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A non-interventional study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in Nordic countries

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Author	[redacted]

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
AvoHILMO	Finnish Register of Primary Health Care Visits (Avohoidon hoitoilmoitus)
CABG	Coronary artery bypass graft
CGRP	Calcitonin Gene-related Peptide
CI	Confidence Interval
CNS	Central Nervous System
CV	Cardiovascular
DDD	Defined daily dose
DUS	Drug Utilization Study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GRACE	Good Research for Comparative Effectiveness
GVP	Good Pharmacovigilance Practices
HA	Health Authority
HILMO	Finnish Care Register for Health Care (Hoitoilmoitusjärjestelmä)
ICD-10	The International Classification of Diseases, 10th Revision
ICD-11	The International Classification of Diseases, 11th Revision
ICMJE	International Committee of Medical Journal Editors
ICPC-2	International Classification of Primary Health Care
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KUHR	Norwegian Registry of Health Checks and Payments (Kontroll og utbetaling av helserefusjoner)
LMP	Last Menstrual Period
MACE	Non-fatal MI, non-fatal stroke or CV death
MAH	Marketing Authorization Holder
MI	Myocardial Infarction
NCSP	Nordic Medical Statistical Committee Classification of Surgical Procedures
NI	Non-interventional
NIS	Non-interventional Study
PAS	Post-authorization Study
PASS	Post-authorization Safety Study
PCI	Percutaneous intervention
PI	Principal Investigator
PNU	Prevalent New User

PSUR	Periodic Safety Update Report
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient ischemic attack
THL	Finnish National Institute of Health and Welfare (Terveyden ja hyvinvoinnin laitos)

1 Responsible parties

Table 1-1 Responsible parties

Role	
Main protocol author	
Principal investigator (PI), protocol contributor, reviewer	
Coordinating investigator, protocol contributor, reviewer (Finland)	
Coordinating investigator, protocol contributor, reviewer (Norway)	
Coordinating investigator, protocol contributor, reviewer (Sweden)	
MAH contact person	

2 Abstract

Title

A non-interventional study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in Nordic countries

Version and date

01, 12-Sep-2019

Name and affiliation of main author

[redacted]

Rationale and background

Migraine is a common recurrent primary headache disorder and is the most frequent cause of disability among adults younger than 50 years. Prevalence of chronic migraine is 1-2% in the general population and 8% among migraine patients. Chronic migraine has been treated with agents used for other indications, such as beta-blockers or antiepileptic agents. Erenumab, a monoclonal antibody targeting the calcitonin gene-related peptide (CGRP) receptor, is the first specific treatment for chronic migraine. Theoretically, blockage of the CGRP-involving pathways, which are ubiquitous in the human body, may affect compensatory vasodilation during ischemia; furthermore, cardiovascular morbidity among patients with migraine is higher than that in the general population. Initial cardiovascular safety and efficacy of erenumab have been assessed in several randomized controlled trials, including a study among patients with stable angina. However, most trials excluded patients with risk factors for cardiovascular morbidity. For a drug with a novel mechanism of action, such as erenumab, a non-interventional study is needed to characterize the user population and the patterns of drug utilization, including previous prophylactic treatments, comorbidities and concomitant medication, rates of cardiovascular events, and the availability of a suitable comparator population for the long-term assessment of erenumab safety in routine clinical practice. This information is essential for designing a potential future post-authorization safety study (PASS) with a comparative analysis. . Furthermore, there is no experience with erenumab use in pregnancy. This study is a commitment of Novartis to the European Medicines Agency as a component of the erenumab European Union (EU) risk management plan.

Research question and objectives

The primary objective is to describe utilization of erenumab among patients with migraine. The secondary objective is to identify potential comparators for a future erenumab PASS. The exploratory objectives are 1) to estimate rates of cardiovascular outcomes in patients initiating erenumab or other prophylactic migraine medication; and 2) to describe utilization of erenumab and outcome in pregnancy.

Study design

This will be a cohort study. The patient inclusion period will extend from 08 August 2018 to 30 September 2022 and the latest end of follow-up will be 31 December 2022. The maximum baseline period for ascertaining patients' characteristics will extend up to 10 years before the study start date.

Setting and study population

This study, based on secondary data, will be a population-based study based on routinely and prospectively collected data in four Nordic countries: Denmark, Finland, Norway, and Sweden. Each country has tax-funded, universal access to health care and a vast network of interlinkable health and administrative registries, with data linkable on patient level. The study population will be adults (ages 18 years or older) resident of one of the countries above who have established migraine and initiate erenumab or another prophylactic migraine medication during the patient inclusion period.

