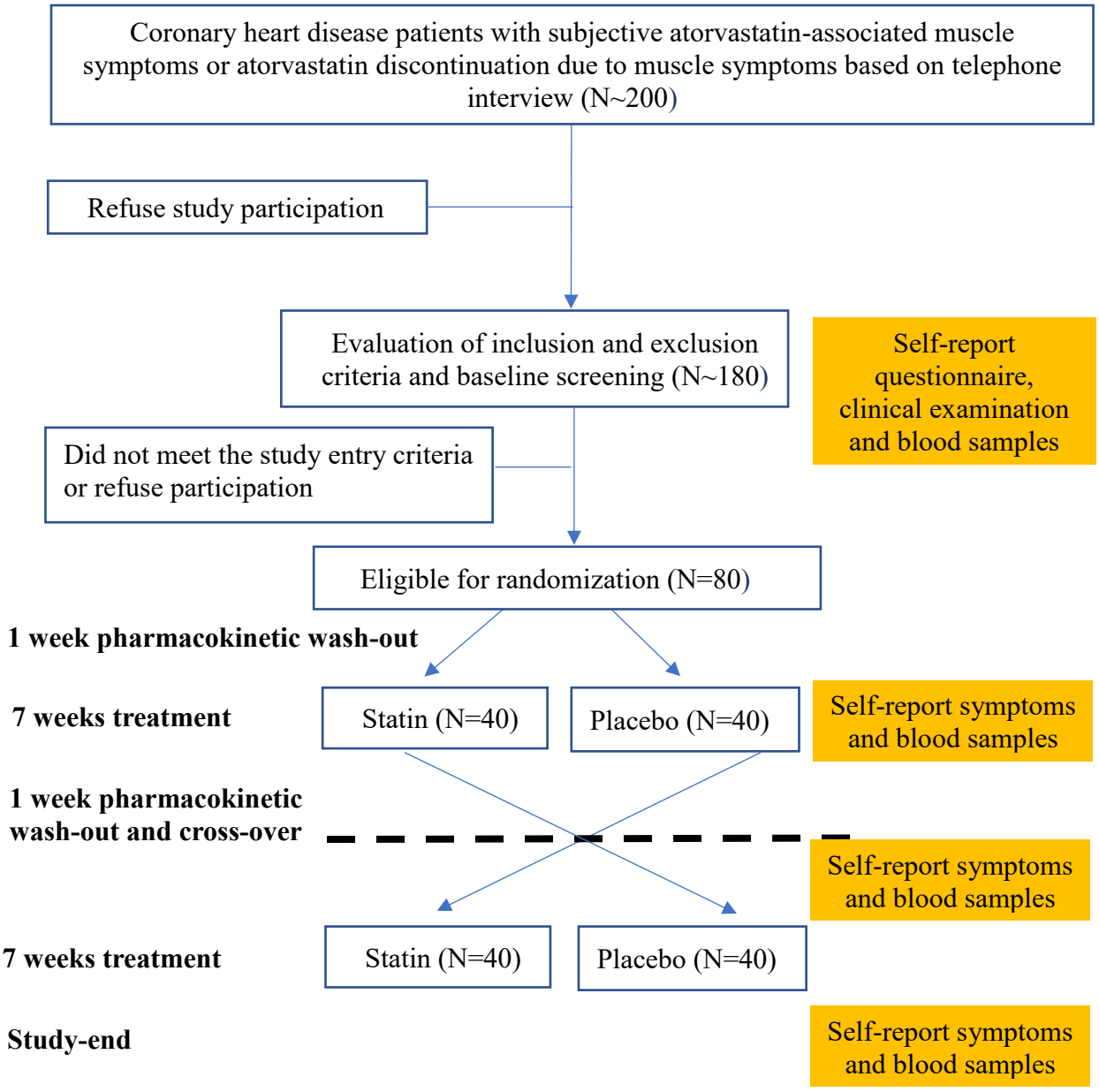
Drug accountability will be performed by local study nurses

9.9 Subject Numbering

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

10 STUDY PROCEDURES

10.4 Flow Chart



Primary end-point: Mean difference in muscle symptoms measured with VAS
Secondary end-points:
- Relationship between confirmed SAMS and atorvastatin and metabolites levels in blood
-Presence of muscle symptoms during statin treatment and not on placebo treatment
- Likelihood of statin discontinuation
-Clinical and psychosocial factors

Table 1. Schedule of activities

Table 2 Study data collection

	The randomized controlled study group (N=80)					**Control group (N=40)**
	Baseline screening (n~180)	**Baseline evaluation/ randomization (n=80)**	**Visit after first 7 weeks treatment period**	**Visit after second 7 weeks treatment period (Study end)**	**With drawal visits**	
	Day-60 to -2	**Day 1**	**Week 8**	**Week 16**		
Inclusion and exclusion evaluation[1)]	X	X				X
Informed consent and randomization[2)]		X				X
Extradition of the IMPs						
Collection of relevant hospital record data[3)]		X				X
Self-reported questionnaires (PROMs)[4)]		X	X	X		X
Collection of blood samples[5)]		X	X	X	X	X
Safety assessment obtained from blood samples[6)]			X	X		
Safety assessment obtained **weekly** from patient self-report[6)]			X	X		

1. Inclusion/exclusion evaluation to the randomized study and to the control group will be performed during the telephone interview (See Appendix A) and at the baseline visit by the study physicians.
2. Randomization 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: Age, gender, ethnicity, medical history (in particular a history of liver failure, rheumatic and thyroid disease), index cardiac event (NSTEMI, STEMI, stable or unstable angina), angiographic findings, coronary treatment (PCI with or without stent implantation,

thrombolysis), prescribed medical treatment at discharge including statin type and doses, and adverse statin reactions including ALT or CK elevations.

4. A self-report questionnaire comprises lifestyle behaviour (smoking history, physical activity), Beliefs about medicines questionnaire (BMQ), 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 (short-form McGill Pain Questionnaire and Brief Pain Inventory)), anxiety and depression (the Hospital Anxiety and Depression Scale), Penn State Worry Questionnaire, Type D personality (DS-14 questionnaire), insomnia (Bergen Insomnia scale), health-related quality of life (Short Form-12). 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 weekly during the treatment periods.
5. 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. The following tests will be included: HbA1c, hemoglobin, 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)
6. 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.

10.4.1 Informed Consent and Randomization

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 generated by Viedoc™ is considered registered (but not yet randomized). A subject who has been assigned to one of the two groups and has been assigned a randomization number is considered randomized.

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.

10.4.2 Data registered from the hospital medical records

The following relevant hospital record data will be registered in an eCRF by specially trained study nurses.

- Age, gender, ethnicity

- Medical history (in particular a history of liver failure, rheumatic and thyroid disease), index cardiac event (NSTEMI, STEMI, stable or unstable angina), angiographic findings, coronary treatment (PCI with or without stent implantation, thrombolysis, CABG),

- Prescribed medical treatment at discharge including statin type and doses, and adverse statin reactions including ALT or CK elevations.

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

- Lifestyle behaviour: Smoking history, physical activity and alcohol consumption .

- Statin treatment,
  - Current statin treatment including type and doses
  - Previous statin discontinuation or dose reduction due to muscle symptoms

- 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

- Psychosocial factors:
  - Anxiety and depression: The Hospital Anxiety and Depression Scale (HADS)(27), contains 14 items covering symptoms of anxiety (HADS-A) and depression (HADS-D). Cut-off scores $\geq$8 on each subscale define clinical significant symptoms of distress (27). Patient Health Questionnaire-2 (PHQ-2) a 2-item screening questionnaire for depression.

  - Type D personality: DS-14 questionnaire(28), contains 14 items, with 7 items each on subscales of negative affectivity and social inhibition. To be categorized with type D personality a score ≥10 points on both subscales is required.

  - Bergen Insomnia scale(29): Contains 6 items about sleep onset, maintenance of sleep and early morning wakening. In addition the average sleep duration will be measured

  - Penn state worry questionnaire(30)

  - Beliefs about medicines questionnaire (BMQ)(31)

  - Short Form-12 (SF-12)(32): Provides information on mental and physical health status and may be used for measurement of the patients quality of life.

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.

10.4.4 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 (i.e. haematology, clinical chemistry and lipids), pharmacological analyses and biobanking. Details on the collections, shipment of samples and reporting of results will be prepared in a laboratory manual.

Hematology
The following tests are included in the haematology: HbA1c and haemoglobin,

Clinical chemistry
The following tests are included in the chemistry: hsCRP creatinine, CK, myoglobin, AST,ALT, LD, total protein, albumin.

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

Pharmacological biomarker analyses
Concentrations of atorvastatin in blood will be quantified by a direct liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods and pharmacokinetic (concentrations), pharmacogenetic (known CYP enzymes SLCO1B1 and CYP3A associated with uptake and metabolism of atorvastatin) and direct drug-related metabolites(atorvastatin acid, atorvastatin lactone, atorvastatin 4-hydroxy [OH] lactone and acid, and atorvastatin 2-hydroxy [OH] lactone and acid) associated with SAMS.

Pharmacokinetic pilot data
We have pilot data indicating that the atorvastatin lactone/acid ratio was is three-fold higher in peripheral blood mononuclear cells compared with plasma. Atorvastatin and metabolites levels in white blood cells will therefore also be a relevant candidate marker for SAMS. Furthermore, pilot data from our clinical study indicate higher dose-normalized levels of the potential myotoxic 4-OH-atorvastatin lactone in patients reporting muscle symptoms (n = 4) compared with those not reporting muscle symptoms (n = 6). At 1 and 3 hours after dosing the patients with muscle symptoms had on average 3.0-fold higher lactone concentration (0.39 ±+/- 0.30 vs. 0.13 ±+/- 0.09 nmol/L) and 1.7-fold higher level concentration (0.38 ±+/- 0.27 vs. 0.23 ±+/- 0.10 nmol/L), respectively.

