EpisodicStatinMig

A multicentre, triple blind, placebo controlled, parallel group study of atorvastatin in episodic migraine

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Protocol change history:

Date	From version	To version	Description of change
25.05.23	N/A	5	Initial Application – Part 1
04.09.23	5	6	Substantial Modification – Part 1
01.12.23	6	7	Substantial Modification – Part 2
03.04.24	7	8	Updated investigator details, clarified objectives, expanded background, revised WOCBP definition, updated blood sampling schedule, clarified randomization, and updated statistical plan.
25.06.24	8	9	Reduced number of centers, refined inclusion/exclusion criteria, added pregnancy test after last dose, revised blood sampling plan, updated protocol deviation definitions, adjusted informed consent process, and updated references/statistical assumptions.
07.02.26	9	10	Clarification and restructuring of objectives and endpoints, refined protocol deviation and breach handling, clarifications to informed consent, updates to safety monitoring arrangements, refinements to statistical analysis section, editorial updates and consistency improvements.

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CONTENTS

SIGNATURE PAGE

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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:

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OVERVIEW

Study number: CTIS number2022-502176-23-01

Title: A multicentre, triple blind, placebo controlled, parallel group study of atorvastatin in episodic migraine.

Objectives:

The primary objective is to evaluate the efficacy of atorvastatin 40 mg compared to placebo for the preventive treatment of episodic migraine in adults. Secondary objectives include assessing the efficacy of atorvastatin 20 mg, evaluating the safety profile of both atorvastatin doses, and comparing tolerability across the three study arms.

Primary trial endpoints:

The primary trial endpoint is the between-group difference in change in migraine days per 28 days from the baseline period to the treatment period (weeks 9-12) for the group receiving 40mg atorvastatin versus the group receiving placebo.

Secondary trial endpoints: Secondary endpoints are change in number of migraine days per 28 days from baseline period to the treatment period in the 20 mg atorvastatin group versus placebo and the 40mg atorvastatin group versus the 20 mg atorvastatin group. Additional endpoints are the proportion of responders (defined as ≥ 50% improvement from baseline), the incidence and severity of adverse events, the total doses of triptans or analgesics per 28 days, and the number of days missed from work per 28 days in all three intervention groups.

Trial design: A multicentre, randomized, triple blind (blinded to participants, study personnel, and statistician), parallel group study, comparing atorvastatin 20 mg and 40 mg against placebo. There will be five Norwegian centres participating in the study.

Trial population: 450 adults with episodic migraine aged 18-65 years having 4-14 migraine days during the 28 days baseline period. They should not be using other migraine prophylactics, not have kidney or liver/gallbladder disease, and use highly effective contraception if they are women of childbearing potential.

Interventions: One placebo tablet per day, one tablet of atorvastatin 20 mg per day or one tablet of atorvastatin 40 mg per day for 12 weeks (84 days).

Ethical consideration: Atorvastatin has been on the Norwegian market for many years, and the occurrence of severe side effects is well known and low. The potential positive migraine

preventive effect of atorvastatin may be helpful to migraine patients worldwide. The main drawback is that the participants need to fill in an electronic headache diary for 21 weeks.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
HMGCR	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
CK	Creatine Kinase
DMP	Data Management Plan
SF	Safety Monitor
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICHD-3	International Classification of Headache Disorders, version 3
GP	General Practitioner
ISF	Investigator Site File
IMP	Investigational Medicinal Product (includes active comparator and control group)
MOH	Medication-Overuse Headache
NCI	National Coordinating Investigator
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Adverse Reaction

1. STUDY OBJECTIVES

1.1 PRIMARY EFFICACY OBJECTIVE

To investigate the efficacy of atorvastatin 40 mg versus placebo for the preventive treatment of episodic migraine in adults.

1.2 SECONDARY EFFICACY OBJECTIVE

To investigate the efficacy of atorvastatin 20 mg for the preventive treatment of episodic migraine in adults.

1.3 SAFETY OBJECTIVES

To investigate the safety profile of the use of atorvastatin 40 mg and atorvastatin 20 mg, and if there are any between-group differences in reported adverse events.

1.4 TOLERABILITY OBJECTIVES

To compare tolerability between the three study arms.

1.5 EXPLORATIVE OBJECTIVE

To explore changes in self-reported general health status from the inclusion visit to the final visit.

To assess baseline exercise habits and explore their potential association with migraine outcomes (e.g. migraine frequency reduction and treatment response).

To conduct a health economic analysis assessing the overall impact of atorvastatin as a migraine preventive treatment, considering medication costs and productivity loss.

2. BACKGROUND AND RATIONALE

2.1 BACKGROUND - DISEASE

Headache is a major global health concern. According to the Global Burden of Disease 2019 Study, headache disorders are ranked second on the list of the disorders causing most functional impairment on the population level, and the first cause in people under 50 years of age (1). A large proportion is caused by migraine, affecting around 14% of the population globally (2).

2.2 BACKGROUND - THERAPEUTIC INFORMATION

The treatment of migraine patients includes avoidance of headache triggers, optimization of attack treatment, and prophylactic treatments with various medications. However, for a large proportion of patients, standard migraine prophylactic medicines are not effective or well tolerated, and many patients fail to adhere to the treatment regimen, or they overuse acute medications and develop medication overuse headache.

Based on evidence, beta-blockers and angiotensin receptor blocker (candesartan), some antiepileptic's (valproate, topiramate), and tricyclic antidepressants (amitriptyline) have been used for migraine prophylaxis (3-11). However, contraindications and side effects have to some degree limited their use. More recently, use of monoclonal antibodies acting on the calcitonin gene related peptide (CGRP) or its receptor is indicated for individual with frequent episodic migraine or with chronic migraine (12). However, in Norway the costs of CGRP inhibitors are only reimbursed by the government for chronic migraine, and the high price makes CGRP antibodies unavailable for many people who could benefit from them.

Prophylactic treatment is indicated in around 30% of people with migraine, but in most countries the percentage actually using prophylactic treatment is in the range of 5-10% (13). Lack of diagnosis, limited efficacy of available drugs, side effects and high cost are the main barriers for utilization of prophylactics.

During the last decade, the preventive effect of simvastatin (14), rosuvastatin (15) and atorvastatin (16-18) among migraine patients have been evaluated in some small randomized, controlled studies. Although all studies indicated an efficacy on migraine frequency, the majority of the studies evaluated statins combined with other drugs (14, 15, 17, 18), or statins compared to another preventive drug (16). Thus, a randomized triple-blind controlled trial evaluating a statin against placebo in a larger group of migraine patients is needed (14-18).

2.3 PRE-CLINICAL & CLINICAL EXPERIENCE WITH INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS)

Statins are the first-line therapy for hypercholesterolemia and act by inhibition of β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase (19) and has been on the Norwegian market for more than 30 years (26).

2.3.1 ATORVASTATIN

: Atorvastatin has comparable effect compared to other statins (27, 28), is well tolerated (29) and lipophilic with good properties to penetrate the blood-brain barrier into the CNS (30). The most common adverse effects are usually mild (29), affecting less than 5% of the patients. Skin rash, musculoskeletal pain and gastrointestinal symptoms are most commonly (26) reported. The oral bioavailability of atorvastatin is 14%, and the peak plasma level is about 14 hours (27). Atorvastatin has an extensive first-pass metabolism in the gut wall and in the liver (27), and cytochrome P450 (CYP) 3A4 is responsible for the formation of two active metabolites. The total plasma clearance of atorvastatin acid is 625 mL/min and the half-life is about 7 hours, and between 7-14 hours for other metabolites (27).

Previously, five randomized, controlled studies have evaluated the effect of statins in migraine patients, all including few participants (14-18). In a 24-week randomized, double-blind, placebo-controlled trial, the efficacy of simvastatin 20 mg plus vitamin D3 was evaluated in 57 adults with episodic migraine during a 24-week period (14). In intervention weeks 13-24, the active group had a reduction of 9 migraine days compared to baseline period, whereas the placebo group had an increase of 3 migraine days (14).

