EpisodicStatinMig

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

Protocol Identification Number: EU CT number: 2022-502176-23-01

Version number: Version 8

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SIGNATURE PAGE

Title: EpisodicStatinMig:

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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 whether the favourable preventative effect of atorvastatin in two different doses seen in three smaller studies, can be confirmed in a larger multicentre randomized, controlled study. Secondary objectives include number of responders and evaluation of side effects.

Main trial endpoints: The primary endpoint is change in number of migraine days/4 weeks from the baseline period to the treatment period.

Secondary trial endpoints: Secondary endpoints are number of responders (≥ 50% improvement from baseline), number of patients with adverse events, doses of triptans or analgesics per 4 weeks, and days with sick leave per 4 weeks.

Trial design: A multicentre, randomized, triple blind (blinded to patients, study personnel, and statistician), parallel group study, comparing atorvastatin 20 mg and 40 mg against placebo. There will be six Norwegian Centres.

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

Interventions: One placebo tablet/day or atorvastatin 20 mg or 40 mg one tablet/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 preventive effect of atorvastatin may be helpful for 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
AE	Adverse Event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
DAE	Discontinuation due to Adverse Event
DMP	Data Management Plan
DSMC	Data Safety Monitoring Committee
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
ISF	Investigator Site file
IMP	Investigational Medicinal Product (includes active comparator and control group)
MOH	Medication overuse headache
NCI	National coordinating investigator
RCT	Randomised 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 objective

The study aims to evaluate the prophylactic effect of atorvastatin 40 mg against episodic migraine headache in a large, multicentre study. To this end, the change from baseline to treatment period in number of days with migraine headache per 4 weeks is selected as a primary endpoint.

1.2. Secondary objective

The study also aims to explore whether a smaller dose (20 mg) atorvastatin is effective, and whether the favourable side effect profile seen in previous studies can be confirmed. Secondary endpoints also include number of responders (≥ 50% improvement from baseline), number of patients with adverse events, doses of triptans or analgesics per 4 weeks, and days with sick leave per 4 weeks. In addition, a health economic analysis will be performed, taking into consideration the cost of atorvastatin, the cost of acute medication for migraine and the cost of lost worktime.

2. BACKGROUND AND RATIONALE

2.1 Background- Disease

Headaches are among the major public health issues globally. 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 prophylactic medication, 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 for CGRP inhibitors are only reimbursed by the state for chronic migraine, and the high price makes CGRP antibodies unavailable for many people who could benefit from migraine prophylaxis.

Prophylactic treatment is indicated in around 30% of patients 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 causes for the under-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 have 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 groups 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 patients 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 week two, three and four (15).

Moreover, in a triple-blind controlled 2-month trial, 68 patients 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 patients (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 patients with episodic migraine (16). During the 3-month follow-up, less adverse effects was 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 effects on endothelial cells and vascular inflammation (21-23), platelets aggression (21), depressive symptoms (24) and also potent neuromodulatory effects (25).

The influence of vitamin D deficiency on the efficacy of statins in migraine patients is very unclear. A cross-sectional population-based study performed in United States reported that statin use in those with normal vitamin D levels were associated with less migraine, whereas such relationship was less clear for those with vitamin D deficiency (35). The results in this cross-section study published in 2015 was the reason why Simvastatin was combined with Vitamin D in the placebo-controlled study performed by the same authors in 2015 (14). Similar mandatory vitamin D supplement has not been performed in the later studies evaluating rosuvastatin on migraine (15) or atorvastatin on migraine (16-18), although migraine patients with definite Vitamin D deficiency got vitamin D supplement in the study evaluating atorvastatin plus sodium valproate (17). Serum vitamin D3 was also checked at baseline in the study evaluating rosuvastatin and propranolol (15) and atorvastatin plus nortriptyline (18).

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 place group (36). On the other hand, one large-scale randomized placebo-controlled trial including more than 10 000 patients 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 part of the Norwegian Headache Research Centre – NHRC that got a large grant 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 preventative 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 group receiving placebo tablets only. Thus, a large-scale randomized triple-blind controlled trial evaluating a statin versus placebo are needed (14-18). Many episodic migraine patients have limited response of available preventive treatment, and a potential positive effect of statin treatment in episodic migraine will benefit a large group of patients.