10.5 Data Collected During Treatment and Follow-up

10.5.1 Clinical data

Muscle symptoms and blood samples for statin analyses will be assessed during the follow-up period from randomization until study-end.

- Muscle symptoms will be assessed weekly in a diary by the patients on a VAS Likert scale and a 1-10 Numeric Ratin Scale (NRS). Simultaneously, the likelihood for these symptoms to result in statin discontinuation will be assessed on a corresponding scale.

- Blood samples for concentration measurements of atorvastatin and their lactones (incl. reactive acylglucuronide) in plasma and in white blood cells (i.e. lymphocytes) will be collected in the end of each 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. At the last day on each treatment period, blood samples will be collected immediately before the morning dose and 1 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: Age, gender, weight, renal and liver function, concomitant medication and pharmacogenetic variants in SLCO1B1 and CYP3A. (6, 7)

10.5.2 Safety data

The Steering Committee has chosen the following events considered important for safety reasons:
- Intolerable muscle symptoms reported by the patients will result in discontinuation from the actual treatment arm and blood sample collections within 48 hours. The patient can then cross-over to the 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.
- 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.

10.6 Withdrawals and Procedures for Stopping Data Collection

Once randomized into 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 randomized patients will be included in the study population. Patients who withdraw or are withdrawn from the study after randomization will not be replaced.

10.7 Procedures for Discontinuation

10.7.1 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

10.7.2 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.

10.8 End of Study and post-trial care

The study period ends the day after the last treatment day has been completed and the study blinding is uncovered. All study patients will then be thoroughly informed about the study results by the study cardiologists at the hospital outpatient clinics. This will be considered as the end of trial for participants, and recommendations for further lipid management will be given in written form to the patients and their primary care physicians. In patients with confirmed SAMS, we will recommend treatment with rosuvastatin and subsequently proprotein convertase subtilisin kexin 9 [PCSK 9] inhibitors if indicated.(24) Three months after completion of the randomized trial, all patients will receive a phone call from the study PI to evaluate their experiences with study participation, their current statin medication and whether muscle symptoms still are present or not. 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, weekly during the treatment periods and at study end.

Other secondary end-point will be:

- The proportion of patients who report muscle symptoms on atorvastatin treatment and not on placebo (dichotomous SAMS classification)
- Individual mean difference in likelihood of statin discontinuation between treatment periods with statin and placebo, reported by the patients over the last three weeks (i.e. week 4-7) measured with aggregated scores on a 1-10 Likert scale.
- Statin adherence measured with indirect (self-reported questionnaires and pill counts of returned packages) and direct (liquid chromatography-tandem mass spectrometry method) methods
- Levels of atorvastatin and its metabolites in blood plasma and white blood cells

7.1.1. Explorative endpoints:

- Features of SAMS characterized by McGill Pain Questionnaire (SF-MPQ) and Brief Pain Inventory (BPI-SF)
- Sociodemographic, clinical, and psychosocial factors ascertained through self-reported questionnaires, clinical examinations, and blood samples

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 the patients 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.

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 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. 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 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 and will be used to define whether serious adverse event is a serious adverse reaction.

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.

SUSARs will be reported using the CIOMS form.

8.4. Safety and Reporting

Safety assessments will be continuously monitored throughout the study. Please see Section 6.3and 7.2 were this is described in detail.

8.4.1. Annual Safety Report

The study is planned to be completed within 1 year 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 unblinding should only be undertaken when knowledge of the treatment allocation is essential for treating the patient safely and efficaciously. Accordingly, unblinding can be indicated when either *statin treatment* may have caused the emergency situation (i.e. acute liver failure, myopathy or rabdomyolysis) or when *no statin treatment* (i.e. placebo 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. Since immediate knowledge of the treatment allocation (i.e. emergency unblinding) will not influence how these patients are treated in the acute phase, we do not consider a 24-hour guard preparedness for emergency unblinding necessary. Potentially, the need for treatment initination with any of the drugs listed in 5.3 (that interact with atorvastatin) may also require unblining. However, none of these drugs will be initiated within 24 hours following acute hospitalizations.

In case of need for emergency unblinding the envelopes with the code will be opened within 12 hours after the SAE event has occurred after discussions with the medical officer and/or the study PI. Emeregency unblinding will be performed by research cardiologists who are not a part of the study to prevent unblinding of the study physicians.

9. DATA MANAGEMENT AND MONITORING

Study monitoring will be performed by two research cardiolgists, one from each center, who are not participating in the study.

A risk assessment of the study will be performed by the study medical officer (JM) prior to study start under supervision of a representant at the Clinical Trial Unit at OUH.

9.1. Case Report Forms

Electronic Case Report Forms (eCRFs)

The Clinical Data Management System (CDMS) used for the eCRF in this study is Viedoc™. The setup of the study specific eCRF in the CDMS will be performed by the Clinical Trial Unit at Oslo University Hospital. The eCRF system will be FDA Code of Federal Regulations 21 Part 11 compliant.

The designated investigator staff will enter the data required by the protocol into the eCase report forms (eCRF). The Investigator is responsible for assuring that data entered into the eCRF 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 eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections will also be recorded.

After database lock, the investigator will receive a digital copy of the subject data for archiving at the investigational site.

Paper Case Report Forms (pCRF)

Paper forms are only relevant for patient reported data (questionnaires), which will be produced by the Clinical Trial Unit, Oslo University Hospital.

The data will be entered into Viedoc™ by the study staff.

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 two research cardiologists at Drammen hospital and the hospital of Vestfold 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

Data management will be performed by the Clinical Trial Unit, Oslo University Hospital. The Data management procedures will be performed in accordance with the department's SOPs and ICH guidelines. The data management process will be described in the study specific data handling plan and the study specific data handling report after database closure.

Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customized checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g. laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality.

All updates to queried data will be made by authorized study center personnel only and all modifications to the database will be recorded in an audit trail. Once the queries have been resolved, eCRFs will be signed by electronic signature Any changes to signed eCRFs will be approved and resigned by the Investigator.

Once the full set of eCRFs have been completed and locked, the Sponsor will authorize database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

The data will be stored in a dedicated and secured area at Vestre Viken, Drammen Hospital. Data will be stored in a de-identified manner, where each study participant is recognisable by his/her unique trial subject number. The data will be stored until 31.12.2038.

Adverse events and medical history will be coded from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities, MedDRA.

Once the database has been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement.

9.6. Determination of Sample Size and Power Calculation

9.6.1. Sample Size

Power calculations are based on our being able to detect a 1 cm difference in the VAS symptom score between the treatment periods on atorvastatin and placebo since the smallest change in VAS symptom score corresponding to 'a little more' or 'a little less' symptoms was 1.3 cm, with a lower limit of the CI at 1 cm in

a previous study.(23) Gallagher et al. (23) report a standard deviation (SD) of 1.7 for a difference of 1.0 between two VAS symptom scores. Because of the differences in both populations and specific VAS scale between that study in this one, we use SD=2.5 to account for a much larger variation in this study. With n=68, we shall will have 90% power to detect a difference of 1.0, using a one-sample T test. With n=68, we will also have 80% power to detect a difference of 40% SAMS under statins vs. 15% SAMS under placebo, using the McNemar test for paired probabilities. To account for some missing information data due to drop-outs or and protocol deviations, we plan to include 80 patients.

9.7. Randomization

9.7.1. Allocation- sequence generation

Eligible patients will be randomized by the study physicians to double-blinded prescription of atorvastatin or a matched placebo tablet in a 1:1 ratio using the electronic randomisation system of the clinical trials unit (CTU) at OUH. Block randomization with block size 4 and 6 in random order, stratified according to centre (Drammen Hospital and Hospital of Vestfold) and previous statin discontinuation (yes/no), will be used.

Details of block size and allocation sequence generation will be provided in a separate document that is unavailable to those who enrol patients or assign treatment.

9.7.2. Blinding and emergency unblinding

The participant and trial team will all be blind to the participant's sequence allocation. Placebo will be manufactured specially to match the atorvastatin by the manufacturer. Capsules and packaging will be identical in appearance for both active treatment and placebo.The primary investigator will be responsible for assuring that there are procedures and expertise available to cope with emergencies during the study. Emergency unblinding will be performed in the following situations:

- in case of a SUSAR

-in case of Serious Adverse Events that could be related to atorvastatin discontinuation including hospitalization for subsequent myocardial infarction, stable/unstable angina or ventricular arrytmias requiring coronary revascularization and death.

Doubtful cases will be discussed with the medical officer and senior cardiologists in the steering committee (Gullestad, Otterstad) before unblinding.

Emergency unblinding will be performed within 24 hours by two research cardiologists at Drammen Hospital and at the Hospital of Vestold who otherwice are not participating in the study.

9.8. 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.

9.9. Statistical Analysis

The primary outcome and all other continuous outcomes will be estimated with linear regression models with the stratification factors in the randomization (i.e. centre and previous statin discontinuation) as covariates. Dichotomous outcomes will be analysed with conditional logistic regression models with treatment, centre, and previous statin discontinuation as covariates. Methods for analysis of ROC curves and measures of diagnostic accuracy will be used to identify cut-off values of metabolite concentrations that can discriminate between confirmed SAMS from other muscle symptoms. The correlations between individual mean difference in muscular symptom intensity between treatment periods with statin and placebo and levels of atorvastatin and its metabolites in blood plasma and white blood cells will be estimated with Spearman correlation coefficients and linear regression analyses.