Furthermore, in a triple-blind controlled 4-week trial, 120 participants with migraine received rosuvastatin 10 mg once a day combined with propranolol 10 mg twice daily or propranolol 10 mg twice daily and placebo (15). The number of migraine attacks decreased significantly for the group receiving rosuvastatin and propranolol in weeks two, three and four (15).

Moreover, in a triple-blind controlled 2-month trial, 68 participants having migraine with aura received atorvastatin 20 mg combined with sodium valproate or placebo plus sodium valproate (17). At the end of follow-up, participants with atorvastatin plus sodium valproate had less migraine days than the group receiving placebo plus sodium valproate (17). Furthermore, in a 24-week triple-blind, placebo-controlled trial the combination of atorvastatin 40 mg plus nortriptyline was evaluated among 68 migraine participants (18). At the end of follow-up, more participants had less than 1 migraine attack per week in the active group compared to the placebo group (86% versus 47%). Finally, in a double-blind study atorvastatin 40 mg was evaluated against sodium valproate among 82 participants with episodic migraine (16). During the 3-month follow-up, less adverse effects were reported among those who received atorvastatin compared to the sodium valproate group, whereas no difference was found in migraine frequency between the two groups (16).

The exact mode of action of statins in migraine is not known (20). However, it may be of relevance that statins have a positive effect on endothelial cells and vascular inflammation (21-23), platelets aggression (21), depressive symptoms (24) and also potent neuromodulatory effects (25).

Regarding adverse events of statins, summary data of 14 randomized placebo-controlled trials have found slightly increased risk of diabetes (absolute risk of 0.5%) and asymptomatic liver transaminase elevation (0.4%) among user of statins compared to the placebo group (36). On the other hand, one large-scale randomized placebo-controlled trial including more than 10 000 participants reported a similar rate of adverse events among participants randomly assigned to atorvastatin or placebo with the exception of renal and urinary adverse events (37). Among the three RCTs testing Atorvastatin in migraine (16-18), the evaluation of side effects is hampered by the fact that Atorvastatin was used in combination with respectively sodium valproate or nortriptyline (17, 18).

2.4 RATIONALE FOR THE STUDY AND PURPOSE

EpisodicStatinMig is a clinical trial initiated by the Norwegian Centre for Headache Research (NorHead), and is supported by a grant awarded from the Research Council of Norway in 2021.

There is no doubt that migraine is a large public health problem, which is both disabling and costly, and that safe and efficient preventive treatment is needed for a large proportion of patients.

Although five randomized controlled studies have evaluated statins as migraine prophylactic treatment (14-18), they have all included few participants. In addition, the vast majority of them have combined statins with other drugs and not evaluated statins alone with groups receiving placebo tablets only. Thus, a large-scale randomized triple-blind controlled trial evaluating a statin versus placebo is needed (14-18). Many participants with episodic migraine respond poorly to available preventive treatments, so a potential positive effect of statin therapy could benefit a large patient population.

The overarching goal of the present study is to evaluate whether atorvastatin is an effective, safe and cost-saving prophylactic treatment of episodic migraine on 4-14 days per month.

2.4.1 RATIONALE FOR THE CHOICE OF DOSE

The recommended starting dose of atorvastatin according to the product information (31) is 10 mg per day with a maximum dose of 80 mg per day. The previous migraine studies evaluating atorvastatin used either 20 mg (17) or 40 mg (16, 18), and two of the three studies combined atorvastatin with other preventive drugs (17, 18). Atorvastatin 40 mg was well tolerated in the study using atorvastatin 40 mg as monotherapy in the active group (16). Based on the previous studies, we will evaluate efficacy and side effects in two active groups with respectively 20 mg and 40 mg, to evaluate whether a dose-response relationship exists for atorvastatin in migraine prevention.

3. ENDPOINTS

3.1 PRIMARY ENDPOINT

Difference in change in the mean number of migraine days per 28 days from baseline to weeks 9–12 of the treatment period between the atorvastatin 40 mg and the placebo arm.

3.1.1 PRIMARY ENDPOINT VARIABLE DEFINITION

The primary endpoint variable is migraine day, defined according to IHS/ICHD-3 guidelines (33) as a day with either

A) headache lasting at least 30 minutes without intake of analgesics and meeting ICHD-3 criteria for migraine or probable migraine.

B) headache that successfully responds to acute treatment with a migraine-specific medication (triptan, ditan, gepant, ergotamine, etc.).

Eligible participants must be able to identify migraine and to correctly enter the electronic headache diary.

Operational definition of a migraine day for this trial;

A migraine day is any headache day that meets one of the following criteria:

A) the participant self-reports it as a migraine day in the electronic diary

B) the participant does not self-report it as a migraine day, but has used an acute migraine medication (triptan or gepant) and recorded a successful response

3.2 SECONDARY ENDPOINTS

For each endpoint, differences will be assessed between:

- Atorvastatin 40 mg and placebo
- Atorvastatin 20 mg and placebo
- Atorvastatin 20 mg and atorvastatin 40 mg

1. Migraine days: Change from baseline to weeks 9–12 in the mean number of migraine days per 28 days.

2. Any headache days: Change from baseline to weeks 9–12 in the mean number of any headache days per 28 days.

3. Moderate or severe headache days: Change from baseline to weeks 9–12 in the mean number of moderate or severe headache days per 28 days (as per guideline recommendation).

4. Headache intensity: Change from baseline to weeks 9–12 in mean headache intensity score (1–10 scale) on headache days.

5. Days using acute migraine medication: Change from baseline to weeks 9–12 in the mean number of days using acute migraine medication per 28 days.

6. 50% responder rate: Proportion of participants achieving ≥50% reduction in migraine days compared with baseline.

7. Days missed from work: Change from baseline to weeks 9–12 in the mean number of workdays missed due to headache per 28 days.

3.3 SAFETY ENDPOINTS

3.3.1 PRIMARY SAFETY ENDPOINT

The primary safety endpoint is the total number of Adverse Events (AEs), Serious Adverse Events (SAEs), and Adverse Drug Reactions (ADRs) reported in each of the three treatment groups.

An Adverse Drug Reaction is defined as an AE assessed as possible, probable, or related to the investigational medicinal product (39).

3.3.2 SECONDARY SAFETY ENDPOINT

The secondary safety endpoint is the between-group difference in the incidence of Adverse Drug Reactions (ADRs) across the three study arms.

3.4 TOLERABILITY ENDPOINT

The following endpoints will be assessed to evaluate the tolerability of the investigational medicinal product (IMP).

1. Overall satisfaction with the IMP, measured on a 7-point scale ranging from extremely dissatisfied to extremely satisfied. This will be assessed at the final visit.
2. Adverse effect burden, reported by the participant during the treatment period, measured on a 5-point scale ranging from very bothersome to not bothersome at all. This will be assessed at the final visit.
3. Discontinuation rate of IMP, recorded in the eCRF with the reason for discontinuation, categorized as adverse effect related.

3.5 EXPLORATIVE ENDPOINTS

3.5.1 PHYSICAL ACTIVITY AND GENERAL HEALTH

Change in self-reported general health status from inclusion visit to final visit, assessed using a 4-point scale ranging from poor to very good.

Exploratory correlation between baseline exercise habits, migraine frequency reduction, and treatment response. Baseline exercise frequency will be assessed at the inclusion visit using a self-reported 5-point scale ranging from never to almost every day.

3.5.2 HEALTH ECONOMIC ENDPOINTS

- Overall economic burden per participant (sum of direct and indirect costs).
- Total cost of atorvastatin therapy
- Total cost of acute migraine medications

- Estimated cost of lost work time due to migraine attacks
- Combined economic burden (sum of above components).

4. OVERALL STUDY DESIGN

The study is a phase II study exploration of a new therapeutic approach, randomized, triple blind (participants, study personnel, statistician), placebo-controlled, multicenter study.