The overarching goal of the present study is to evaluate whether atorvastatin is an effective, safe and cost-saving prophylactic treatment of frequent, episodic migraine.

2.4.2 Rationale for the choice of dose

The recommended starting dose of atorvastatin according to the product information (31) is 10 mg/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 given atorvastatin 40 mg alone 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 exist for atorvastatin in migraine patients.

3. STUDY OBJECTIVES AND RELATED ENDPOINTS

3.1 Aims of the study

These are to evaluate whether atorvastatin is an effective, safe and cost-saving prophylactic treatment of frequent, episodic migraine. More specifically, we wish to answer the following questions:

Primary objective:

1) Can the favourable effect of atorvastatin 40 mg, seen in three smaller studies (16-18), be confirmed in a larger multicentre study?

Secondary objectives:

2) Is there any effect of a daily dose of 20 mg?

3) Is the favourable side effect profile, seen in the previous studies, replicated in this larger study, and is it even better with a daily dose of 20 mg as compared to 40 mg?

4) What is the cost of atorvastatin treatment, considering cost of the medicine, of acute medicines for attacks, and lost worktime?

3.2 Endpoints

3.2.1 Primary endpoint

1. Difference between groups receiving atorvastatin 40 mg daily and placebo in change from baseline in number of migraine days per 4 weeks.

Migraine days are defined as days with moderate or severe headache accompanied by nausea, and/or phono- and photophobia, and lasting ≥ 4 hours or is treated with the patient's usual migraine medication (usually a triptan). This is in accordance with the Guidelines for controlled trials with migraine prophylactics (32).

3.2.2 Secondary endpoints

2. a) A difference between groups receiving atorvastatin 40 mg daily and placebo in change from baseline in number of days with headache (defined by headache intensity > 0 and/ or intake of the patient's acute headache medication)

- Days with sick leave
- Headache intensity (0-3 scale) on days with headache
- Number of responders (≥ 50% decrease in migraine days compared with baseline)

2. b) Per 4 weeks, difference in change from baseline between groups receiving atorvastatin 20 mg daily and placebo in number of:

- Days with headache (defined by headache intensity > 0 and/ or intake of the patient's acute headache medication)
- Days with sick leave
- Headache intensity (0-3 scale) on days with headache
- Number of responders (≥ 50% decrease in migraine days compared with baseline)

3. Number of reported side effects in the placebo and atorvastatin treatment groups (20 mg and 40 mg)

4. Health economic analysis: Comparison of cost in the placebo and atorvastatin treatment groups (20 mg and 40 mg), taking into consideration price of the medicine, price of acute medication, and lost worktime.

4. OVERALL STUDY DESIGN

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

4.1. Study population

4.1.1 Recruitment of study population

The webside of NorHead, the Norwegian Headache research centre, include a long list of available treatment studies. Every day many migraine patients read about these studies and contact the NorHead centre using a contact form by the webside of NorHead under the "participation in Research" tab, or by using an email address (hodepine@ntnu.no). In the structured form, they could tic of the relevant study and that they allow to be contacted. A nurse employed at NorHead will then make an informal contact by email or telephone in an unstructured way to discuss if they really are interested in study participation, and in which of the many available studies they fit. Usually they forward the trial's informed consent form so that migrainuers can read about the studies in more details. The correspondence with these persons will not be part of the present study. Individuals with interest will be offered a clinical interview by performed by a neurologist at St. Olav's Hospital, Haukeland University Hospital, Oslo University Hospital (Ullevål and Rikshospitalet), or Akershus University Hospital depending on the patient place of residence. Information about the study and the trial's informed consent would be given by an independed qualified study nurse or study doctor and not by the treating physician, and no study related procedures would be performed before the patient have signed the informed consent form.

Some potential participants can be identified by ordinary patients evaluated by the outpatient clinics of the neurological departments of the study hospitals St. Olav's Hospital, Haukeland University Hospital, Oslo University Hospital (Ullevål and Rikshospitalet), and Akershus University Hospital. In such case, information about the study and the trial's informed consent would be given by an independed qualified study nurse or study doctor and not by the treating physician. No study related procedures would be performed before the patient have signed the informed consent form. The present study will not needs access to information from patient medical records to identify potential participants.