Variables

Migraine will be identified using diagnostic or medication proxies. Based on the dispensing on the global index date, patients will be initially classified into the erenumab cohort or the other prophylactic migraine medication cohort. Characteristics of utilization of erenumab and other prophylactic migraine medications will be defined based on dispensing data and defined daily doses. Baseline characteristics measured on all patients before inclusion into the study will include risk factors for cardiovascular diseases, including history of cardiovascular morbidity at baseline; other relevant chronic somatic and psychiatric morbidity; baseline history of medication use, including medications used in treatment of migraine; lifestyle characteristics; and indicators of health care utilization. Following initiation of erenumab or other prophylactic migraine medications, rates of cardiovascular endpoints of interest will be calculated for erenumab and for other prophylactic migraine medications. Finally, utilization of erenumab in pregnancy and characteristics of these pregnancies will be described. In addition, pregnancy outcomes, including hypertensive disorders, placenta previa, and premature separation of placenta will also be provided.

Data sources

In each country data will originate from relevant registers or registries of routinely collected data: prescription registries, patient registries, primary care registries, population registries, birth registries, and cause of death registries.

Study size

All eligible patients initiating erenumab or other prophylactic migraine medications will be included.

Data analysis

This will be a descriptive study. For the primary and secondary objectives, class descriptive characteristics will be summarized using frequencies and proportions. Continuous variables will be summarized using means with standard deviations and/or medians with interquartile ranges, and ranges, as appropriate. Continuous variables may be additionally categorized as appropriate clinically. For the exploratory objective related to rates of cardiovascular endpoints, rates will be computed as the number of patients with an event during the follow-up divided by the total person-time at risk. In each treatment cohort, the follow-up for each patient will begin on the treatment cohort index date and will end on the date when the endpoint is observed, switch to a

new treatment cohort, treatment discontinuation, emigration, death, or 31 December 2022, whichever comes first. Assumptions about length of the risk period attributable to a discontinued treatment following discontinuation will be explored in sensitivity analyses. For the exploratory objective related to pregnancy, number and prevalence of pregnancies with a dispensing of erenumab and pregnancies with dispensing of other prophylactic migraine medications will be reported as well as prevalence of each prespecified pregnancy outcome according to the exposure to erenumab and other prophylactic migraine medications.

Milestones

Planned dates of study milestones:

- Start of data collection for the final report: 29 May 2024;
- End of data collection for the final report: 28 August 2024;
- Interim report 1 reported in PSUR: 20 December 2022;
- Interim report 2 reported in PSUR: 20 December 2023;
- Final report of study results: 30 March 2025.

3 Amendments and updates

- None

4 Milestones

Table 4-1 presents the planned dates for the study milestones based on the most up-to date information regarding data lags in the different data sources.

The patient inclusion period will be from 8 August 2018 to 30 September 2022. Patients will be followed until 31 December 2022.

Table 4-1 Planned dates of study milestones

Milestone	Planned date
Start of data collection for the final report (the date from which data extraction starts)	29 May 2024
End of data collection (date from which the analytical dataset is completely available)	28 August 2024
Interim results 1 for inclusion in Periodic Safety Update Report (PSUR) for regulator	20 December 2022
Interim results 2 for inclusion in PSUR for regulator	20 December 2023
Final report of study results submitted to EMA (1 year after end of data collection)	30 March 2025

5 Rationale and background

Migraine is the second, after tension-type headache, most prevalent neurologic disorder and is a leading contributor to loss of disability-adjusted life-years (Feigin et al 2017). Since 2015, migraine has advanced from the third to the first position in the ranking of the most frequent causes of disability among adults younger than 50 years (Collaborators 2017, Steiner et al 2018).

Migraine is a recurrent primary headache disorder, with attacks lasting 4-72 hours (Headache Classification Committee of the International Headache 2013 (Headache Classification Committee of the International Headache 2013) (Headache Classification Committee of the International Headache 2013)). One-third of the patients experience migraine with aura, which is a collective term for visual and sensory disturbances that may accompany a migraine attack (Dodick 2018). Migraine is 2-3 times more prevalent in women than in men, and its incidence rate peaks at age 30-39 years in both men and women (Vetvik et al 2017). With respect to the attack frequency, migraine requiring treatment can be classified as episodic (0-14 monthly headache days) or chronic (≥15 monthly headache days, including ≥8 monthly migraine days) (Katsarava et al 2011, Katsarava et al 2012). Prevalence of chronic migraine is 1-2% in the general population and 8% among migraine patients. Annually, 3% of patients with episodic migraine progress – reversibly – to chronic migraine. Risk factors for episodic and chronic migraine include overuse of acute migraine medications, obesity, age, sleep disturbances, psychiatric morbidity, female sex and low education (Buse et al 2013, May et al 2016, Minen et al 2016, Klenofsky et al 2019). Migraine-associated genetic loci have also been identified (Gormley et al 2016).