4.1 STUDY POPULATION

4.1.1 RECRUITMENT OF STUDY POPULATION

The Norwegian Centre for Headache Research (NorHead) website features an extensive list of ongoing treatment studies. Every day, many migraine patients visit the site to learn about these studies and reach out to NorHead either through the contact form under the "Participation in Research" tab or via email (hodepine@ntnu.no). In the structured form, participants can select the relevant study and provide consent to be contacted. A study nurse at NorHead will make initial informal contact by email or phone to confirm interest and identify which study will be suitable. They usually forward the trial's informed consent form so potential participants can review details. This correspondence is not part of the present study. Interested individuals will be offered a clinical interview with a neurologist at St. Olav's Hospital, Haukeland University Hospital, Oslo University Hospital Ullevål, or Akershus University Hospital, depending on residence. Study information and the informed consent process will be handled by an independent qualified study nurse or doctor, not by the treating physician. No study-related procedures will occur before the consent form is signed. The informed consent form will be emailed at least 24 hours before the inclusion visit. At the visit, the participant and investigator will sign the paper form, and a copy given to each.

Some potential participants may be identified among regular patients seen at the outpatient clinics of the neurological departments of the study hospitals St. Olav's Hospital, Haukeland University Hospital, Oslo University Hospital Ullevål, and Akershus University Hospital. In such cases, study information and informed consent form will be provided by an independent qualified study nurse or doctor, not by the treating physician. No study-related procedures will occur before the participant has signed the informed consent form. This study does not require access to patient medical records to identify potential participants.

The proportion of eligible episodic migraine patients at each centre is not easy to predict. An inclusion period of at 4 years can be expected. As a consequence, the last visit of the last included participant is estimated to be before 31/12/2028.

4.1.2 NUMBER OF PARTICIPANTS

450 participants (See 9.2) will be included in this trial. There will be competitive inclusion, in the sense that if a department fulfils its quota before end of the study, it can include more. Inclusion at all centres is terminated when 450 participants have been included altogether.

4.1.3 PARTICIPATING INVESTIGATORS AND DEPARTMENTS

MD, PhD, neurologist Lise Rystad Øie	St. Olavs Hospital 7006 TRONDHEIM
MD, PhD candidate Joakim Høgsteggen Østhus	St. Olavs Hospital 7006 TRONDHEIM
MD, PhD, neurologist Marte-Helene Bjørk	Haukeland University Hospital 5021 BERGEN
MD, PhD, Kjersti Grøtta Vetvik	Akershus University Hospital 1478 LØRENSKOG
MD, PhD, Bendik Slagsvold Winsvoll	Ullevål- Oslo University Hospital 0424 OSLO
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4.2 INCLUSION CRITERIA

1. Age 18 to 65 years

2. Signed informed consent

3. Episodic migraine with or without aura according to ICHD-3 criteria (33)

4. At inclusion, participants should retrospectively have from 4 to 14 migraine days per 28 days during the last 3 months. This frequency must be confirmed in the headache diary before randomization to treatment (See below).

5. Debut of migraine at least one year prior to inclusion based on information in the patient record or by careful examination of previous headache history

6. Start of migraine before age 50 years.

7. No use of other migraine prophylactics during the study

8. For women of child-bearing potential (WOCBP, see below) there must be no pregnancy or planned pregnancy during the study period, and use of highly effective contraception (See below).

After the baseline period and immediately prior to randomization, inclusion criteria will be reassessed, and the headache diary reviewed. If the diary indicates fewer migraine days than 4 or more than 14 per 28 days, the baseline period may be extended to 8 weeks (range 6-10 weeks). At the randomization visit, the number of baseline migraine days will be calculated based on the most recent 28 days, regardless of whether the baseline period was prolonged.

4.2.1 WOMEN OF CHILD-BEARING AGE POTENTIAL (WOCBP)

This is defined as fertile women, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. WOCBP must agree to perform urinary pregnancy tests and can only be included in the study if they have a negative test result. During the treatment period, a home pregnancy test should be taken every month (week 4 and week 8) and about 3 days after the end of the treatment period. A pregnancy test will also be performed after the final visit.

4.2.2 HIGHLY EFFECTIVE CONTRACEPTION

Such methods include combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal occlusion; vasectomised partner; sexual abstinence, in women for whom that is the preferred and usual lifestyle. This group of patients should not be using other drugs that might interact and reduce the efficacy of the used anticonceptive medicine.

4.2.3 BLOOD AND URINARY SAMPLES

After signed consent forms are obtained, but before randomization, blood samples evaluating liver and kidney function (creatinine, ALAT), muscle function (creatine kinase [CK]), non-fasting glucose, CRP and LDL-cholesterol will be performed for all participants. This will be performed at the laboratory on the study centre, immediately after the inclusion visit. Creatinine and ALAT must be within normal limits before randomization (see table 1). In the case of known previous liver failure or deviant ALAT, additional tests will be taken to assess ASAT, gamma GT and total bilirubin within 2-4 weeks. If any of the additional tests are above the upper reference value, the patient will be excluded. CK must be below 5 times the upper reference value before randomization. Deviation in the CRP-value will be assessed individually by the study physician before randomization. Participants with increased LDL-cholesterol at baseline will be randomized but will be asked to control their lipid status with their own doctor after the end of the study. Because non-fasting glucose will be tested, serum glucose should be <11,0 mmol/l. The blood samples will be destroyed immediately after analysis.

To rule out pregnancy, a negative urine test is required before dispensing the study medicine at the randomization visit. The participant will perform the urine test at the start of the randomization visit and report the result to the study investigator. During the treatment period, participants should perform a home pregnancy test monthly (week 4 and week 8) and approximately three days after completing the treatment period.

Around weeks 4 and 8 of the treatment period, a new blood sample will be drawn of all participants, evaluating ALAT, CK, non-fasting glucose and CRP. This test can be performed at the laboratory associated with the study centre or by visiting the general practitioner´s (GP's) office. Two pre-filled requisition forms will be handed out at the randomization visit for participants who prefer to take these blood samples at the office of their GP (e.g. participants living far away from the study centres). After the final visit, a new blood sample will be drawn of all participants, evaluating creatinine, ALAT, CK, non-fasting glucose and CRP. All these analyses are performed to detect rare, but potential harmful side effects of atorvastatin. The final blood sample can be performed at the laboratory associated with the study site, or at the office of their GP. The blood samples will be destroyed immediately after the analysis.

If the participants have severely increased CK (>5 times upper reference value) and report new onset occurrence of muscle pain, proximal paresis, or muscle atrophy an additional blood sample will be collected to assess the presence of HMGCR-antibodies. Testing for HMGCR-antibodies will be initiated by the study investigator or principal investigator at the relevant centre and the sample will be sent to the University Hospital of Oslo for analysis. The blood samples will be destroyed immediately after the analysis.

Table 1: reference values of blood samples

Blood sample	**Reference value**
Creatinine	Women ≥ 15 years: 45 - 90 µmol/L
	Men ≥ 15 years: 60 - 105 µmol/L
ALAT	Women ≥ 18 years: 10 - 45 U/L
	Men ≥ 18 years: 15 - 70 U/L
ASAT	Women ≥ 18 years: 15 - 35 U/L
	Men ≥ 18 years: 15 - 45 U/L
Creatine Kinase (CK)	Women >=18 years: 35 - 210 U/L
	Men 18-50 years: 50 - 400 U/L
	Men >=50 years: 40 - 280 U/L
Glucose (non-fasting)	<11,0 mmol/L
CRP	<5 mg/L
Gamma-GT	Women 18-40 years: 10 - 45 U/L
	Women ≥40 years: 10 - 75 U/L
	Men 18-40 years: 10 - 80 U/L
	Men ≥40 years: 15 - 115 U/L
Bilirubin, total	≥18 years: 5 - 25 µmol/L
LDL-cholesterol	<30 år: 1,3 – 4,7 mmol/L
	30-50 år: 1,5 – 5,1 mmol/L
	≥50 år: 2,2 – 5,8 mmol/L

4.3 EXCLUSION CRITERIA

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

1) Interval headache not distinguishable from migraine

2) Chronic migraine, chronic tension-type headache, medication-overuse headache or other headache occurring on ≥ 15 days/month

3) Pregnancy, planning to get pregnant, inability to use contraceptives (See inclusion criteria, point 7), and lactating

4) Clinical information on or signs of cholestasis or decreased hepatic or renal function.