The proportion of eligible episodic migraine patients at each centre is not easy to predict, as other similar RCT studies with e.g. candesartan is still ongoing. Thus, an inclusion period of at 4 years can be expected. As a consequence, the last included patients being to the last visit is estimated to be before 31/12/2028.

4.1.2 Number of patients

450 patients (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 departments is terminated when 450 patients have been included altogether.

4.1.3 Participating investigators and departments

MD, PhD, neurologist Lise Rystad Øie	St. Olavs's Hospital 7006 TRONDHEIM
MD, PhD, neurologist Marte-Helene Bjørk	Haukeland Hospital 5021 BERGEN
MD, PhD, Kjersti Grøtta Vedvik	Akershus University Hospital 1478 LØRENSKOG
MD, PhD, Anne Hege Aamodt	Rikshospitalet -Oslo University Hospital 0424 OSLO
MD, PhD, Bendik Slagsvold Winsvoll MD, PhD Linn Hofsøy Steffensen	Ullevål- Oslo University Hospital 0424 OSLO University hospital of North Norway 9038 Tromsø

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, patients should retrospectively have from 4 to 14 migraine days per month during the last 3 months. This frequency must be confirmed in the headache diary before randomisation 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, just before randomisation to the study drug, inclusion criteria will be evaluated once more, and the headache diary will be evaluated. If there are, according to the headache diary, fewer attacks than 4 or more than 14 per month, the baseline period can be extended to 8 weeks, and the patient can be randomized to a treatment then if there is a mean of 4-14 attacks per 4 weeks during the 8-week's period.

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 sterilisation 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, home pregnancy test should take every month (week 4 and week 8) and until 3 days after the end of the treatment period.

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, ASAT, ALAT, Gamma GT and bilirubin), muscle function (creatine kinase), glucose, high sensitivity (hs) CRP, LDL cholesterol, and status of Vitamin D will be performed for all patients. All analyses except for vitamin D must be within normal limits before randomisation. Because non-fasting glucose will be tested, serum glucose should be <7 mmol/l. To eliminate pregnancy, a negative urinary test is required. The blood samples would be destroyed immediately after the analyses, and the test is useful as reference values for the follow-up tests.

Approximately in week 4 of the treatment period, a new blood sample will be drawn of all participant, evaluating liver transaminase, glucose, hs-CRP, LDL-cholesterol and creatine kinase (CK). In week 8 and 12, ALAT, CK and glucose will be analysed. All these analyses is performed to detect rare, but potential harmful side effect of Atorvastatin. The blood samples would be destroyed immediately after the analyses.

As stated in 4.2.1, fertile women should take a home pregnancy test in week 4, week 8, and until 3 days after the end of the treatment period.

During the treatment period, home pregnancy test should take every month (week 4 and week 8) and until 3 days after the end of the treatment period.

If the participants report new onset occurrence of muscle pain or other severe side effects during the treatment period, ad-hoc supplementary blood tests evaluating ALAT, CK, hs-CRP and glucose will be initiated by principle investigator at the relevant centre and performed at the hospital or in primary care, but evaluated at the nearest hospital. If myositis is suspected additional blood test blood sample evaluating SLOC1B regarding risk of statin induced myositis (SLOC1B) will be forwarded to St. Olavs Hospital sykehus for analyses. After these analyses, the blood samples will be destroyed immediately after the analyses.

4.3 Exclusion criteria

Patients 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 medicines for migraine prophylaxis less than 4 weeks, or of botulinum toxin less than 16 weeks, prior to start of study

9) Current use of antiviral treatment against hepatitis C

10) Significant psychiatric illness

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

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 buy marketed Atorvastatin Xiromed 20 mg firm-coated tablets which have to be covered not showing the correct mg of the tablet. 40 mg tablets vill be made by covered two 20 mg tablets. Identical film-coated placebo tablets will be made. 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 the departments' regular medicine 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

Patients will be randomized in blocks decided by independed persons at the Clinical trial unit. A randomisation list containing 450 patient numbers is made before the start of the study by the Clinical trial unit. This list will be sent to the medicine producer, who will label each medicine box with a number from 1 to 450 and make the content of the capsules as indicated on the list. The producer sends medicine boxes to each centre. As patients are randomised, they are given the lowest available box number at that centre. This number is written in the electronic CRF and the headache diary, and is also noted in the hospital records. The patients will take one capsule orally every day (see 5.3). Each box will be labelled with box number, inclusion number, name of drugs in the trial, name of project leader and sponsor, and contact telephone number. For all patients, there will be a sealed envelope containing information about the content of capsules in the box, in case of emergency (see 7.2.3).