Migraine initiates in the central nervous system (CNS), which is followed by activation of the trigeminal system and release of neuropeptides, including the calcitonin gene-related peptide (CGRP), a 37-aminoacid neuropeptide, believed to play a role in the maintenance of the headache and possibly in other migraine symptoms, although the mechanism by which CGRP contributes to migraine is not yet fully understood (Bigal et al 2015, Iyengar et al 2017). CGRP is a potent vasodilator and neurotransmitter, whose blood level rises and falls correlate with migraine attack onsets and terminations, and which triggers migraine attacks on administration (Bigal et al 2015, Levin et al 2018). CGRP and its receptor are ubiquitous in the human body, including the CNS, the cardiovascular (CV) system, and the gastrointestinal system (Dodick 2018).

Erenumab, a monoclonal antibody, is a human IgG_2 targeting the CGRP receptor (Bigal et al 2015). Initial safety and efficacy of erenumab have been assessed in several phase 2 and phase 3 randomized controlled trials (RCTs) (Tepper et al 2016, Ashina et al 2017, Goadsby et al 2017, Lipton et al 2017, Tepper et al 2017, de Hoon et al 2018, Dodick et al 2018, de Hoon et al 2019) . Two phase 3 placebo-controlled RCTs evaluated safety and efficacy of erenumab for migraine prophylaxis among adult patients with episodic migraine (Goadsby et al 2017,Dodick et al 2018). In the STRIVE trial of 955 patients with a mean of 8.3 monthly migraine days at baseline, the mean reduction of monthly migraine days in months 4-6 of follow-up was 3.2 in the 70-mg erenumab arm, 3.7 in the 140-mg erenumab arm, and 1.8 in the placebo arm (Goadsby et al 2017). In the ARISE trial of 570 patients with a mean of 8.1-8.4 monthly migraine days at baseline, in month 3 of follow-up, mean reduction of monthly migraine days was 2.9 in patients in the 70-mg erenumab arm, and 1.8 days in the placebo arm (Dodick et al 2018). In that study, allocation to erenumab was associated with a reduced use of acute migraine-specific medications (Dodick et al 2018). Safety and efficacy of erenumab for prophylaxis of chronic migraine in adults were evaluated in a phase 2 placebo-controlled RCT

of 667 patients with a mean of 17.8 to 18.2 monthly migraine days, followed for up to 12 weeks. The mean reduction of monthly migraine days was 6.6 in the erenumab 70-mg and 140-mg arms, and 4.2 days in the placebo arm (Tepper et al 2017). In all three RCTs, a substantial proportion of participants had failed another preventive migraine treatment (Goadsby et al 2017, Tepper et al 2017, Dodick et al 2018). In subgroup analysis of RCT participants with chronic migraine and medication overuse, erenumab reduced migraine frequency and acute migraine-specific medication treatment days (Tepper et al 2019). Clinically relevant improvements in of patient-reported outcomes have also been reported with erenumab (Lipton et al 2019). Tolerability of erenumab was reported in a meta-analysis of RCTs (Vo et al 2019) and from an open-label extension trial after a median of 3.2 years on-treatment (Ashina et al 2019). Per European Medicines Agency (EMA) Summary of Product Characteristics, the recommended erenumab dose is 70 mg subcutaneously every 4 weeks, with some patients potentially benefiting from the dose 140 mg subcutaneously every 4 weeks (EMA 2018a).

CV morbidity among patients with migraine is higher than that in the general population (Bigal et al 2010, Adelborg et al 2018). Theoretically, blockage of the CGRP-involving pathways may affect compensatory vasodilation during ischemia (Dakhama et al 2004, MaassenVanDenBrink et al 2016, Tepper 2018). Data to date from the RCTs do not indicate an increased CV risk associated with erenumab use (Goadsby et al 2017, Tepper et al 2017, Depre et al 2018, Dodick et al 2018, Tepper et al 2018, Winner et al 2018), as measured by short-term changes in blood pressure (Tepper et al 2018); by CV side effects among migraine patients with CV risk factors (Winner et al 2018); or by exercise time among patients with stable angina (Depre et al 2018). In the latter RCT, erenumab was assessed in patients with stable angina to determine any potential deleterious effects on ischemia-induced vasodilation. The study evaluated the effect of 140 mg intravenous erenumab compared with intravenous placebo on exercise capacity as measured by total exercise time during an exercise treadmill test. The secondary endpoint was exercise-induced angina ST-segment depression. At baseline, all patients in the trial had prior coronary artery disease, 40% had prior myocardial infarction, 62% had a prior percutaneous cardiac interventional procedure, and 33% had a history of coronary artery bypass surgery. The adjusted mean difference in the total exercise time for erenumab vs. placebo arm was –11.0 (90% confidence interval –44.9, 22.9) seconds, with the lower 90% boundary not reaching the non-inferiority margin of –90 seconds. (Depre et al 2018). However, most RCTs excluded patients with myocardial infarction, stroke, transient ischemic attacks, unstable angina, coronary artery bypass surgery or other revascularization procedures within 12 months to screening, limiting generalizability of the findings to patients in routine clinical practice (Sorensen et al 2006, Sacco et al 2019).