5) High degree of comorbidity and/or frailty associated with reduced life expectancy or high likelihood of hospitalization, at the discretion of the investigator

6) Hypersensitivity to statins or previous use of statins

7) History of angioneurotic oedema

8) Use of oral migraine prophylactic drugs less than 4 weeks prior to start of study. Use of erenumab, fremazumab 225mg or galkanezumab less than 8 weeks prior to start of study. Use of local anaestethic block of greater occipital nerve (with or without glucocorticosteroids) less than 12 weeks prior to start of study. Use of botulinum toxin, fremanezumab 675mg or eptinezumab less than 16 weeks prior to start of study.

9) Current use of antiviral treatment against hepatitis C

10) Significant psychiatric illness at the discretion of the investigator

12) Having tried > 3 prophylactic drugs against migraine during the last 10 years

13) Requiring detoxification from acute medication (triptans, opioids)

14) Consistently failing to respond to any acute migraine medication

15) Alcohol or illicit drug dependence

16) Inability to understand study procedures and to comply with them for the entire length of the study

17) Treatment for hypothyroidism

18) Lactose intolerance (confirmed diagnosis and consequently abstaining from dairy products)

5 STUDY INTERVENTION

5.1 INVESTIGATIONAL MEDICINAL PRODUCT

For this study, atorvastatin is defined as Investigational Medicinal Product(s) (IMP).

5.2 DRUG IDENTITY

Atorvastatin has marketing authorization in Norway. Film-coated tablets containing Atorvastatin Xiromed 20 mg will be bought on the marked (Medical Valley Xiromed Sweden). Identical film-coated placebo tablets will be produced by Kragerø tablettproduksjon AS. They will purchase marketed Atorvastatin Xiromed 20 mg film-coated tablets, which will be masked

to conceal the dosage. A 40 mg dose will be prepared by combining two masked 20 mg tablets. Identical film-coated placebo tablets will also be manufactured. Lactose is used as a supplement in Atorvastatin, and will also to be included in the placebo tablets. These tablets will be sent in plastic boxes with appropriate labels to participating centres where they will be stored in appropriate medicinal storerooms.

5.3 DOSAGE AND DRUG ADMINISTRATION

Authorized site personnel will hand out the study medicine box to participants. There will be one box for each participant, each box containing 84 encapsulated tablets. The participant will take one capsule orally each day, preferably at the same time of the day.

5.4 RANDOMIZATION AND BLINDING OF MEDICINE

Eligible participants will be randomly assigned (1:1:1) to receive either 40 mg atorvastatin, 20 mg atorvastatin, or placebo. Randomization will be performed by staff at the Unit for Applied Clinical Research at St. Olavs Hospital using block randomization. The staff responsible for randomization will not otherwise be involved in the trial.

Stratified randomization will not be implemented because the relatively large sample size is expected to ensure baseline balance, and the prespecified analysis model will include adjustments for any potential baseline imbalances.

To maintain masking, the randomization list will be provided directly to the drug manufacturer (Kragerø Tablettproduksjon, Kragerø, Norway), which will encapsulate both active treatments and placebo in identical opaque capsules. Each medicine box will be labelled with a unique trial medicine number linked to the randomization list and shipped to study sites. This number is written in the electronic CRF and the headache diary, and is also noted in the hospital records. Participants will take one capsule orally every day (see 5.3).

Allocation concealment will be ensured by assigning the lowest available medicine box number to eligible participants after baseline data collection. This number will be recorded in both the electronic case report and the hospital record.

During the final visit the participants will be asked to indicate what they believe they received during the study: Placebo / Atorvastatin / Don’t know. If the participants believe they received atorvastatin, they will be asked to identify the major reason for this guess: Reduced intensity or frequency of headache / Adverse effects / Other reason. They will then be asked if there are additional reasons beyond the major reason: No other reason / Reduced intensity or frequency of headache / Adverse effects / Other reason.

5.5 EMERGENCY UNBLINDING

In the event that unblinding is required due to an unexpected and serious adverse reaction (SUSAR), the on-call primary neurologist at St. Olavs Hospital must be contacted via the hospital switchboard at +47 72 57 30 00. The neurologist will have access to the sealed envelopes (marked with the box number) containing information of the content in the capsules.

Unblinding should only occur when it is essential for participant safety with all instances documented along with justification and context, including:

- The reason for unblinding.
- The date and time of the request.
- The individual authorizing and performing the unblinding.
- Any subsequent actions taken.

The sponsor must be notified immediately following any unblinding event. All documentation related to unblinding must be retained in the Trial Master File (TMF).

5.6 SUBJECT NUMBERING

Each participant is identified in the study by a unique subject number that is assigned when the participant signs the Informed Consent Form. Once assigned, the subject number cannot be reused for any other subject. The same primary identifier will be used throughout the study.

5.7 DURATION OF THERAPY

Participants will take the medicine every day for 12 weeks (84 days).

5.8 CONCOMITANT THERAPY

Migraine prophylactic drugs are prohibited during study participation (see exclusion criteria).

All concomitant medications (including vitamins, herbal preparation and other “over-the-counter” drugs) used by the participant will be recorded in the patient’s file and clinical record form (CRF).

5.9 SUBJECT ADHERENCE

5.9.1 DEFINITIONS

• **Protocol deviations** will be defined as any divergence from the approved protocol that does not materially affect participant rights, safety, or welfare, and does not materially compromise data quality or completeness.

• **Important protocol deviations** (IPD) will be defined as a subset of deviations likely to significantly affect data completeness/accuracy/reliability or participant rights, safety, or well-being.

• **Serious breach** will be defined as non-compliance likely to significantly impact participant safety/rights/well-being or the reliability of trial results. Such events will be reported by the sponsor to regulatory authorities without delay and in accordance with applicable requirements (CTIS within 7 calendar days). Examples of serious breaches include: Failure to implement a protocol amendment critical for participant safety.

Systematic errors in investigational medicinal product dosing.

Breaches in the informed consent process that compromise participant rights.

Failure to report SAEs.

Enrollment of ineligible participants.

Falsification of trial data.

If the sponsor has reasonable grounds to suspect a serious breach, reporting should occur immediately, even if all details are not yet available. Follow-up updates can be provided as more information becomes available.

The sponsor must ensure that all involved parties (including investigators and service providers) are trained to report potential serious breaches immediately to the sponsor via designated contact points (email and phone). All related assessments, communications, and actions must be archived in the Trial Master File (TMF).

5.9.2 GOVERNANCE, ROLES, AND RISK-BASED HANDLING

The Sponsor holds overall responsibility for deviation management and ensures risk-based, proportional oversight and documentation.

The PI, study nurse, monitor, and other site personnel are responsible for timely reporting of deviations and implementing corrective and preventive actions. Each deviation will undergo risk assessment (impact on safety/rights/data reliability) to determine classification (minor, IPD, serious breach) and required actions (e.g., participant retention, data handling, regulatory reporting).

5.9.3 TYPES OF DEVIATIONS

5.9.3.1 PREDEFINED IMPORTANT PROTOCOL DEVIATIONS (IPD)

The following are defined as important protocol deviations:

- Non-adherence to headache diary: fewer than 90% of diary days completed during the treatment period.
- Initiation of new migraine preventive medication during the treatment period.
- Pregnancy occurring post-randomization.

Participants meeting any of these criteria will be classified as protocol violators and included in the Intention-to-Treat (ITT) analysis.

5.9.3.2 OTHER DEVIATIONS

- Baseline period (Screening failures): e.g. cannot be contacted, withdraw consent prior to randomization, fail inclusion/exclusion criteria, incomplete diary (<90%), initiation of preventive medication.
- Post-randomization (Early termination): e.g. withdrawal of consent, loss to follow-up, pregnancy and/or participant decision to discontinue (reason documented if available). Accelerated end-of-study visit will be performed where feasible.
- Minor protocol deviations will not prevent a participant from being considered per protocol. All deviations will be recorded at the relevant visit in the eCRF. Examples include:
    - Study staff errors: e.g. incorrect/missed dispensing; missing blood-sample requisition, failure to perform pregnancy test at randomization, missed AE reporting.
    - Participant-related deviations: e.g. missed doses, incomplete diary entries, missed blood samples.

5.9.4 DOCUMENTATION AND REPORTING

All deviations will be documented in Viedoc or in the ISF as a Note to File, where applicable.

Serious breaches/serious non-compliance will be escalated to the sponsor immediately and notified to regulatory authorities and/or IRB/IEC (CTIS within 7 calendar days).