9.9.1. 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 – Screening letter sent by postal prior to telephone interview

Opplever du muskelplager når du tar dine kolesterolmedisiner?

MUscle Side-Effects of atorvastatin in coronary patients (MUSE)

Kjære hjertepasient!

Vi planlegger en studie der vi skal kartlegge sammenhengen mellom muskelplager og behandling med den kolesterolsenkende medisinen atorvastatin (salgsnavn Lipitor eller Atorvastatin) hos pasienter med påvist sykdom i hjertets kransårer (hjerteinfarkt, angina). Vi vet lite om hvorfor mange pasienter opplever bivirkninger fra musklene under behandling med slike medisiner. Studien inngår i det forebyggende hjerteprosjektet NOR-COR som gjennomføres ved sykehusene i Drammen og Vestfold.

Da du tilhører denne pasientgruppen, mottar du dette enkle og uforpliktende spørreskjemaet som en kartlegging rundt hvorvidt du kan være en kandidat for å delta i studien.

Dersom du enten bruker eller tidligere har brukt atorvastatin/Lipitor og opplever eller har opplevd muskelbivirkninger er du hjertelig velkommen til å kontakte oss for en uforpliktende samtale om mulig deltagelse i denne studien. Hvis vi ikke hører fra deg vil vi ta kontakt deg per telefon om noen dager. Vi vil da stille deg følgende spørsmål:

1. Bruker du kolesterolsenkende medisin av typen atorvastatin eller lipitor?
2. Dersom ja, opplever du vesentlige muskelplager som du relaterer til behandlingen med atorvastatin?
3. Har du tidligere brukt atorvastatin eller lipitor og sluttet med medisinen grunnet muskelplager?

Med vennlig hilsen

Oscar Kristiansen
Lege og forsker, Medisinsk avdeling,
Drammen sykehus
Telefon: 47682535
e-post: osckri@vestreviken.no

Kari Peersen
Spesialfysioterapeut og forsker
Hjerteavdelingen Sykehuset i Vestfold
Telefon: 99267726
E-post: kari.peersen@siv.no

15.2. APPENDIX B – Informed consent letter

FORESPØRSEL OM DELTAGELSE I FORSKNINGSPROSJEKT

MUscle Side-Effects of atorvastatin in coronary patients (MUSE)

Kjære hjertepasient

Dette er en forespørsel til deg om å delta i forskningsprosjektet, MUSE, som har til hensikt å undersøke sammenhengen mellom kolesterolmedisinen atorvastatin og muskelsymptomer hos pasienter med påvist koronar hjertesykdom. Vi vet fortsatt for lite om hvorfor mange pasienter rapporterer bivirkninger fra muskler under behandling med statiner. Studien inngår i det forebyggende hjerteprosjektet NOR-COR ved sykehusene i Drammen og Vestfold og ledes fra Medisinsk avdeling, Drammen sykehus. Studien skal inkludere til sammen 120 pasienter.

HVA INNEBÆRER DELTAGELSE I DENNE DELSTUDIEN?

Pasienter som har gjennomgått hjerteinfarkt, fått utført PCI behandling (utblokking) eller utført by-pass operasjon (byttet kransårer) i tidsrommet 2016-18 vil bli kontaktet og forespurt om deltagelse via et telefonintervju. Dersom du opplever muskelplager (bl.a. smerter, stivhet, svakhet, ømhet, kramper) som du tror skyldes din kolesterolmedisin eller du har sluttet med kolesterolmedisiner på grunn av slike plager vil du bli invitert til vår poliklinikk på sykehuset for å vurdere om du er kandidat for å kunne delta. Dersom du vurderes å være kandidat for å delta, vil du få behandling med kolesterolmedisinen atorvastatin i 7 uker og behandling med en identisk tablett uten kolesterolmedisin (placebo) i 7 uker. Det blir bestemt ved tilfeldig uttrekk (randomisert) hvorvidt du får tablett med kolesterolmedisin den første 7 ukers perioden eller den siste. Verken du eller studielegen vil vite rekkefølgen på behandlingen før etter at studien er gjennomført. Hensikten med dette er å undersøke best mulig i hvor stor grad dine muskelplager er forbundet med kolesterolmedisin. Den siste uken før og etter hver behandlingsperiode skal du ikke ta studiemedisin i det hele tatt. Dette for å sikre at all studiemedisin er gått ut av blodet før neste behandlingsperiode starter. Du skal registrere dine muskelplager i en dagbok en gang per uke i de 16 ukene som studien pågår. I tillegg skal du komme på laboratoriet på sykehuset for å ta to blodprøver med 2 timers mellomrom til analyse av kolesterolprofil, muskelproteiner og nivåer av kolesterolmedisin før og etter hver 7 ukers behandling. Du skal også komme til sykehuset dersom dine muskelplager er såpass ubehagelige at du ikke ønsker å fortsette med medisinen.

Vi vil også invitere et utvalg pasienter med koronarsykdom som bruker atorvastatin og som *aldri* har opplevd muskelplager til å delta i denne studien. Dersom du tilhører denne gruppen vil du bli bedt om å kutte ut din kolesterolmedisin i 1 uke og deretter ta kolesterolmedisin daglig i 7 uker før du kommer til laboratoriet på sykehuset for å ta en blodprøve til analyse av nivåer av kolesterolmedisin i blodet.
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

Formålet med studien er å undersøke sammenhengen kolesterolmedisinen atorvastatin og muskelsymptomer hos pasienter med etablert koronar hjertesykdom. Det er ofte krevende både for

pasienten og legen å vite om pasientens muskelplager skyldes kolesterolmedisinen eller ikke. Denne studien vil gi ny og svært etterspurt kunnskap om sammenhengen mellom kolesterolmedisiner og muskelplager og kan kanskje gi oss en blodtest som kan si hvorvidt muskelplager skyldes medisinen eller ikke. Dette kan i så fall bidra til mer skreddersydd og bedre kolesterolbehandling til den enkelte pasient enn det som er tilfelle i dag.

MULIGE FORDELER, ULEMPER OG ALVORLIGE BIVIRKNINGER

Siden kolesterolmedisin gis rutinemessig til koronarpasienter i dag, er den ukjente potensielle risikoen i denne studien forbundet med å erstatte kolesterolmedisin med en tablett uten kolesterolmedisin. Imidlertid har vi data fra over 15000 hjerteinfarktpasienter som ikke viser noen økt risiko for nye hjerte-kar hendelser hos pasienter som kutter ut kolesterolmedisin noen uker når det gjøres i forbindelse med en studie under nøye oppfølging av hjertelege slik som i denne studien. Risikoen ved å få behandling med kolesterolmedisin er legemiddelets kjente bivirkninger (muskelplager, kvalme og diare). Dersom du opplever at du får muskelplager eller andre bivirkninger som er så plagsomme at du ikke ønsker å fortsette, kan du når som helst be om å få avslutte behandlingen og komme for å ta blodprøve til analyse av kolesterolmedisin.

Ved å delta i denne studien vil de ansvarlige hjerteleger gi den en grundig personlig gjennomgang av din kolesterolprofil og informasjon om i hvilken grad dine muskelplager skyldes kolesterolmedisinen eller ikke. Du og din fastlege vil også få en detaljert anbefaling for videre kolesterolbehandling. I de tilfeller hvor det viser seg at dine muskelplager ikke skyldes medisinen, vil vi gi råd til din fastlege om mulige alternative behandlinger.

Ved å delta i studien bidrar du også med ny kunnskap som potensielt kan bidra til mer skreddersydd og korrekt kolesterolbehandling til et stort antall pasienter med og uten hjertesykdom som opplever muskelplager når de tar kolesterolmedisin.

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 14 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 vedlagte spørreskjemaet som du besvarer før og etter studien
- Dagboken som du fyller ut ukentlig gjennom studien
- Undersøkelser og blodprøver av deg ved oppstart, underveis og ved avslutning 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 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

I denne samtykkeforespørselen ber vi deg også ta stilling til om vi kan ta blodprøver 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 eksiterer 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 blodprøver og avidentifiserte opplysninger også kan oppbevares, analyseres og behandles ved Avdeling for klinisk Farmakologi ved Oslo Universitetssykehus.

GENETISKE UNDERSØKELSER

Studien ber også, som et tredje samtykke, om tillatelse til å gjennomføre genetiske undersøkelser (gensekvenser og sammensetning i arvestoffet DNA, spesifikke genuttrykk målt som RNA, samt spesifikke proteiner, peptider og metabolitter) av blodprøvene som er samlet inn. Studiens analyser er begrenset til genetiske markører som enten har eller som kan ha betydning for legemiddelomsetning eller bivirkninger ved behandling med kolesterolmedisiner og andre hjertemedisiner. Analyser av kjente genetiske markører som har betydning for legemiddelomsetning og bivirkninger med kolesterolmedisiner vil bli gjennomført underveis i studien og svar på disse undersøkelsene vil bli gitt til studiedeltagerne siden det potensialt kan få betydning for videre 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. Genetiske undersøkelser som skal gjennomføres frem i tid vil ikke bli gjennomført før man har innhentet nye godkjenninger fra REK.

- 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 (2018/2302]. Studien er også godkjent av Statens legemiddelverk (SLV) (nr. 18/17102-7).

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, PhD stipendiat Oscar Kristiansen på tlf. 476 82 535 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.

SAMTYKKE TIL DELTAGELSE

Du kan velge kun å gi samtykke til deltakelse alene. Du kan også velge å gi tillatelse til deltakelse og biobank men ikke genetiske analyser, eller du kan samtykke til alle fire spørsmål. Den som har spurt deg om deltakelse kan besvare eventuelle spørsmål du måtte ha.