5.5 Subject numbering

Each subject is identified in the study by a unique subject number that is assigned when subject 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.

5.6 Duration of therapy

Patients will take the medicines every day for 12 weeks (84 days).

5.7 Concomitant therapy

The following medication is not allowed while the patient is included in the study of the study:

- Any migraine prophylactic drug (See exclusion criteria)

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

For participants with Vitamin D deficiency defines as <50 nmol/l measured at baseline screening, vitamin D supplement will be recommended, but not mandatory.

5.8 Subject adherence

5.8.1 Definitions

The definition of protocol deviation and violation are based on the following statement (33), and should in this study cover all incidences of participant non-adherence to study procedures after enrolment, as defined in the protocol and standard operating procedures (SOP). Study personnel non-compliance with protocol, SOP and other study requirements is defined in section 10.3.2.

Protocol deviation

A protocol deviation occurs when, without significant consequences to the quality or completeness of the data, the activities of a study participant diverge from the study requirements, e.g., missing a visit window because the subject is traveling. A protocol deviation should not have a significant effect on the subject's rights, safety, or welfare.

Protocol violation

Serious participant non-adherence: A divergence from the protocol that materially reduces the quality or completeness of the data or have a significant consequence on the subject's rights, safety, or welfare.

Headache diary and medication adherence assessment

Adherence to the study regimen (per-protocol patients) is defined as registration of at least 90% of days (i.e. 76 days) in the Headache Diary during the treatment period (weeks 5 – 16). Participants with less days registered will be counted as protocol violators and included in the intention-to-treat (ITT) analysis.

5.9 Drug accountability

The drug will be sent from 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 (Patient number and initials, number of tablets, date of dispensing)
- Information on returned medicine (number of tablets, date of returning)
- Date of destruction of medicines

6. STUDY PROCEDURES

6.1 Trial flow chart

TABLE 1: 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 AE: Adverse event; WOCBP: Women of child-bearing potential. [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.

6.1.1 Informed consent

Informed consent must have been given voluntarily by each subject before any study specific procedures are initiated. The information about the study and the Informed consent Form (ICF) should be given by an independed qualified study personal. The ICF would be sent by helsenorge.no by a process in eFORSK run by Hemit AS in cooperation with "Norsk Helsenett (NHN)." The participant can read the ICF in helsenorge.no and consider to participate, and can re-consider by seeing the ICF during the study period in helsenorge.no.

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 (cor/pulm), 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 WOCB (See 4.2.1), and if so, whether they use highly effective contraception (see 4.2.2).

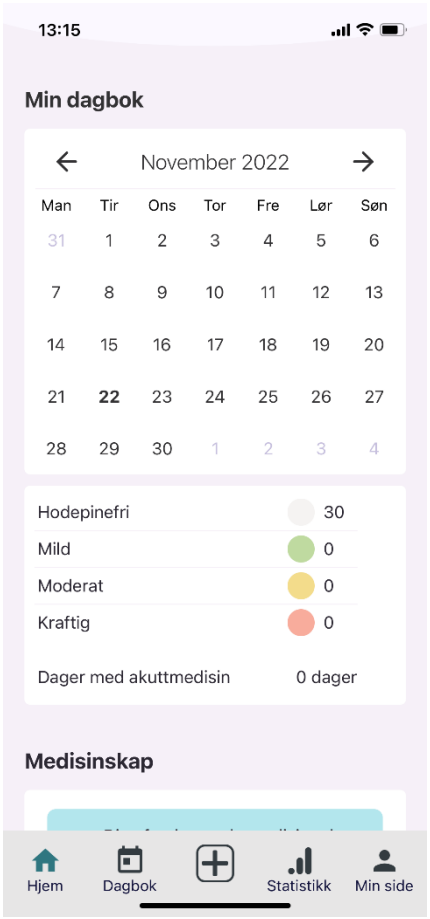
Blood samples evaluating liver and kidney function (serum creatinine, ASAT, ALAT, Gamma GT and bilirubin), muscle function (creatine kinase), hs-CRP and LDL cholesterol, and status of Vitamin D will be performed for all patient (see 4.2.3). All analyses except for vitamin D must be within normal limits before randomisation.