The PI will be responsible for notifying the CI for assessment, categorization (minor, IPD, serious breach), and Viedoc or TMF logging (by sending a note to file to CI).

5.10 DRUG ACCOUNTABILITY

The drug will be sent from the producer to each department and stored in the department's medicine room. A drug accountability form will be kept at each department. Dispensing entries on the Drug Accountability Record Form includes:

Protocol number and title, study medication (name/strength) and manufacturer, study site and local investigator, storage location and conditions.

Information on reception of medicines (medication ID, batch and expiry date, number, and date of reception).

Information on dispensing medicine (Participant number and initials, number of tablets, date of dispensing).

Information on returned medicine (number of tablets, date of return).

Date of destruction of medicines.

6. STUDY PROCEDURES

6.1 TRIAL FLOW CHART

TABLE 2: STUDY PLAN

Inclusion period		**Baseline period**[1]				**Treatment period**											**Follow-up period**				**End**
Week	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Visit doctor	X					X																X
Informed consent	X																					
Inclusion/exclusion	X																					
Medical history	X																					
Previous treatment	X																					
Physical examination	X																					
BP/pulse	X					X																X
Exclusion/inclusion criteria	X					X																
Pregnancy test (WOCBP)						X				X				X				X[3]				(X)[4]
Blood samples	X									X				X								X
Randomization						X																
Diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispensing						X																
Drug retrieval																						X
Telephone from study nurse			X						X				X									
AE/SAE recording			X			X			X				X									X
Withdrawal visit[2]		Can happen any time during the study[2]																				

[1]If needed, the baseline period can be extended to 8 weeks, see 4.2 [2] The participants can withdraw their consent to participate during the study without providing a reason for this. If natural, they will be asked if they want to take part in a final visit or meeting with a representative from the study group. [3]The final pregnancy test should be taken 3 days after the last intake of study medicine. [4] If the final pregnancy test in week 17 was not performed, WOCBP should perform this before the final visit in week 21. AE: Adverse event; WOCBP: Women of child-bearing potential.

6.1.1 INFORMED CONSENT

Informed consent must be obtained voluntarily from each participant before any study-specific procedure is initiated. The study information and the Informed Consent Form (ICF) should be presented by an independent, qualified study staff member who is not involved in the participant´s routine clinical care. Participants must be given adequate time to read the ICF, ask questions, and decide whether to participate. They should also have continuous access to the ICF throughout the study period and may reconsider their participation at any time.

6.1.2 CLINICAL STATUS AT WEEK 0

After the informed consent form is signed, medical history (including disease history and corresponding treatment details), physical examination (neurological status), vital signs (blood pressure and pulse) will be obtained and recorded in the CRF. Also, all planned other treatments must be registered. It will be checked if women are of child-bearing potential WOCBP (See 4.2.1), and if so, whether they use highly effective contraception (see 4.2.2). Blood samples will be performed for all participants (see 4.2.3).

6.1.3 CONCOMITANT MEDICATION

All concomitant medications (incl. vitamins, herbal preparation and other “over-the-counter” drugs) used by the subject within 28 days of treatment start will be recorded in the CRF.

6.1.4 ELECTRONIC HEADACHE DIARY

All included participants must fill in an electronic headache diary during the baseline period, the 12-week treatment period, and the four-week follow-up period (in total 21 weeks). Participants are given a unique QR-code during the inclusion visit, which provides access to the study version of the electronic headache diary named Brain Twin. The participants get a reminder every day from Brain Twin asking if they have headache or not. AEs are reported in a dedicated notes section of the headache diary. If they have headache, they have to report the intensity (1-10, with a description under each number to simplify the explanation), total duration of headache (one day is counted from 00:00 to 23:59), whether they recognize the headache as migraine (ICHD-3 criteria is explained during the inclusion visit), absence from work or school/studies due to their headache, the use of analgesics, and personal notes as demonstrated in Figure 2. During the inclusion visit, the study investigator explains that the personal note section is intended exclusively for documenting medical adverse events. Participants are permitted to retrospectively enter headache diary entries for up to 7 days after the date of occurrence. Beyond this timeframe, the system will restrict any further additions or modifications to ensure data integrity and compliance with protocol requirements.

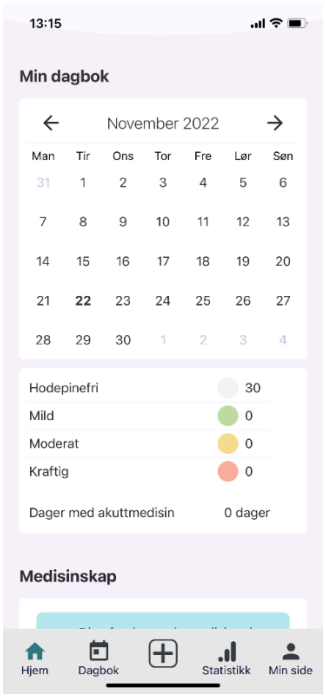

Figure 1. Headache diary

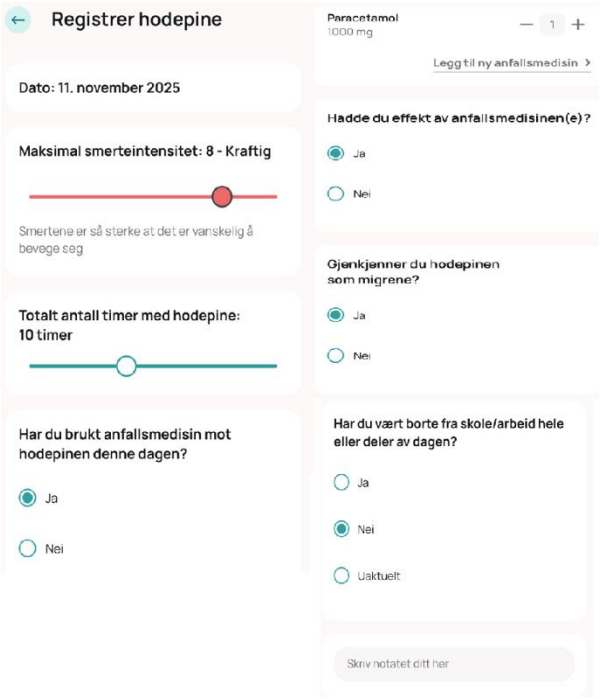

Figure 2. Headache diary

6.1.5 BASELINE PERIOD

If needed, the baseline period can be extended to 8 weeks if the participant does not meet the criteria for episodic migraine or if certain blood test results are outside normal limits for unclear reasons. The baseline period is always calculated based on the last 28 days, regardless of whether the baseline period is extended.

6.1.6 TELEPHONE CONTACT BY THE STUDY NURSE AND BLOOD SAMPLE AT FOLLOW-UP

The participant is asked about AEs and whether he or she is keeping the headache diary and whether there are problems with keeping it, and whether there are any health issues (AEs). Fertile women are asked about the results of home pregnancy tests. In the telephone call in week 3 and week 7 of the treatment period, the study nurse will remind the participant to bring the blood test form related to week 4 and week 8 of the treatment period for a new blood sample.

6.1.7 RANDOMIZATION VISIT (WEEK 5)

The visit can be postponed to week 9 if more registrations in the baseline period is needed (See 4.2). The headache diary is reviewed, AEs are registered, and a pregnancy test performed in WOCBP (as defined in 4.2.1). Vital signs are measured. The headache diaries are reviewed and collected from the participant. If cholestasis or renal/hepatic disease was suspected at inclusion, negative blood analyses must be documented (See 4.2.3).

If the participant is still eligible (inclusion and exclusion criteria, negative pregnancy test in WOCBP), the participant can receive the boxes containing the tablets (atorvastatin 20 or 40 mg or placebo). For randomization of drugs, see 5.4.