Jeg er villig til å delta i HOVEDstudien

Sted og dato

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Deltakers signatur Deltakers navn med BLOKKBOKSTAVER

Jeg er villig til å gi materialet til biobank (blodprøve)

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

15.3 Baseline and 16 weeks questionnaire

Spørreskjema MUSE studien

Kjære NOR-COR MUSE studiedeltager. 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 15-20 minutter på å svare.

Bor du alene eller sammen med andre?
Sett ett kryss.

Bor alene…… ☐
Bor sammen med ektefelle eller samboer…….... ☐
Bor alene etter separasjon/skilsmisse……..... ☐
Bor for tiden på sykehjem, aldershjem eller liknende……..…... ☐

Hvilken utdanning er den høyeste du har fullført?
Sett ett kryss

Grunnskole 7-10 år, framhaldsskole, folkehøgskole……. ☐
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole…… ☐
Artium, øk. gymnas, allmennfaglig retning i videregående skole…….. ☐
Høgskole/universitet, mindre enn 4 år……. ☐
Høgskole/universitet, mer enn 4 år…….. ☐

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

Opplever du bivirkninger når du tar dine kolesterolmedisiner i dag?
Nei…… Ja ……

I så fall kan du beskrive hvilke bivirkninger? ……

……

Er bivirkningene så plagsomme at du har sluttet å ta kolesterolmedisinen i perioder eller vurdert å slutte med de?

Nei…….. Ja ……

Har du <u>tidligere</u> opplevd bivirkninger ved inntak av kolesterolmedisiner?

Nei…….. Ja…….

I så fall hva het medisinen(e) som gav deg bivirkninger? ……..

……

Kan du beskrive hvilke bivirkninger du opplevde? ……

……

……

Har du tidligere sluttet med kolesterolmedisiner pga. bivirkninger?

Nei……. Ja……..

I så fall hva het medisin (ene)? ……..…… og hvilken dose tok du?.....mg

……..…… og hvilken dose tok du?.....mg

……..…… og hvilken dose tok du?.....mg

Har du tidligere redusert dose eller byttet dine kolesterolmedisiner pga. bivirkninger?

Nei…… Ja…… I så fall hvilken medisin/dose? ……..……

Hvor ofte tok du dine kolesterolsenkende medisiner som forskrevet sist uke?
Sett ett kryss

Hver dag ☐ 6 av 7 dager ☐ 5 av 7 dager ☐ 4 av 7 dager ☐ < 4 av 7 dager ☐ Jeg tar dem ikke ☐

Hvor sannsynlig er det at du vil komme til å slutte med dine kolesterolmedisiner på grunn av bivirkninger de neste ukene?

Usannsynlig 0 1 2 3 4 5 6 7 8 9 10 Svært sannsynlig

Her følger noen spørsmål om ditt syn på medisinene som du har fått foreskrevet inkludert dine kolesterolmedisiner. Vennligst indiker om du er enig eller uenig ved å sette en strek under utsagnet som passer best med ditt syn. Ingen svar er rett eller galt. Vennligst sett en strek per rute.

1) Min helse for tiden er avhengig av mine kolesterolmedisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

2) Det å matte ta kolesterolmedisiner bekymrer meg

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

3) Mitt liv ville vært umulig uten mine kolesterolmedisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

4) Uten mine kolesterolmedisner vil jeg bli svært syk

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

5) Av og til bekymrer jeg meg for langtids effektene av mine kolesterolmnedisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

6) Mine kolesterolmedisner er et mysterium for meg

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

7) Helsen min i fremtiden er avhengig av mine kolesterolmedisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

8) Mine kolesterolmedisiner forstyrrer livet mitt

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

10)Mine kolesterolmedisiner beskytter meg mot å bli værre av hjertesykdommen min.

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

11) Leger foreskriver for mange medisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

12) Pasienter som tar medisiner burde av og til stoppe å ta sin behandling for en periode

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

13) De fleste medisiner er avhengighetsskapende.

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

15) Medisiner gjør mer skade enn nytte

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

14) Naturlegemidler er tryggere enn medisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

16) Alle medisiner er giftige

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

17) Leger har for stor tro på medisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

18) Hvis legene hadde hatt mer tid til pasientene ville de foreskrevet færre medisiner

Svært enig ☐ Enig ☐ Usikker ☐ Uenig ☐ Svært uenig ☐

LIVSSTIL

Hvor ofte driver du med fysisk aktivitet? (Ta et gjennomsnitt)
Sett ett kryss

Aldri……..
Sjeldnere enn 1 gang i uken……
En gang i uken……
2-3 ganger i uken……..
Omtrent hver dag……

Dersom du driver fysisk aktivitet så ofte som en eller flere ganger i uken:
Hvor hardt tar du i? (Ta et gjennomsnitt)

Tar det rolig uten å bli andpusten eller svett……
Tar det så hardt at jeg blir andpusten og svett ……..
Tar meg nesten helt ut……..

Hvor lenge holder du på hver gang? (Ta et gjennomsnitt)

Mindre enn 15 minutter ……
16-30 minutter……
30 minutter – 1 time……
Mer enn 1 time……

Hvor mye veier du uten klær? …… kg

Hvor høy er du?..... cm

Røyker du? (sett ett kryss under alternativet som passer)

Nei, jeg har aldri røykt
Ja, jeg røyker av og til
Nei, jeg har sluttet å røyke
Ja, jeg røyker daglig

Alkoholbruk

I løpet av de siste 12 måneder, hvor ofte vil du si at du har drukket alkohol?
Sett strek under alternativet som passer

Aldri Månedlig eller sjeldnere 2-3 x pr mnd 2-3 x pr uke 4 x pr uke eller mer

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

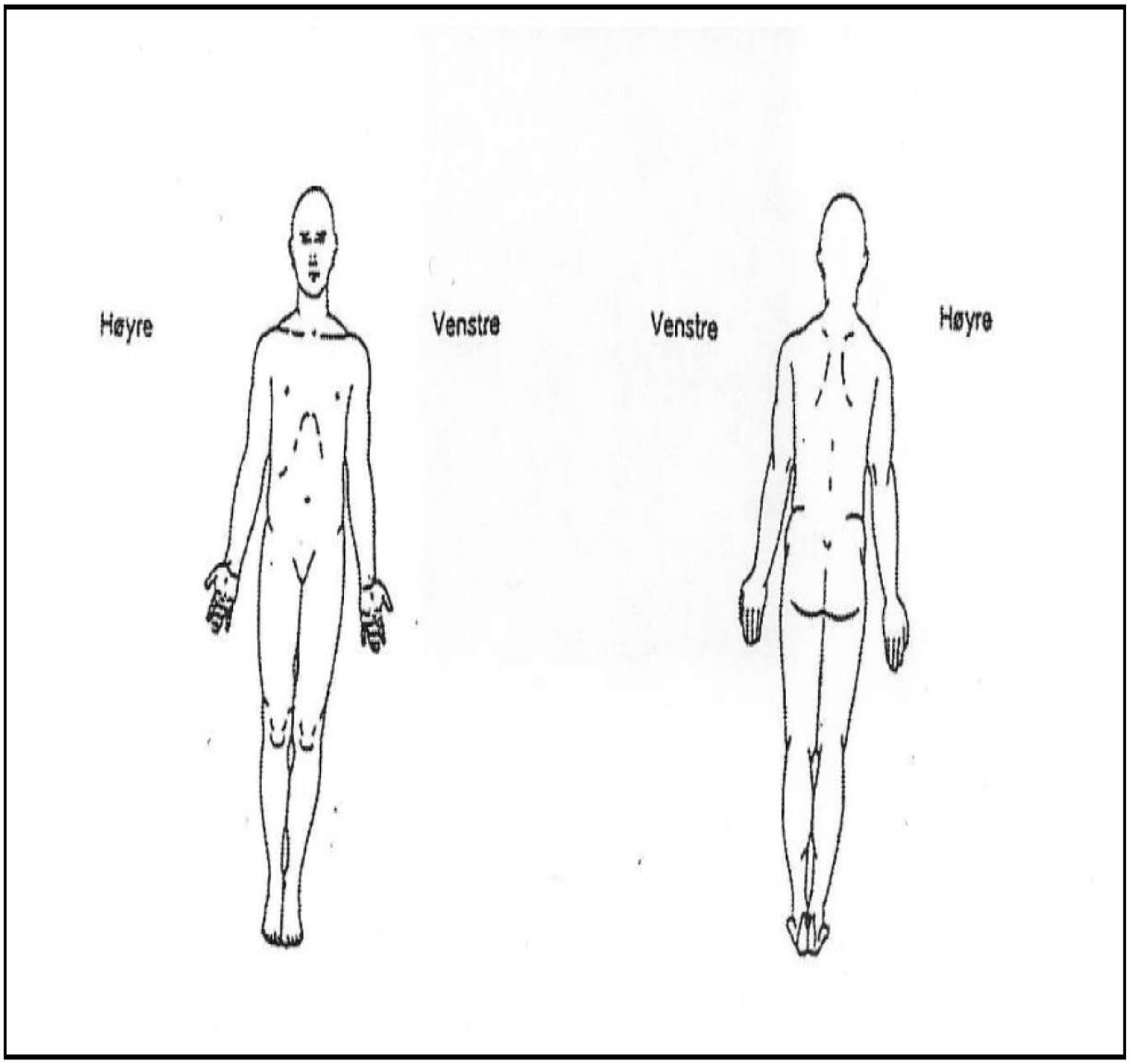
Smerteskjema:

1. Gjennom livet har de fleste av oss hatt smerter (som lett hodepine, forstuelser eller tannpine).

Har du i dag smerter av et eller annet slag enn slike dagligdagse smerter?