6.1.3 Concomitant medication

All concomitant medication (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 patients have to fill in an electronic headache diary during the baseline period, the 12 weeks treatment period, and the four-week follow-op period (in total 21 weeks). The patients have to log on with a personal code in a study version of BrainTwin. The participants get a reminder every day from Brain Twin asking if they have headache or not. AE could not be reported in the current version, but mat be included in an updated version before the present study will be started. If they have headache, they have to report the intensity (mild, moderate or severe) and the use of analgesics as demonstrated in Figure 1:



6.1.5 Baseline period

If needed, the baseline period can be extended to 8 weeks if the patients did not fulfil the criteria of chronic migraine, or some blood tests for unclear reason are outside normal limits.

6.1.6 Telephone contact by the study nurse and blood sample at follow-up

The patient 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). In the telephone call in week 3 of the treatment period, the study nurse will remind the patient to bring the blood test form related to week 4 of the treatment period to the hospital for a new blood sample at the hospital evaluating liver transaminases, glucose, CK, hs-CRP and plasma LDL (to avoid unblinding) immediately.

Study patients who report severe side effect, the principle investigator will initiate additional ad-hoc blood sample evaluating CK, transaminases and hs-CRP, in particular for patients report new onset of myalgia pain during the study. If myositis is suspected additional blood test blood sample evaluating SLOC1B and will be forwarded to St. Olav's hospital for analyses. After these analyses, the blood samples will be destroyed immediately**.** In 8 and week 12 of the treatment period and in the final visit, a new blood sample will be drawn of all participant, evaluating liver transaminase, CK and glucose.

6.1.8 Genetic analyses

As stated in 4.2.3, ad hoc blood samples will be drawn If myositis is suspected and forwarded to forwarded to St. Olav'S Hospital for analyses of SLOC1B because SLOC1B increase rthe risk of statin induced myositis. After the analyses of genetic panel, the blood samples will be destroyed immediately.

6.1.9 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 patient. If cholestasis or renal/hepatic disease was suspected at inclusion, negative blood analyses must be documented (See 4.2.3).

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

6.1.10 Evaluation of blood samples at baseline and follow-up

The baseline blood samples should be in the normal limit, e.g. ASAT should be < 50 and hs-CRP <5. Non-fasting blood samples will be drawn, and plasma glucose should be <7 mmol/l.

In the additional blood test in week 4, week 8and week 12 of the treatment period, 2 times higher values of ALAT can be accepted, because asymptomatic elevated transaminases (3 times higher values) occur in 0.4% among user of statins compared to the placebo group (35). Non-fasting glucose should be below <7.

6.1.11 Patient withdrawal

The participants can withdraw their consent to participate during the study without providing a reason for this. The patient can contact the study personal or by using a study-specific email for such withdrawal. 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. If so, AEs and the reason for withdrawal can be noted.

6.1.12 After end of treatment (follow-up period)

After end of medication intake (week 16), patients will use a headache diary for another 4 weeks in order to register potential rebound effects. After this, no follow-up is planned in patients without complications. However, all ongoing AEs will be followed-up at least until at least 30 days after last IMP

administration, resolve or return to baseline value.

6.1.13 End of study visit treatment (follow-up period)

The electronic headache diary is reviewed, and SAE/AEs are registered. All headache diaries are collected from the patient if a paper version was used.

7. SAFETY ASSESSMENTS

7.1 Definitions of adverse events

7.1.1 Adverse Event (AE)

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

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

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

Symptoms or signs that are clearly related to migraine will not be recorded. This includes typical migraine headache with concomitant nausea, vomiting, phono- or photophobia, and of visual or sensory migraine aura if present before randomisation to study medicine.

7.1.2 Adverse event severity evaluation

Mild: The adverse event is transient and easily tolerated.