6.1.8 EVALUATION OF BLOOD SAMPLES AT BASELINE AND FOLLOW-UP

The baseline blood samples for creatinine and ALAT (if applicable, also ASAT, total bilirubin and gamma-glutamyl transferase) must be within the normal limit, e.g. ALAT should be <45 for women and <70 for men. CK must be below 5 times upper reference value. Deviation in the CRP-value will be assessed individually by the study physician before randomization. Participants with increased LDL-cholesterol at baseline will be randomized, but will be asked to control their lipid status with their own doctor after the end of the study. Non-fasting blood samples will be drawn, and plasma glucose should be <11,0 mmol/l. In the additional blood tests in weeks 4 and 8 of the treatment period, 3 times higher values of ALAT can be accepted, because asymptomatic elevated transaminases (3 times higher values) occur in 0.4% of users of statins compared to the placebo group (35).

6.1.9 PARTICIPANT WITHDRAWAL

Participants may withdraw their consent to participate in the study at any time without providing a reason. Withdrawal can be communicated directly to study personnel or via the study-specific email address. If appropriate, participants will be asked whether they wish to attend a final visit or meeting with a study representative. During this visit, any adverse events and, if provided, the reason for withdrawal will be documented.

6.1.10 AFTER END OF TREATMENT (FOLLOW-UP PERIOD)

Participants must complete the headache diary for an additional four weeks after the treatment period to monitor and document any potential rebound effects. After this, no further follow-up is planned for participants without complications. However, all ongoing adverse events will be monitored until they resolve, return to normal, or for at least 28 days after last administration of the investigational medicinal product (IMP).

6.1.11 END OF STUDY VISIT TREATMENT (FOLLOW-UP PERIOD)

The electronic headache diary is reviewed, and SAE/AEs are registered.

7. SAFETY ASSESSMENTS

7.1 DEFINITIONS OF ADVERSE EVENTS

7.1.1 ADVERSE EVENT (AE)

An AE is defined as any unfavorable and unintended medical occurrence in a participant who has received a pharmaceutical product, which does not necessarily imply a causal relationship with the treatment.

An AE may include any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease that is temporally associated with the use of a medicinal (investigational) product, whether or not related to that product.

The term AE encompasses both serious and non-serious events.

Symptoms or signs clearly attributable to migraine will not be recorded as AEs. This includes typical migraine headache with concomitant nausea, vomiting, phonophobia or photophobia, and visual or sensory aura if present prior to randomization to study medication.

7.1.2 ADVERSE EVENT SEVERITY EVALUATION

Mild: The adverse event is transient and easily tolerated.

Moderate: The adverse event causes the subject's discomfort and interrupts the subject's usual activities.

Severe: The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening.

7.1.3 SERIOUS ADVERSE EVENT (SAE)

Any untoward medical occurrence that at any dose:

- 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 a congenital abnormality or birth defect
- 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 (i.e., elective or scheduled surgery arranged prior to the start of treatment) for pre-existing condition is not considered to be a serious adverse event.

7.1.4 EXPECTED ADVERSE EVENTS

These are those listed for the Summary of Product Characteristics (SmPC) of atorvastatin.

7.1.5 UNEXPECTED ADVERSE EVENT

An experience not previously reported in the SmPC for atorvastatin.

7.1.6 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

SAE (see section 7.1.3) that is unexpected as defined in section 7.1.5 and possibly related to the investigational medicinal product(s) (See 7.1.8).

7.1.7 CAUSALITY OF AES

All available evidence for the cause of the AE should be considered, such as, the pharmacology of the IMP, the nature of the event, timing with respect to IMP administration, and other causes. Possible other causes could include:

- The subject's medical history.
- Lack of efficacy or worsening of the treated condition.
- Other treatment, concomitant or previous.
- Withdrawal of study treatment.
- Treatment error.
- Protocol-related procedure.
- Other factors.

7.1.8 AE RELATIONSHIP TO IMP

The causal relationship between the IMP and the AE should be indicated, such as:

Unrelated: No evidence of a relationship with IMP use.

Unlikely: There is a temporal relationship only with IMP use; there is little or no pharmacological plausibility to suggest a relationship; there is at least one other more likely cause for the AE.

Possible: There is a temporal relationship with IMP use; it is pharmacologically plausible that the IMP is the cause of the AE; there may be one or more other possible causes for the AE.

Probable: There is a strong temporal relationship with IMP use; it is pharmacologically likely that the IMP is the cause of the AE; other causes of the AE are unlikely.

Definite: All available evidence indicates that the IMP is the cause of the AE.

For data analysis and SAE reporting purposes, AEs classified as 'unrelated' and 'unlikely' will be regarded as 'not related'; AEs classified as 'possible', 'probable' and 'definite' will be regarded as 'related'.

7.2 FOLLOW UP OF AES AND SAES

7.2.1 FOLLOW-UP OF UNRESOLVED AES

All ongoing (S)AEs will be followed up until at least 28 days after the last IMP administration.

7.2.2 TIME PERIOD FOR REPORTING AE AND SAE

All study investigators at each hospital shall report SAEs to the sponsor without any delay and not later than within 24 hours of obtaining knowledge of the events. Where relevant, the investigator shall send a follow-up report to the sponsor to allow the sponsor to assess whether the SAE has an impact on the benefit-risk balance of the clinical trial. For each participant the standard time period for collecting and recording AE and SAEs will begin after the first dose has been taken and continue for at least 12 weeks (84 days) throughout the study. During the study all AEs and SAEs will be proactively followed up for each participant as described in the section above; events will be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying disease. Every effort will be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. If the participant should become pregnant, despite the precautions taken, the outcome of the pregnancy will be recorded.

An Annual Safety Report will be submitted each year during the study period, as well as upon study completion, to the relevant Competent Authority. The report will include MedDRA codes for all adverse events (AEs) and serious adverse events (SAEs) recorded during the preceding year.

7.2.3 REPORTING OF SUSARS

SUSARs will be reported to the EudraVigilance system operated by The European Medicines Agency (EMA). The timeline is the following:

1) In the case of fatal or life-treating SUSARs, as soon as possible and in any event not later than 7 days after the sponsor becomes aware of the reaction.

2) In the case of non-fatal or non-life-threating SUSARs, not later than 15 days after the sponsor become aware of the reaction.

3) In the case of a SUSAR which was initially considered to be non-fatal or non-life threating but which turns out to be fata or life-treating, as soon as possible and in any event not later than 7 days after the sponsor become aware of the reaction being fatal- or life-treating.

The current practice in Norway is that report of SUSARs in the EudraVigilance system is performed by Haukeland University Hospital with an encrypted datafile using a CIOMS report form in an unblinded manner.

7.2.4 PROCEDURES IN CASE OF EMERGENCY

In cases of emergency, the participants will be referred to the nearest relevant hospital department.

7.3 STUDY MONITORING

Monitoring the study will be coordinated by the research department, St Olav's Hospital. The investigator will be visited on a regular basis by the Clinical Study Monitor, who will check the following:

- Informed consent process
- Reporting of adverse events and all other safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Study Supply accountability
- Facilities and equipments (example: laboratory, pharmacy) if applicable
- Data completion on the CRFs including source data verification (SDV).

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required.

The monitor will provide to the Sponsor a recommendation regarding continuation, termination or other modifications of the study based on the cumulative experience, including the observed adverse effects of the treatment under study.

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

7.3.1 QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements regulatory agencies may conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

8. INTERVENTION DISCONTINUATION

8.1 CRITERIA FOR SUBJECT DISCONTINUATION

8.1.1 PARTICIPANTS' RIGHTS

In accordance with the Declaration of Helsinki, the investigator must explain to the participants that they have the right to withdraw from the study at any time, and that this will in no way prejudice their future treatment.
As stated in section 6.1.9, if the participants contact the study personnel for such withdrawal, and it is natural, they will be asked if they want to take part in a final visit or meeting with a representative from the study group. If so, adverse events (AEs) and the reason for withdrawal can be noted and recorded in the CRF.

8.1.2 SCREENING FAILURE

An included study participant is regarded as a screening failure if:

- Incorrect inclusion, i.e., the participant does not meet the required inclusion/exclusion criteria for the study in the baseline period (see sections 4.2 and 4.3).
- Participant's non-compliance with completing the headache diary during the baseline period.
- Participant starts on novel headache prophylactic medication during baseline.

See also chapter on protocol deviations, which describes handling of screening failures.