JA NEI

2. Vil du skravere alle de områdene av kroppen hvor du har smerter. Marker med et kryss der du har mest vondt.



3. Vennligst sett ring rundt det tallet som best beskriver de sterkeste smertene 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

4. Vennligst sett ring rundt det tallet som best beskriver de svakeste smertene 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

5. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har i gjennomsnitt de siste 24 timer:

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

6. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har akkurat nå:

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

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

……..

……

……

8. 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

Nåværende grad av muskelsymptomer

Sett ring rundt ett tall

1. Ingen symptomer
2. Milde
3. Ubehagelig
4. Meget ubehagelig
5. Forferdelig
6. Uutholdelig

OPPFØLGING HOS FASTLEGE

Har du tidligere diskutert bruk av kolesterolmedisiner og bivirkninger med din fastlege siste året?

Ja, 3 ganger eller mer ☐ Ja, 1-2 ganger ☐ Nei, ingen ganger ☐

Dersom du har diskutert bivirkninger med fastlege, hvor fornøyd er du med svarene du fikk og tiltakene som ble iverksatt på en skala fra 0 til 10?

Svært misfornøyd 0 1 2 3 4 5 6 7 8 9 10 Svært fornøyd

Tidligere sykdommer og medisiner

Har du noen av disse sykdommene eller plagene?

Reumatisk sykdom (som leddgikt, Bekhterevs sykdom)….. ja ☐ nei ☐

Slitasjegikt (artrose)…….. ja ☐ nei ☐

Fibromyalgi……. ja ☐ nei ☐

Andre muskel/skjelett plager…… ja ☐ nei ☐

Lavt stoffskifte (hypothyreose)…… ja ☐ nei ☐

Høyt stoffskifte (hyperthyreose)…… ja ☐ nei ☐

Bruker du medisiner av typen kortikosteroider (kortison, prednisolon)?

ja ☐ nei ☐

LIVSKVALITET, PSYKSISK HELSEPLAGER OG SØVN

1. Stort sett, vil du si at din helse er
Sett ett kryss

Utmerket ☐ Meget god ☐ God ☐ Nokså god ☐ Dårlig ☐

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig uke. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

2. Moderate aktiviteter som å flytte ett bord, støvsuge, gå en tur eller drive med hagearbeid

Ja, begrenser meg mye ☐ Ja, begrenser meg litt ☐ Nei, begrenser meg ikke i det hele tatt ☐

3. Gå opp trappen flere etasjer

Ja, begrenser meg mye ☐ Ja, begrenser meg litt ☐ Nei, begrenser meg ikke i det hele tatt ☐

I løpet av den siste uken, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

4. Du har utrettet mindre enn du hadde ønsket Ja ☐ Nei ☐

5. Du har vært hindret i å utføre visse typer arbeid eller gjøremål Ja ☐ Nei ☐

I løpet av de siste 4 ukene, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som for eksempel å være deprimert eller engstelig)?

6. Du har utrettet mindre enn du hadde ønsket Ja ☐ Nei ☐

7. Du har utført arbeidet eller andre gjøremål mindre grundig enn vanlig Ja ☐ Nei ☐

8. I løpet av de siste 4 ukene, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye ☐

De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste 4 ukene. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av siste 4 ukene har du:

9. Følt deg rolig og harmonisk?

Hele tiden ☐ Nesten hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt ☐

10. Hatt mye overskudd?

Hele tiden ☐ Nesten hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt ☐

11. Følt deg nedenfor og trist?

Hele tiden ☐ Nesten hele tiden ☐ Mye av tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt ☐

12. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?

Hele tiden ☐ Nesten hele tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt ☐

Her kommer noen spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser **den siste uken**. Ikke tenk for lenge på svaret – de spontane svarene er best.

1. Jeg er nervøs eller anspent	**8. Jeg føler meg som om alt går langsommere**
☐ For det meste ☐ Ofte ☐ Noen ganger ☐ Ikke i det hele tatt	☐ Nesten hele tiden ☐ Svært ofte ☐ Fra tid til annen ☐ Ikke i det hele tatt
2. Jeg gleder meg fortsatt over ting jeg pleide å glede meg over	**9. Jeg føler meg urolig liksom jeg har sommerfugler i magen**
☐ Avgjort like mye ☐ Ikke fullt så mye ☐ Bare lite grann ☐ Ikke i det hele tatt	☐ Ikke i det hele tatt ☐ Fra tid til annen ☐ Ganske ofte ☐ Svært ofte

3. Jeg har en uroføIelse som om noe forferdelig kommer til å skje	**10. Jeg har sluttet å bry meg om hvordan jeg ser ut**
☐ Helt sikkert og svært ille ☐ Ja, men ikke så veldig ille ☐ Litt ille, men det bekymrer meg ikke så mye ☐ Ikke i det hele tatt	☐ Ja, helt klart ☐ Jeg bryr meg ikke så mye som jeg burde ☐ Det kan nok hende jeg ikke bryr meg nok ☐ Jeg bryr meg utseendet like mye som jeg alltid har gjort
4**. Jeg kan le og se det morsomme i situasjoner**	**11. Jeg føler meg rastløs som om jeg stadig må være i aktivitet**
☐ Like mye som jeg alltid har gjort ☐ Ikke like mye nå som før ☐ Avgjort ikke så mye nå som før ☐ Ikke i det hele tatt	☐ Uten tvil svært mye ☐ Ganske mye ☐ Ikke så veldig mye ☐ Ikke i det hele tatt
5. Jeg har hodet fullt av bekymringer	**12. Jeg ser med glede frem til hendelser og ting**
☐ Veldig ofte ☐ Ganske ofte ☐ Av og til ☐ En gang i blant	☐ Like mye som jeg alltid har gjort ☐ Heller mindre enn jeg pleier ☐ Avgjort mindre enn jeg pleier ☐ Nesten ikke i det hele tatt
6. Jeg er i godt humør	**13 Jeg kan plutselig få en følelse av panikk**
☐ Aldri ☐ Noen ganger ☐ Ganske ofte ☐ For det meste	☐ Uten tvil svært ofte ☐ Svært ofte ☐ Ikke så veldig ofte ☐ Ikke i det hele tatt
7.Jeg kan sitte i fred og ro og kjenne meg avslappet	**14. Jeg kan glede meg over en god bok eller et radio eller et TV program**
☐ Ja, helt klart ☐ Vanligvis ☐ Ikke så ofte ☐ Ikke i det hele tatt	☐ Ofte ☐ Fra tid til annen ☐ Ikke så ofte ☐ Svært sjelden

I løpet av de siste 2 ukene, hvor ofte har du vært plaget med ett eller flere av disse problemene?
sett ring rundt ett tall

A. Liten interesse for eller glede over å gjøre ting?

0. Ikke i det hele tatt 1. Noen dager 2.Mer enn 7 dager 3. Nesten hver dag

B. Følt deg nedfor, deprimert eller fylt av håpløshet

0. Ikke i det hele tatt 1. Noen dager 2 Mer enn 7 dager 3. Nesten hver dag

SØVNPLAGER
Instruksjon. På spørreskjemaet under er det 6 spørsmål knyttet til søvn og tretthet. Vær vennlig og sett ring rundt det alternativet (antall dager pr uke) som passer best for deg. 0 er ingen dager i løpet av en uke, 7 er alle dager i løpet av en uke.

	Antall dager pr. uke
1. I løpet av den siste måneden, hvor mange dager pr. uke har du brukt mer enn 30 minutter for å sovne inn etter at lysene ble slukket?	0 1 2 3 4 5 6 7
2. I løpet av den siste måneden, hvor mange dager pr. uke har du vært våken mer enn 30 minutter innimellom søvnen?	0 1 2 3 4 5 6 7
3. I løpet av den siste måneden, hvor mange dager pr. uke har du våknet mer enn 30 minutter tidligere enn du har ønsket uten å få sove igjen?	0 1 2 3 4 5 6 7
4. I løpet av den siste måneden hvor mange dager pr. uke har du følt deg for lite uthvilt etter å ha sovet?	0 1 2 3 4 5 6 7
5. I løpet av den siste måneden, hvor mange dager pr. uke har du vært så søvnig/trett at det har gått ut over skole/jobb eller privatlivet?	0 1 2 3 4 5 6 7
6. I løpet av den siste måneden, hvor mange dager pr. uke har du vært misfornøyd med søvnen din?	0 1 2 3 4 5 6 7

Hvor mange timer sover du vanligvis per døgn i gjennomsnitt? …. timer og …... min.

Har du brukt sovemedisiner siste uke? (sett kryss) Ja ___Nei____

Dersom du har svart JA:
Navn _____Styrke (mg)_____ Antall dager siste uke:_____

Nedenfor følger en rekke påstander som man ofte bruker for å beskrive seg selv. Vær vennlig å lese hver påstand og kryss av for det svaret som passer. Det finnes ingen riktige eller gale svar, din egen vurdering er den som teller.