Moderate: The adverse event causes the subject 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 hospitalisation, 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 at least until at least 30 days after last IMP administration, resolve or return to baseline value.

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 patient 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 patient 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 patient should become pregnant, in spite of the precautions taken, the outcome of the pregnancy will be recorded.

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 become aware of the reation.

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

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 fata- 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 patients will be referred to the nearest relevant hospital department.

7.3 Safety monitoring

7.3.1 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, ECG machine, etc…) 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.

7.3.2 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

In accordance with the Declaration of Helsinki, the Investigator must explain to the subject 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 6.1.9, if the patient contact the study personal 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, AEs and the reason for withdrawal can be noted and recorded in the CRF.

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 4.2 and 4.3)

• Patient's non-compliance to completing the Headache Diary during the baseline period;

• Patients starting on novel headache prophylactic medication

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

• Patient lost to follow-up

• Withdrawal

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

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 Data Safety Monitoring Committee

An indepeneded Data Safety Monitoring Committee (DSMC) may give advice that the trial should be temporary or permanently discontinued based on accumulated safety data. The final decision will be made by the Sponsor in collaboration with regulatory authorities.

9. STATISTICAL CONSIDERATIONS

9.1 Hypotheses

The study has mainly been powered to answer the following hypothesis:

H1: Alternative hypothesis: Atorvastatin 40 mg per day results in significantly fewer migraine days /4 weeks than placebo

H2: Null hypothesis: There is no difference in change from baseline in mean migraine days/4 weeks during the treatment period between the Atorvastatin 40 mg and placebo

In addition, it is also an aim of the study to evaluate several secondary hypotheses:

H3: Atorvastatin 20 mg results in significantly fewer migraine days /4 weeks than placebo
H4: Atorvastatin 20 or 40 mg results in significantly fewer headache days /4 weeks than placebo

H5: Atorvastatin 20 or 40 mg results in significantly fewer doses of analgesics of any type /4 weeks than placebo
H6: Atorvastatin 20 or 40 mg results in significantly fewer days with sick leave /4 weeks than placebo

H7: There are more responders (reduction in migraine days with more than 50% compared to baseline) in the Atorvastatin groups (20 or 40 mg) than in the placebo group

H8: Placebo and Atorvastatin 20 mg give significantly fewer side effects than Atorvastatin 40 mg

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.

As to the second hypothesis (H2), whether Atorvastatin 20 mg daily is superior to placebo, no power analysis has been made for this, but we wish to see whether an effect can be detected with the same group size as we use to test H1.
A reduction of 1 headache day per month is considered as clinically meaningful reduction for patients with episodic migraine (6, 7). Using data from our previous studies for migraine (6, 7), with the same inclusion/exclusion criteria and primary

efficacy variable (days with migraine per 4 weeks) very similar to the ones in the present study, it was calculated that a sample of 123 in each group was needed (alpha 0.05, 80 % power) to detect a reduction in mean frequency of migraine days per month of 1 day (from 8 (SD 2.8) to 7). Expecting a dropout rate of at maximum 20 %, 150 patients will have to be included in each group. With 3 treatment arms, that is 450 patients altogether.

9.3 Interim analyses

An interim analysis of efficacy will not be performed. However, throughout the study, safety data will be reviewed by the DSMC as described in section 7.3.1. The study will be stopped temporarily or permanently if the Sponsor, based on the recommendations from the DSMC, finds that the risk of participation for the patients is greater than the expected benefit of the study; or if the regulatory authorities decides this.

9.4 Procedure for statistical analyses

The main statistical analysis will be performed when the planned number of patients have been included, when all included patients 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 the Clinical Study Report. 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 lock.

We plan to let the statistician be blinded as to which treatment each group has been given. This can be achieved by letting our data manager break the randomisation code and make groups labelled A, B or C) on which the statistical tests are run. In this way we will obtain a statistician-blinded study.

The primary population for ITT analysis will include all randomized participants whether they receive treatment or not (intension-to-treat strategy). The null hypothesis to be tested is that there is no difference in change from baseline in mean monthly headache days during the treatment period between the active treatment and the control group (See 9.1, H_1).
The primary endpoint will be analyzed using parametric method with t-test. Differences between analyzed groups is defined as statistically significant using two-side test at a p-value

<0.05. Supplementary sensitivity analyses will be done for per protocol completers (defined as registration of at least 90% of days (i.e. 76 days) in the Headache Diary during the treatment period (weeks 5 – 16). We may 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).