8.1.3 DISCONTINUATION AFTER RANDOMIZATION

Included study participants may also be discontinued at any time for the following reasons:

- Participant lost to follow-up.
- Withdrawal.

Participants found not to qualify in accordance with the study inclusion and exclusion criteria or lost for other reasons in the baseline period are excluded from the study as screening failures. Otherwise, participants are included in the intention-to-treat analysis, but not the per-protocol analysis.

See also chapter on protocol deviations for details on handling discontinuations after randomization.

8.2 PROCEDURES FOR DISCONTINUATION

If possible, a final assessment shall be made (end of study visit). As states in section 4.3.4 of the ICH E-6 Good Clinical Practice: Consolidated Guidance “Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.“ Thus, if possible, the reason for discontinuation shall be recorded.

8.3 THE ROLE OF THE SAFETY MONITOR

The study will appoint an independent Safety Monitor (SM) responsible for ongoing safety oversight. The SM will regularly review all newly reported Adverse Events (AEs) and Serious Adverse Events (SAE). In the case of an SAE, the Principal Investigator (PI) will notify the Coordinating Unit (CU), which will assess whether the event qualifies as a Suspected Unexpected Serious Adverse Reaction (SUSAR). Based on accumulated safety data, the SM may recommend temporary suspension or permanently discontinuation of the trial. The final decision will rest with the Sponsor in consultation with regulatory authorities.

9. STATISTICAL CONSIDERATIONS

9.1 HYPOTHESES

This trial has a confirmatory statistical strategy that pre-specifies just one single null hypothesis relating to the primary endpoint. The novelty of the treatment approach in this trial merits the inclusion of several non-confirmatory secondary and exploratory endpoints, to investigate potential treatment benefit and thus inform future study designs, even if this study should not meet its primary endpoint.

Primary hypotheses

H0: Null hypothesis: There is no difference in change from baseline in mean migraine days per 28 days during the treatment period between atorvastatin 40 mg and placebo

H1: Alternative hypothesis: Atorvastatin 40 mg per day results in significantly fewer migraine days per 28 days compared to placebo

9.2 DETERMINATION OF SAMPLE SIZE

This trial has a confirmatory statistical strategy that pre-specifies just one single hypothesis (See 9.1: H1) relating to the primary endpoint. The study is powered to answer whether this hypothesis (atorvastatin 40 mg daily is superior to placebo) should be rejected.

Sample size was estimated using data from previous migraine prevention studies (6, 7) with similar eligibility criteria and primary endpoint. A total of 123 participants per group was calculated to provide 80% power to detect a mean difference in change from baseline in mean migraine days per four weeks of 1,0 between groups (change of 4.2 vs 3.2), assuming a standard deviation of 2.8 for the change in both groups and a two-sided significance level of 5%. To account for an anticipated dropout rate of 20%, we aimed to recruit 150 participants per treatment group. No formal power analysis was performed for secondary hypotheses; these will be explored using the same group sizes.

9.3 INTERIM ANALYSES

An interim analysis of efficacy will not be performed. However, throughout the study, safety data will be reviewed by the Safety Monitor (SM) as described in section 8.3. The study will be stopped temporarily or permanently if the Sponsor, based on the recommendations from the SM, determines that the risks to participants outweigh the anticipated benefits of the study, or if required by regulatory authorities

9.4 PROCEDURE FOR STATISTICAL ANALYSES

The main statistical analysis will be performed when the planned number of participants have been included, when all included participants have either finalized their last assessment or is withdrawn according to protocol procedures, and when all data have been entered, verified and validated according to the data management plan. Prior to the main statistical analysis, the data base will be locked for further entering or altering of data. Deviation from the original statistical plan will be described and justified in an appendix. Amendments to plan can be done until the day of database lock.

9.5 DATA ANALYSES

In addition to the summarized analysis plan outlined below, a separate Statistical Analysis Plan (SAP) will provide further details on the planned statistical analyses. The SAP will be finalized, signed, and dated prior to database locking.

Blinding of statistician

The study statistician remains blinded to treatment allocation. The data manager will break the randomization code and assign anonymized group labels (e.g., A, B, C) for analysis. To further minimize the risk of unblinding, efficacy endpoints will be analyzed first, followed by safety endpoints, in accordance with the pre-specified Statistical Analysis Plan (SAP).

Analysis Populations

- Intention-to-Treat (ITT): All randomized participants with at least one post-baseline measurement of migraine days per four-week period.
- Safety Set: All randomized participants who take at least one dose of study medication.
- Per-Protocol (PP): Subset of ITT completing the trial without major protocol deviations; used for sensitivity analyses. We expect that 80% of the participants complete per protocol, based on our experiences with four previous performed RCTs with preventive treatment in migraine patients (38).

Efficacy Analyses

The primary endpoints are planned to be analyzed using mixed-effects logistic regression. Conditional odds of migraine from the mixed-effects logistic model will be transformed to population-averaged number of migraine days per 28. Analyses will be based on observed data only, with no imputation for missing values. Demographics and baseline characteristics will be summarized by treatment arm using descriptive statistics. Any major changes to analysis methods will require a protocol amendment. The detailed specifications, including any alternative or sensitivity analyses, will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock.

Safety Analyses

Safety data are summarized descriptively within the safety data set.

Health economic analyses

Health economic analysis based on the data will be published separately, and will only be conducted if the study demonstrates superiority of atorvastatin 40 mg over placebo.

Multiplicity

The trial tests a single confirmatory hypothesis for the primary endpoint. Secondary endpoints are exploratory; no adjustment for multiplicity is applied, consistent with EMA guidance (EMA/CHMP/44762/2017). We argue that this approach will enable us to generate hypotheses on potential treatment benefit and inform future study designs in this patient population, even in the event of a negative study (this study not meeting its primary endpoint).

Data Handling:

Responses will be recorded in the electronic Case Report Form (eCRF). These data will be used for descriptive analyses and inferential statistics to explore correlations between expectations, perceived treatment allocation, satisfaction, and clinical outcomes. In addition, responses may be considered as covariates in exploratory analyses of treatment effects and patient-reported outcomes.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 DATA COLLECTION FORMS

The Sponsor provides participating centres with web-based Case Report Forms (CRFs) via Viedoc™ (Viedoc Technologies AB), specifically designed for this trial. Site personnel will be trained in CRF completion. The CRF will be configured to ensure completeness, accuracy, reliability, and consistency with trial requirements. Each authorized user receives a personal login to maintain an audit trail relating for all study data.

If paper CRFs are used, completed forms, informed documents, participant lists, prescreening logs, and paper copies of study personnel CVs will be retained at the study site until study completion. Original documents will be collected by a Sponsor representative after the active study phase, which is expected to conclude before December 31st, 2028.

10.2 DATA MANAGEMENT

The five centres are responsible for collecting and safe storing of all relevant documents, signed informed consent (for those signing a paper version), participant list, and prescreening lists included. They are encouraged to enter data in Viedoc™-platform in a timely manner. Only certified personnel have access to the CRF. The data will be stored in a dedicated and secured area. Each study participant is recognizable by his/her unique participant study identification (ID) numbers. All included participants are required to complete an daily electronic headache diary (eDiary) during the baseline period, the 12-week treatment period, and the four-week follow-up period (21 weeks in total). The eDiary is administered via the smartphone application BrainTwin™ (Nordic Brain Tech AS). Participants access the study-specific version of the application using a personal access code. eDiary data are transferred in de-identified form to a secure, approved server located in Stavanger, managed by Microsoft Azure Norway. Subsequently, headache diary data are migrated to a secure area within HUNT Cloud, after which the data stored on Microsoft Azure Norway are permanently deleted.

10.2.1 DATA MANAGEMENT PLAN (DMP)

The Data Management Plan (DMP) is included in a separate document (R2_Data Management Plan 2022-502176-23-01). The DMP describes the main elements of the data management policy for the project. It describes the responsibilities of institutions, how data are to be collected and stored. In addition to an evaluation of issues related to protection of privacy.

10.2.2 ELECTRONIC DATA CAPTURE SYSTEM (VIEDOC)

10.2.2.1 VALIDATION OF VIEDOC SETUP

The Viedoc EDC system will be validated following testing of the electronic test version at all study sites. The eCRF questions will be developed by study personnel at St. Olavs Hospital.