	Uriktig	Ganske uriktig	Verken riktig eller uriktig	Ganske riktig	Riktig
	0	1	2	3	4
1. Jeg oppnår lett kontakt når jeg møter mennesker.	☐	☐	☐	☐	☐
2. Jeg lager ofte oppstyr rundt uviktige ting.	☐	☐	☐	☐	☐
3. Jeg snakker ofte med fremmede..	☐	☐	☐	☐	☐
4. Jeg føler meg ofte ulykkelig.	☐	☐	☐	☐	☐
5. Jeg er ofte irritert.	☐	☐	☐	☐	☐
6. Jeg føler meg ofte hemmet i sosialt samvær.	☐	☐	☐	☐	☐
7. Jeg har et negativt/pessimistisk syn på ting.	☐	☐	☐	☐	☐
8. Jeg finner det vanskelig å starte en samtale.	☐	☐	☐	☐	☐
9. Jeg er ofte i dårlig humør.	☐	☐	☐	☐	☐
10. Jeg er en lukket person.	☐	☐	☐	☐	☐
11. Jeg foretrekker å holde andre mennesker på avstand.	☐	☐	☐	☐	☐
12. Jeg bekymrer meg ofte for noe.	☐	☐	☐	☐	☐
13. Jeg er ofte ''nede i grøfta''.	☐	☐	☐	☐	☐
14. Når jeg snakker med andre, finner jeg ikke de rette tingene å snakke om.	☐	☐	☐	☐	☐

For hvert av utsagnene nedenfor krysser du av for det svaralternativet som beskriver deg best, eller som er mest typisk for deg.

	Ikke be-skrivende		Noe be-skrivende		Veldig be-skrivende
	1	**2**	**3**	**4**	**5**
1. Jeg blir ikke bekymret selv om jeg ikke har tid å gjøre alt.	☐	☐	☐	☐	☐
2. Jeg blir overveldet av mine bekymringer.	☐	☐	☐	☐	☐
3. Jeg pleier ikke å bekymre meg.	☐	☐	☐	☐	☐
4. Jeg blir bekymret i mange situasjoner.	☐	☐	☐	☐	☐
5. Jeg vet jeg ikke burde bekymre meg, men jeg klarer ikke la være.	☐	☐	☐	☐	☐
6. Jeg bekymrer meg mye når jeg blir stresset.	☐	☐	☐	☐	☐
7. Jeg bekymrer meg alltid for noe.	☐	☐	☐	☐	☐
8. Jeg synes det er lett å se bort fra bekymringer.	☐	☐	☐	☐	☐
9. Straks jeg er ferdig med en oppgave begynner jeg å bekymre meg for alt annet jeg må gjøre.	☐	☐	☐	☐	☐
10. Jeg bekymrer meg aldri for noe som helst.	☐	☐	☐	☐	☐

11. Når det ikke er noe jeg kan gjøre med et problem, slutter jeg å bekymre meg. ☐ ☐ ☐ ☐ ☐

12. Jeg har vært en som bekymrer seg hele mitt liv. ☐ ☐ ☐ ☐ ☐

13. Jeg har merket meg at jeg har bekymringer. ☐ ☐ ☐ ☐ ☐

14. Har jeg først begynt å bekymre meg, kan jeg ikke slutte. ☐ ☐ ☐ ☐ ☐

15. Jeg bekymrer meg hele tiden. ☐ ☐ ☐ ☐ ☐

16. Jeg bekymrer meg for oppgaver inntil de alle er gjennomførte. ☐ ☐ ☐ ☐ ☐

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

15.4 APPENDIX D – Patient diary with self-reported questionnaire to be completed during the treatment periodes

Please refer to the attached document.

15.5. APPENDIX E – PHONE GUIDE TO PATIENTS FOR WEEKLY SAFETY ASSESSMENTS

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?

15.6. APPENDIX F – Drug label IMP

Products will arrive with this label applied to the front of each packet

3. Etikettforslag MUSE
Studiekode: 2018-004261-14

Etikett-del 1): Felles etikett-del (lik for alle enhetene)

TIL KLINISK UTPRØVING
Studiekode: 2018-004261-14
Utprøver: Dr. John Munkhaugen
Medisinsk avdeling
Drammen sykehus
Dronninggata 41, 3004 Drammen
Tlf: +4797524194/32803000

***Stolpe:** **49 kapsler Atorvastatin 40 mg/Placebo**
(vertikal) **PasientID.:** **Boks 1 av 2***
Utlevert dato:……..Sign:……..
BRUKSANVISNING
1 kapsel daglig.
Tas mellom kl 07:00 og kl 10:00
Oppbevares tørt, beskyttet mot lys
i utleveringsemballasjen og ved
temp. mellom +15 og 25°C
Oppbevares utilgjengelig for barn

***Stolpen: (På pasientspesifikk del – vertikalt i venstre side)**
Kragerø Tablettproduksjon AS
P.nr.:(for begge preparatene)
Utløpsdato:

MERK:
Etiketten blir en felles etikett 40 x 120 mm med den Pasientspesifikke delen (Etikett 2) i venstre side og høyre del av etiketten er Fellesetiketten (nr. 1). Det er et klart skille mellom de to etikett-delene.

Det vil bli satt på en streif-etikett med tekst «Svelges hele» på hver boks

***Dette er en dobbelblind cross-over studie og hver pasient skal ha 2 bokser med studiemedisin – både aktivt legemiddel og placebo i hht en randomiseringsliste – hver pasient skal derfor ha 2 bokser utlevert.**

Etikettprøve:

Kragerø, 12.01.2019

Anne Hopstock
MPharm
QP Kliniske studier
Kragerø Tablettproduksjon AS

15.7. APPENDIX G – Biobank procedure

RR HF

Instruction to the users: This template is a guide

instr

Generell informasjon

- Hos pasienter med selvrapporterte muskelsymptomer (n = 80).
  Blodprøver tas ved tre visitter (5 prøvetakinger):
  - Visitt 1, baseline (T0): Prøver til medisinsk biokjemi + biobank
  - Visitt 2, uke 8 (T0 og T2): Prøver til medisinsk biokjemi + biobank
  - Visitt 3, uke 16 (T0 og T2): Prøver til medisinsk biokjemi + biobank

  - Dersom pasienter ønsker å slutte ila. studien skal det tilstrebes å gjennomføre en fremskyndet visitt med standardisert prøvetaking (= uke 8/16, T0 og T2)

- Hos pasienter uten selvrapporterte muskelsymptomer (kontrollgruppe, n = 40).
  Blodprøver tas ved to visitter (3 prøvetakinger):
  - Visitt 1, baseline (T0): Prøver til medisinsk biokjemi + biobank
  - Visitt 2, uke 8 (T0 og T2): Prøver til medisinsk biokjemi + biobank

- Visitt 1, 2 og 3: Pasientene skal møte medikamentfastende (dvs. uten å ha tatt morgendosene av medisiner) slik at T0-prøve kan tas i tidsrommet kl 8-10.
- Visitt 2 og 3: T2-prøve tas 2 timer (±10 min) etter dose

- Prøver til medisinsk biokjemi tas ved T0
- Prøver til biobank tas ved T0 og T2

- 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, EDTA-plasma, heparin-plasma, celler)
  - Alt alikvotert materiale til biobank fryses i ultrafryser (**- 80 °C**)

Uke 0 Baseline (test + kontroll) **Visitt 1**	**Uke 8** (test + kontroll) **Visitt 2**	**Uke 16** (test) **Visitt 3**
T0: Medisinsk biokjemi	T0: Medisinsk biokjemi	T0: Medisinsk biokjemi
T0: Biobank*	T0: Biobank	T0: Biobank
	T2: Biobank	T2: Biobank

Dose tas i tidsrommet kl 8-10. T0 = like før dose. T2 = 2 timer (±10 min) etter dose.

Medisinsk biokjemi: *HbA1C, hemoglobin, hs-CRP, kreatinin, eGFR, CK, ALAT, ASAT, total protein, albumin, myoglobin, INR, fastende lipid profil (triglyserider, total kolesterol, HDL-kolesterol, LDL-kolesterol). Myoglobin analyseres på OUS.*
Biobank: *Legemiddelanalyser, biomarkører. *Inkludert DNA-prøve.*

NB: Prosedyren som følger nedenfor gjelder kun prøver til biobank (ikke T0-prøver til medisinsk-biokjemiske analyser som spesifisert i tabellen ovenfor. Medisinsk-biokjemiske analyser: Utføres fortløpende i Drammen. I Vestfold fryses prøvemateriale ned og sendes senere til Drammen for batch-analyse.

Merking og sporing av prøver som skal lagres i biobank

- Sykehus kode
  - D = Drammen, V = Vestfold
- Pasientnr (XXX) = randomiseringsnr
- Visittnr 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
    - EDTA-plasma RNA-stabilisert (P-RNA)
    - 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
  - Kun ved visitt 3, 5 og 1K:
    - Ta med pasientnr (skriv individuelle pasientnr utenpå esken)
  - Visitt: 1, 2, 3, 4, 5 eller 1K
  - Materiale: EDTA-B, EDTA-P, serum eller celler

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

    3-5-9-11-2-20-14

Merking av alikvoterte rør:

*Eksempel A: Pasientnr. 12, **baseline**, 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, tilsvarende rød og blå)

*Eksempel B: Pasientnr. 12, **visitt 5**, **T1**, Drammen sykehus, celler*

- Alternativ 1
  Studie ; sykehus – pasient - visitt – tidspunkt mht. dose; materiale
  - MUSE
  - D12-5-T1
  - Celler (evt. blå farge)

- Alternativ 2
  - MUSE
  - Sykehus: D
  - Pasient: 12
  - Visitt: 5
  - Tidspunkt: T1
  - 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

Visitt 1: Uke 0, baseline, testgruppe og kontrollgruppe

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 3mL	PAX RNA	Grå	RT	Ingen (2 timer henstand v/RT)	Ingen, fryses direkte (RNA)
	1 x 5mL	EDTA u/gel	Lilla	På is	Kjøl *(2500 rct, 15 - 20 min)*	Plasma: x 2 aliq (+1 aliq ca 200 uL plasma + 600 uL *RNA later* reagens, blandes)
	1 x 5mL	Uten tilsetning, u/gel	Rød	RT	Henstand ca. 30 min, vanlig *(2000 rct 10-15 min)*	Serum: x 2 aliq