Included patients with episodic migraine would have baseline migraine frequency between 4-14 days/months. We may expect that more Individuals have 4-7 days/month than higher values (Poisson distribution), and parametric model evaluating treatment effect from generalized linear mixed models presented using odds ratios and associated 95% confidence. This method allows adjustments for known confounders as age, gender distribution, years lived with migraine, and number of previous preventive treatment attempts if they differ between the two groups at baseline. In the generalized linear mixed models, potential difference in dropouts caused by e.g. side effects could be considered. It should be mentioned that such difference was not found in our previous four performed RCTs with preventive medical treatment in migraine patients. The overall dropout rate was 10% (38) and caused by several different reasons, including pregnancy, co-occurrence of other diseases needing treatment, hospitalization needing unblinding, or by unspecified reasons. Demographics and baseline characteristics, including known confounders, will be presented separated by treatment arms (i.e. active treatment and placebo) using descriptive statistics.

This trial has a confirmatory statistical strategy that pre-specifies just one single null hypothesis relating to the primary variable. Secondary hypotheses are considered non-confirmatory. It is not considered necessary to adjust for multiplicity when there is a single primary outcome, as findings for secondary outcomes in this study will be considered subsidiary and exploratory, rather than confirmatory. This is in line with “Guideline on multiplicity issues in clinical trials EMA/CHMP/44762/2017”. Rather than adjust for multiplicity or applying fixed sequence or gatekeeping approaches, the trial explores a number of secondary endpoints. Their analysis will be prespecified in the statistical analysis plan (SAP). We argue that this approach will enable us to generate hypothesis 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).

Any change to the data analysis methods in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data collection forms

The Sponsor will supply the centres with web-based Case Report Forms (Viedoc) specific for the particular trial. Site personnel will be trained in how to complete the CRF by using Viedoc. The

Viedoc will be designed with special focus to fulfil the requirements for completeness, accuracy, reliability and consistency with the intended trial. A personal log-in will be provided for all responsible personnel to allow for an audit trail relating to the study data to be maintained.

Completed paper version (if used), as well as the informed consent declarations for those who signed a paper version rather than via helsenorge.no, participant list, prescreening lists and a paper version of the CVs of study personnel, will be kept at the study centres until the end of the study and before estimated active part of the study ending before 31/12/2028. A sponsor representative will collect the originals.

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 in a timely manner. Only certified persons using two-factor login procedure have access to Viedoc. The data will be stored in a dedicated and secured area in Viedoc Each study participant is recognizable by his/her unique participant study identification (ID) numbers. All included patients have to fill in an electronic headache diary during the baseline period, the 12 weeks treatment period, and the four-week follow-op period (in total 21 weeks). The patients have to log on with a personal code in a study version of BrainTwin with data transferred as deidentified data at a secured approved server located in Stavanger administrated by Microsoft Azure Norway. Headache diary data will be later be transferred to a secured area of HUNT Cloud. After this process, the headache diary data stored at Microsoft Azure Norway will be delated.

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 describe 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.

10.3 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 eFORSK (Training log see Appendix 4).

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 all 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

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/NTNU 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 patient 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 patient’s eligibility for the study;
- Diseases (past and current; both the disease studied and others, as relevant);
- Surgical history, as relevant;
- Treatments withdrawn/withheld due to participation in the study;
- Results of assessments performed during the study;
- Treatments 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 Patient 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 independed qualified study personal without depended relationship as a treating physician. The independed qualified study personal will explain the details of the study and will hand out the Study Information in case the paper version will be used. In most cases, the ICF would be sent by helsenorge.no. The participant can read the ICF in helsenorge.no and consider to participate, and can re-consider by seeing the ICF during the study period in helsenorge.no. Patients 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 patients 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 Liability

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 patient 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 patients, provided patients with serious medical conditions and risk of pregnancy are avoided.

Patients should be thoroughly informed of the possibility of not having an effect of the medicine, and the possible side effects. Patient must not feel pressured to participate and also be given sufficient time to consider.

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 remitted 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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