10.2.2.2 BACKUP SOLUTION OF ECRF

In the event of technical issues such as website downtime, system errors, or delays in activating the production environment, the Viedoc eCRF questions will be available in paper format. Study visits conducted using paper forms will be signed by the responsible study physician or Principal Investigator (PI) and countersigned by another study physician or PI to ensure data integrity. All visits performed using the backup solution will subsequently be entered manually into the electronic CRF (eCRF) as soon as the system becomes available.

10.3 QUALITY ASSURANCE

10.3.1 TRAINING

There will be a meeting with all investigators at all centres before start of the study. In addition, all study personnel at each site will be trained in the study procedures and use of Viedoc and electronic headache diary.

10.3.2 DOCUMENTATION OF STUDY PERSONNEL DEVIATIONS

All deviations from the protocol and standard operation procedures shall be assessed by the principal investigator and documented as a “Note to file” to be stored in the Investigator Site File (ISF). All five centers will store relevant updated documents in the ISF. The trial master file (TMF) kept by the sponsor contain a log with “note to file” from all participating sites. The national coordinating Investigator (NCI) shall be informed by e-mail in the event of a deviation and ensure that the deviation is documented in the TMF. In the case of severe deviations, the NCI decides how to proceed with the participant. Data in the TMF will be stored for 25 years for archiving proposes according to CTR article 58.

All deviations from the protocol and standard operation procedures shall be assessed by the local primary investigator, central primary investigator, and the monitor.

10.3.3 MONITORING

A monitoring plan specific to this study is held separately to the protocol. The monitoring plan will outline the level of monitoring to be performed for the trial and how this will be carried out. The level of monitoring will be based on the phase of the trial and any perceived risks identified by the risk assessment. Monitoring visits will commence after the Sponsor approves the plan.

Clinical study monitors will be assigned, and will visit the investigator in a regular basis according to the monitor plan.

We envisage that the Clinical Research Unit at ST. Olavs Hospital in Trondheim will serve as the lead monitor in Norway, and that other centers will be monitored from here or by monitors in the NorCrin network. The trial will be monitored regularly according to ICH-GCP. On-site initiation visits will be performed at each study site before the inclusion of the first participant to ensure that all requirements are met. Regular on-site monitoring visits and close-out visits will be performed during the trials and after the last visit by the last participant. See also section 7.6.

10.3.4 SOURCE DATA

Source data are specified in a source data list. Variables included directly into the eCRF are considered source data if specified in the source data list.

The medical records for each participant should contain information which is important for the participant's safety and continued care, and to fulfil the requirement that critical study data should be verifiable.
To achieve this, the medical records of each participant should clearly describe at least:

• That the patient is participating in the study, e.g. by including the enrolment number and the study code or other study identification;
• Results of all assessments confirming a participants eligibility for the study;
• Diseases (past and current; both the disease studied and others, as relevant);
• Surgical history, as relevant;
• Treatments withdrawn/withheld due to participation in the study;
• Results of assessments performed during the study;
• Treatments 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)
• Date of, and reason for, withdrawal from study;
• Additional information according to local regulations and practice.

Worksheets provided by the Sponsor can be used to collect relevant information from the participant. The information will be entered from the worksheet into the CRF.

The following data can be considered source data and can be recorded directly in the CRFs:
• Questionnaires
• Extraction of headache Diary data. The electronic diary can be monitored by using a digital code.
• Baseline characteristics and medical history not required in the medical records

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 INSTITUTIONAL REVIEW BOARD (IRB) REVIEW

The study will be conducted in accordance with the Fortaleza 2013 amendment to the Declaration of Helsinki 1964.

The Protocol and the Participant Information Sheet / Informed Consent Form will be approved by the relevant Competent Authorities (the Norwegian Medicines Agency) and national Ethics Committees (REK KULMU), and possibly other public bodies according to local requirements before commencement. If a protocol amendment is necessary, this will be prepared with the agreement of the Principal Investigator, and signed by the relevant parties. If the amendment is considered to be substantial, it will be submitted to the Competent Authorities and Ethics Committees, and possibly other public bodies according to local requirements for review and approval. The protocol amendment will not be implemented before the required approvals are obtained. Minor amendments which do not affect the safety or physical or mental integrity of the clinical trial participants or the scientific value of the trial (i.e. non-substantial amendments) will not be submitted to Competent Authorities or Ethics Committees.

SUSAR reports and Periodic Safety Reports will be sent to Competent Authorities according to international regulations.

11.2 INFORMED CONSENT FORMS

The information about the study and the Informed consent Form (ICF) should be given by an independent qualified study personal without dependent relationship as a treating physician. The independent qualified study personal will explain the details of the study and will hand out the Study Information. The participant can read the ICF and consider to participate and can re-consider by seeing the ICF during the study period. Participants will have sufficient time to read the Study Information and Consent Form and to ask questions. They can take time to think about their participation and to discuss it with family members and friends if they wish.

Because of the use of electronic diary (explained in Norwegian only), the process with multiple blood samples and pregnancy tests, only participants who understand the Norwegian language will be included. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies will be given to each participant and this fact will be documented in the participant's record.

11.3 PARTICIPANT CONFIDENTIALITY

The Investigator must ensure that subject's confidentiality will be maintained. The eCRFs or other documents submitted to the sponsor should only identify subjects by their initials and study number. The Investigator should keep a separate log of subject codes and names in the Investigator site file (ISF) stored at a safe place locked with a key. Documents not for submission

to the Sponsor, e.g., subject's completed Consent Forms, should be retained by the Investigator in strict confidence.

11.4 GCP

The study will be managed and conducted according to the latest International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). A copy of these guidelines can be found in the Investigator Site File (ISF).

11.5 STUDY DISCONTINUATION

Regular Trial Termination

The end of the trial is defined as the last visit of the last subject included in the trial. Within 90 days of the end of the trial, the Sponsor will notify Competent Authorities and Ethics Committees the regular termination of the of the study as required according to national law and regulations.

Premature Trial Termination

For safety reasons, this trial may be terminated prematurely at any time by the sponsor, the principal investigator, DSMC or competent authorities. If the sponsor decides to terminate the trial for any other reason, the investigator, ethics committee and competent authority will be informed about the reason(s) for stopping the study.

11.6 INSURANCE AND IABILITY

Liability insurance in contention with clinical trials of drugs will be paid by the sponsor to the Norwegian Liability insurance company "Norsk legemiddelansvarsforeningen".

11.7 STUDY REPORT

A clinical study report (CSR) will be prepared covering clinical and statistical aspects and summarizing all findings of the clinical study. The study report will be sent to the Investigators, and the Competent Authorities and Ethics Committees.

12. SAFETY DATA

The safety of atorvastatin been described in the RCTs (16-18). Part of the aim of the inclusion and exclusion criteria is to minimize the risk of these complications.

13. ETHICAL CONSIDERATIONS

13.1 INDIVIDUAL PARTICIPANT RISKS AND BENEFITS

The current study will be performed in otherwise relatively healthy patients with episodic migraine, and with study medicines has been on the market for more than three decades and has been used by hundreds of thousands of patients, by many over several years. Hence, the safety profile of the drug is well known, and the contraindications and hazards are reflected in the exclusion criteria (See 4.3). In the earlier migraine studies, there were relatively few side effects related to the drugs. Therefore, with the proposed doses, we foresee little risk to the participants, provided patients with serious medical conditions and risk of pregnancy are avoided.

Participants should be thoroughly informed of the possibility of not having an effect of the medicine, and the possible adverse effects. Participants must not feel coerced into participation and should be given adequate time to consider their decision.

13.2 CHALLENGES OF STUDY DESIGN

The study design is close to clinical real-life practice. In a clinical setting, the majority of the study medicines has been well tolerated. One practical problem may be with recruitment of 450 participants. However, migraine patients who are candidates of preventive drugs are frequently referred to neurological departments.

14. PUBLICATION OF RESEARCH FINDINGS

The results of this trial will be published in international open access medical journals, or such access will be purchased. In addition, the results will be presented at international conferences and in news media. The active part of the study will end before 31/12/2028. The analyses and publication process will start soon after and will be expected to be finished before 31/12/2031.

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