- *T0: I tillegg kommer standard prøveglass til medisinsk-biokjemiske analyser som rekvireres og analyseres som vanlige prøver.*
- *Myoglobin analyseres i biobanket materiale (dvs. trenger ikke eget prøveglass til myoglobin).*
- *Biobanket fullblod fra baseline kan benyttes til CYP-analyser som utføres i Drammen.*

Visitt 2 og 3: Uke 8 og 16, testgruppe (kontrollgruppe kun visitt 2, uke 8)

Tid	Prøveglass	Type	Farge	Temp.	Sentrifugering	Fordeling
T0 + T2 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 2 aliq (+1 aliq ca 200 uL plasma + 600 uL *RNA later* reagens, blandes)
	1 x 5mL	Uten tilsetning, u/gel	Rød	RT	Henstand ca. 30 min, vanlig *(2000 rct 10-15 min)*	Serum: x 2 aliq

Ekstra ved **T0**	1 x 2-3 mL	EDTA u/gel	Lilla	RT	Ingen	Fullblod: x 2 aliq (epigenetikk)
Biobank	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.*
- *Myoglobin analyseres i biobanket materiale (dvs. trenger ikke eget prøveglass til myoglobin).*

Dersom pasienter ønsker å slutte ila. studien skal det tilstrebes å gjennomføre en fremskyndet visitt med standardisert prøvetaking tilsvarende visitt 2/3 (T0 og T2) før de slutter med studiemedisin.

15.8 APPENDIX H- Pharmaceutical and chemical documentation atorvastatin

SAMMENDRAG AV FARMASØYTISK OG KJEMISK DOKUMENTASJON
-VEDLEGG TIL MELDING OM KLINISK UTPRØVING AV LEGEMIDLER

UTPRØVINGSPREPARAT

Navn: **Atorvastatin Mylan**
Kodenavn:
Legemiddelform og styrke(r): **Tabletter 40 mg**
Virkestoff: **Atorvastatin**

SAMMENLIGNINGSPREPARAT

Navn:
Legemiddelform og styrke:
Virkestoff:

PLACEBO-PREPARAT

Navn: **Placebo 6 mm**
Legemiddelform**: Tabletter**

UTPRØVINGEN

EUDRACT-nummer: **2018-004261-14**

Utprøvingsfase (I – IV): IV

Tidligere studier utført i Norge (angi Legemiddelverkets saksnummer) eller i utlandet:

Preparatets utvikling (sammenligning med preparat benyttet i tidligere studier):

UTPRØVINGSPREPARAT

S VIRKESTOFF

S.1 GENERELL INFORMASJON

Kjemisk navn: [R-(R*, R*)]-2-(4-fluorofenyl)-beta, delta-dihydroksy-5- (1-metyletyl)-3-fenyl-4- [(fenylamino)karbonyl]-1H- pyrrol-1-heptanoinsyre

Strukturformel: $C_{33}H_{34}FN_2O_5$

S.2 TILVIRKNING

Tilvirker(e): Mylan og Kragerø Tablettproduksjon AS

Kvalitet (spesifikasjoner) og kontroll av råvarer/utgangsmaterialer (starting materials)
Syntesemetode og/eller isoleringsmetode/genetisk utvikling
Kontroll av mellomprodukt med parametere testet, analysemetode og grenser

S.3 KARAKTERISERING

Metoder brukt til strukturbestemmelse/karakterisering
Stereokjemi og polymorfi (hvis relevant)
Forurensinger

S.4 KONTROLL AV VIRKESTOFF

Spesifikasjonstabell med parametere testet, analysemetode og grenser
Begrunnelse for spesifikasjonene
Beskrivelse av analysemetoder
Validering av metoder brukt til bestemmelse av identitet, renhet og kvantitet
Batch-analyser

S.5 REFERANSEMATERIALE ELLER STANDARDER

S.6 EMBALLASJE

S.7 STABILITET

Holdbarhetsdata/diskusjon
Forslag til holdbarhetstid og oppbevaringsbetingelser

P.1 BESKRIVELSE OG SAMMENSETNING AV PREPARAT:

Styrke Substansnavn	Batch Mengde	Enhet Mengde	Referanse/ standard
Atorvastatin Mylan 40 mg	4600	1	SPC og analysesertifikat
Capsugel DB-caps A Swedish Orange	4600	1	CoA
Total mengde	4600	1	

P.2 FARMASØYTISK UTVIKLING

P.3 TILVIRKING

Tilvirker(e): Mylan og Kragerø tablettproduksjon (Kratab)

GMP-status/tilvirkertillatelse: Tilvirkertillatelse Kratab gyldig til 9. april 2019

Kort beskrivelse av metode:
Overkapsulering (maskering) av 1 tablett Atorvastatin 40 mg i kapsel, ingen andre tilsetningsstoffer. Dosen skal være 40 mg daglig i én dose. Samme prosedyre for Placebo preparat.

Placebo overkapsuleres først, deretter Atorvastatin 40 mg. Manuell produksjonsmetode hvor alle kapsler fysisk kontrolleres at de inneholder det de skal.

Prosessvalidering/prosesskontroller

P.4 KONTROLL AV HJELPESTOFFER

For hjelpestoffer uten farmakopé- referanse, oppgi spesifikasjonstabell med parametere testet, analysemetode og grenser

P.5 KONTROLL AV PREPARAT

Spesifikasjonstabell med parametere testet, analysemetode og grenser
Beskrivelse av analysemetoder
Validering av metoder brukt til bestemmelse av identitet og mengde virkestoff

Test på henfallstid – Ph. Eur. 2.9.1
Test på massevariasjon – Ph. Eur. 2.9.6

P.6 REFERANSEMATERIALE ELLER STANDARDER

P.7 EMBALLASJE

Emballasjetype: Nolato Cerbo plastboks 50 mL
Nolato Cerbo plastlokk 34 mm

Pakningsstørrelse(r): 49 kapsler

P.8 HOLDBARHET OG OPPBEVARINGSBETINGELSER

Holdbarhetsdata/ diskusjon: Begrenset av holdbarhet på innsatsfaktorer.

Forslag til holdbarhetstid og oppbevaringsbetingelser: Settes lik den korteste holdbarhetstiden.

Oppbevaring: I utleveringsemballasjen, tørt og ved temperatur mellom +15°C og +25°C.
Oppbevares utilgjengelig for barn.

A.2 PREPARATETS SIKKERHET MED HENSYN PÅ SMITTESTOFFER

risikovurdering

SAMMENLIGNINGSPREPARAT

PLACEBOPREPARAT

SAMMENSETNING

Styrke Substansnavn	Batch Mengde	Enhet Mengde	Referanse/ standard
Mikrokrystallinsk cellulose	391 g	85 mg	Ph. Eur. 9.6
Maisstivelse	46 g	10 mg	Ph. Eur. 9.6
Magnesiumstearat	23 g	5 mg	Ph. Eur. 9.6
Total vektmengde tabletter	460 g	100 mg	
Total mengde	4600 tabletter	1 tablett	

Direktekomprimert fremstilling av placebo tabletter, 6 mm, 100 mg.

TILVIRKING

Kort beskrivelse av metode (dersom preparatet er sterilt eller aseptisk fremstilt)

SPESIFIKASJONER

Spesifikasjonstabell med parametere testet, analysemetode og grenser. Et minimumskrav er kontroll av utseende og identitet, samt renhet dersom preparatet er sterilt.

Test på henfallstid – Ph. Eur. 2.9.1
Test på massevariasjon – Ph. Eur. 2.9.6

EMBALLASJE

Emballasjetype: Nolato Cerbo plastboks 50 mL
Nolato Cerbo plastlokk 34 mm

Pakningsstørrelse(r): 49 kapsler

HOLDBARHET OG OPPBEVARINGSBETINGELSER

Holdbarhetsdata/ diskusjon: Begrenset av holdbarhet på innsatsfaktorer.

Forslag til holdbarhetstid og oppbevaringsbetingelser: Settes lik den korteste holdbarhetstiden.

Oppbevaring: I utleveringsemballasjen, tørt og ved temperatur mellom +15°C og +25°C. Oppbevares utilgjengelig for barn.

UNDERSKRIFT

Dateres og underskrives av den(de) som er ansvarlig for dokumentets innhold

Kragerø, 27.11.2018

Hilde Kilen

KRAGERØ TABLETTPRODUKSJON AS
KIRKEGATEN 15
BOKS 202 - 3791 KRAGERØ

Hilde Kilen
Master i farmasi
Kontrollfarmasøyt, produksjonssjef
Kragerø Tablettproduksjon AS

KOMMENTARER OG KONKLUSJON

(skrives av Statens legemiddelverk)

Utfyllende informasjon farmasøytisk/ kjemisk dokumentasjon
Atorvastatin – EudraCTnr.: 2018-004261-14

Beskrevet i tilsendt farmasøytisk/ kjemisk dokumentasjon om tilvirkning:

Kort beskrivelse av metode:

Overkapsulering (maskering) av 1 tablett Atorvastatin 40 mg i kapsel, ingen andre tilsetningsstoffer. Dosen skal være 40 mg daglig i én dose. Samme prosedyre for Placebo preparat.

Placebo overkapsuleres først, deretter Atorvastatin 40 mg. Manuell produksjonsmetode hvor alle kapsler fysisk kontrolleres at de inneholder det de skal.

Sammensetning placebo:

Styrke	***Batch***	***Enhet***	***Referanse/***
Substansnavn	***Mengde***	***Mengde***	***standard***
Mikrokrystallinsk cellulose	*391 g*	*85 mg*	*Ph. Eur. 9.6*
Maisstivelse	*46 g*	*10 mg*	*Ph. Eur. 9.6*
Magnesiumstearat	*23 g*	*5 mg*	*Ph. Eur. 9.6*
Total vektmengde tabletter	*460 g*	*100 mg*	
Total mengde	*4600 tabletter*	*1 tablett*	

Direktekomprimert fremstilling av placebo tabletter, 6 mm, 100 mg.

Placebotablettene er runde, hvite med delestrek og er altså 6 mm diameter og veier 100 mg.

Utseendet på selve placebotabletten er ulik fra Atorvastatin, derfor blir begge tablettene maskert, ved hjelp av innkapsling av Capsugel DB str. A Swedish Orange, slik at de blir like i utseende. Både placebo og Atorvastatin vil lage en «ringlelyd» når man rister på kapselen og vekten vil være tilsvarende lik, ca. 0,1-0,2 g forskjell avhengig av vektvariasjon i selve kapslene, slik at man ikke kjenner forskjell ved håndtering. Det vil ikke være mulig å se eller kjenne forskjell på kapslene uten å åpne kapslene (som blir «klikket» igjen, og er dermed vanskelige å åpne).

Kragerø, 16.01.2019

KRAGERØ TABLETTPRODUKSJON A/S
KIRKEGATEN 15
BOKS 202 - 3791 KRAGERØ

Hilde Kilen

Hilde Kilen
Master i farmasi
Kontrollfarmasøyt, produksjonssjef
Kragerø Tablettproduksjon AS

15.9 APPENDIX I- Procedure for production of atorvastatin and placebo

Ad NOR-COR Statinstudien, Atorvastatin – placebo

Prosedyrer for produksjon

All produksjon hos Kragerø tablettproduksjon (Kratab) er innrettet for å unngå sammenblanding av ulike preparater og/ eller batchnummer. Kratab bedriver kampanjeproduksjon, som vil si at vi produserer og behandler ett preparat av gangen.

Praktisk prosedyre for Atorvastatin – placebo

Vi vil først produsere placebotabletter. Dette innebærer pulverblanding og komprimering av tabletter i tablettavdelingen, før vi fortsetter med innkapsling og dispensering i fylleavdelingen. Denne produksjonen er én batch og vil ha klargjøring som innebærer linjeklarering og renhold.

Neste batch som produseres vil være Atorvastatin. Dette vil innebære innkapsling og dispensering i fylleavdeling. Før denne produksjonen starter vil det være en linjeklarering etter batchen med placebo og klargjøring med vask av lokalene.

I praksis vil disse to batchene produseres på ulike dager.

Kragerø, 09.01.2019

Hilde Kilen

Hilde Kilen, produksjonssjef
Kragerø tablettproduksjon

15.10 APPENDIX J- 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

Konst. overlege, PhD, John Munkhaugen
Medisinsk avdeling
Drammen sykehus

Kun sendt per epost: johmun@vestreviken.no

Oslo, 13. februar 2019

Vår ref: #8428595/1

BEKREFTELSE AV MEDLEMSKAP FOR KALENDERÅRET 2019

Vi bekrefter med dette at De har tegnet medlemskap i Legemiddelansvarsforeningen ved å betale premietilskudd for kalenderåret 2019 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 tria.*".

Medlemskapet er tegnet til å gjelde klinisk legemiddelforsøk på 50 pasienter (minstekontingenten) kalenderåret 2019. 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

15.11 APPENDIX K- Approval Regional Committee of Ethics

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Hege Cathrine Finholt, PhD	22857547	18.12.2018	2018/2302 REK sør-øst D
			Deres dato:	Deres referanse:
			06.11.2018	2018-004261-14

Vår referanse må oppgis ved alle henvendelser

John Munkhaugen
Vestre Viken HF

2018/2302 Muskelbivirkninger ved kolesterolmedisiner hos hjertepasienter

Forskningsansvarlig: Vestre Viken HF, Sykehuset i Vestfold HF
Prosjektleder: John Munkhaugen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst D) i møtet 05.12.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hforsknl) § 10.

Prosjektleders prosjektbeskrivelse
Prosjektet gir ny kunnskap om sammenhengen mellom kolesterolmedisinen atorvastatin og bivirkninger hos hjertepasienter. En randomisert kontrollert overkrysningstudie vil inkludere pasienter med koronar hjertesykdom som rapporterer bivirkninger ved kolesterolmedisiner. Studiedata innhentes fra spørreskjemaer som besvares av pasientene, fra kliniske undersøkelser og fra blodprøvetaking.

Vurdering
Det omsøkte prosjektet er en legemiddelutprøving som skal undersøke sammenhengen mellom kolesterolmedisinen atorvastatin og muskelsymptomer hos pasienter med påvist koronar hjertesykdom. Det skal hentes opplysninger fra pasientjournal, gjøres kliniske undersøkelser, og deltakerne skal fylle ut spørrekjema. Det skal tas blodprøver som lagres i den generelle forskningsbiobanken «NORCOR biobank» med John Munkhaugen som ansvarshavende. Det skal gjøres genetiske undersøkelser som kan være prediktive for statinassosierte muskelsymptomer, men ikke for sykelighet eller overlevelse. Pasienter vil bli anbefalt et statin som ikke metaboliseres gjennom påvist enzym dersom det viser seg at de har en genvariant som gjør at de får statinassosierte muskelsymptomer.

I Norge skal det rekrutteres 120 pasienter fra sykehusene i Drammen og Vestfold. Pasientenene randomiseres til 7 ukers dobbeltblindet behandling med atrovastin 40 mg xl og 7 ukers behandling med placebo i et cross-over design. Kontrollgruppen består av pasienter som bruker atorvastatin, men som aldri har opplevd muskelplager. Disse pasientene skal unnlate å ta kolesterolmedisinen i 1 uke og deretter ta kolesterolmedisinen daglig i 7 uker før de avlegger blodprøver på sykehuset. Pasienter som deltar i studien må avstå fra å ta kolesterolmedisin i en viss periode. Det opplyses at dette ikke vil være risikofylt da det allerede foreligger sikkerhetsdata som indikerer at det ikke er økt risiko for hjerte-kar hendelser hos pasienter som ikke tar statin over 6 uker i en studiesetting. På denne bakgrunn, og fordi pasientene vil bli tett fulgt opp, anser komiteen at det er forsvarlig å gjennomføre studien.

Komiteen har ingen innvendinger til studien. Komiteen setter imidlertid følgende vilkår for godkjenning:
- Invitasjon til å delta i studien må skje skriftlig, dvs at man ikke kan invitere pasienter ved å ringe dem.

Besøksadresse: Gullhaugveien 1-3, 0484 Oslo
Telefon: 22845511
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

Det oppgis i søknaden at prosjektslutt er satt til 15.08.2019. I en e-post fra prosjektleder, datert 23.11.2018 påpekes det at endelig slutt for prosjektet ventes mot utgangen av 2020. Komiteen setter derfor sluttdato til 31.12.2020.

Prosjektleder er ført opp som kontaktperson ved en av de to forskningsansvarlig institusjonene. Komiteen gjør oppmerksom på at kontaktperson for forskningsansvarlig institusjon skal være institusjonens øverste leder, eller den som den øverste lederen har delegert oppgaven til. Det bes om navn, stilling og e-post adresse på denne personen.

Vedtak
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.

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.

Tillatelsen gjelder til 31.12.2020. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.12.3035. Forskningsfilen skal oppbevares atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren».

Dersom det skal gjøres vesentlige endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Prosjektet skal sende sluttmelding på eget skjema, senest et halvt år etter prosjektslutt.

Komiteens avgjørelse var enstemmig.

Klageadgang
REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst D. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst D, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Vi ber om at alle henvendelser sendes inn på korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Finn Wisløff
Professor em. dr. med.
Leder

Hege Cathrine Finholt, PhD
Rådgiver

Kopi til: johmun@vestreviken.no; jan.erik.otterstad@siv.no
Statens legemiddelverk: post@legemiddelverket.no
Vestre Viken HF ved øverste administrative ledelse: postmottak@vestreviken.no
Sykehuset Vestfold HF ved øverste administrative ledelse: post@siv.no

15.12 APPENDIX L- Approval the National Medical Agency

Statens legemiddelverk

Vestre Viken HF
Sykehuset Buskerud
3004 DRAMMEN

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

Deres ref.:	Dato:	Vår ref.:	Saksbehandler:
John Munkhaugen	12.02.2019	18/17102-16	Harsha Gajjar Mikkelsen

KLINISK STUDIE – ATORAVASTATIN – EUDRACT NR. 2018-004261-14

Vi viser til korrespondanse i ovenfor nevnte sak, senest vårt brev, datert 2019-01-15 og deres brev, datert 2019-01-30.

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

Anette Solli Karlsen, PhD
Seniorrådgiver/Klinikk utreder

Harsha Gajjar Mikkelsen
Seniorkonsulent/Koordinator

Dokumentet er elektronisk godkjent og har derfor ikke håndskrevne signaturer.

Statens legemiddelverk
Postboks 240 Skøyen, 0213 Oslo
Besøksadresse: Grensesvingen 26, 0663 Oslo
post@legemiddelverket.no
legemiddelverket.no

Brev stiles til Statens legemiddelverk. Vennligst oppgi vår referanse.

Tlf.: 22 89 77 00
Kto.: 7694 05 00903
Org.nr. 974 761 122

16. REFERENCES

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