In the European Union (EU), erenumab (Aimovig) was approved on 26 July 2018 for prophylaxis of migraine in adults with at least 4 migraine days per month (EMA 2018a). Erenumab market entry dates are 12 September 2018 in Sweden, 17 September 2018 in Finland, 1 October 2018 in Norway, and 22 October 2018 in Denmark. Country-specific patterns of erenumab utilization are expected to be affected by local reimbursement policies. In Norway, erenumab is currently not eligible for reimbursement and the decision is expected in winter of 2020. Individual reimbursement may be granted prior to that date, with more information expected in October 2019 (Legemiddelverket 2019). If reimbursement is granted, it would be for chronic migraine (15 or more headache days including 8 or more migraine days). Patients will be required to have failed 3 or more prophylactic drugs, which may not necessary include onabotulinumtoxin A. In Finland, basic reimbursement of erenumab started on 1 April 2019, and it is granted for adults with 8 or more monthly migraine days who have tried at least two

different prophylactic drug treatments for migraine, which were ineffective, contraindicated or not tolerated. Initial reimbursement is granted for 6 months and is renewed if the number of monthly migraine days is at least halved during the first three months of treatment and the effect is sustained over time; a maximum reimbursement is granted for 2 years at a time (FPA 2019). In Sweden, erenumab is partially reimbursed if prescribed by a neurologist or a headache specialist to patients with chronic migraine who have 15 or more monthly headache days, of which 8 or more are migraine days, and have tried at least two other prophylactic migraine medications (Janusinfo 2019, Läkemedelsvärlden 2019). In Denmark, erenumab is recommended as a possible standard treatment alternative to onabotulinumtoxin A for prevention of migraine in patients with chronic migraine who previously failed preventive treatment with at least one antihypertensive and one antiepileptic agent (Medicinrådet 2019). There are also country variations in dispensing practices of onabotulinumtoxin A, a migraine treatment that may be used in patients with similar characteristics as those treated with erenumab. In Norway and Sweden, some patients get the drug prescribed and some dispensed directly to patients at hospitals or by private practitioners. In Denmark, onabotulinumtoxin A is dispensed directly to patients by a specialist at hospitals (Laegemiddelstyrelsen 2019). In Finland, onabotulinumtoxin A is recommended as potentially, although marginally, effective compared with placebo (Käypä_hoito 2015). Some dispensings of onabotulinumtoxin A appear to be dispensed in outpatient pharmacies. However, the Finnish Medicines Agency estimated that 75% of onabotulinumtoxin A sold in Finland in 2018 was sold to hospitals (FIMEA 2019). It is estimated that in 2018 there were approximately 2000 patients dispensed onabotulinumtoxin A in Finland, but the distribution of indications is unknown.

Current Nordic and European guidelines for prophylactic migraine pharmacotherapy list beta-blockers, antiepileptics, calcium channel blockers, antidepressants, and onabotulinumtoxin A, among others; however, there may be country-specific differences in use (Evers et al 2009, Käypä_hoito 2015, Läkemedelsverket 2015, Sundhedsdatastyrelsen 2015, Norsk_legemiddelhåndbok 2018, Huvudvarkssallskapet 2019). Based on treatment practice to date, at least initially, erenumab in Europe will be used primarily in patients with documented history of failure of other preve ntive treatments. Current Swedish guidelines, for example, call for a trial period of 12 months, with initial evaluation after 3 months, whereby dose and frequency of erenumab administration will be tailored to patients' response (Huvudvarkssallskapet 2019).

For a drug with a novel mechanism of action, such as erenumab, a non-interventional study (NIS) is needed to characterize the user population and the patterns of drug utilization, including previous prophylactic treatments, comorbidities and concomitant medication. In addition, estimated rates of CV events and the availability of a suitable comparator treatment are essential for assessing the feasibility and designing a potential future post-authorization safety study (PASS) with a comparative analysis.

As women of reproductive age account for a substantial proportion of patients with migraine, it is important to characterize erenumab use in pregnancy. Although migraine often improves during pregnancy, enabling discontinuation of pharmacotherapy (Amundsen et al 2015, Harris et al 2017), up to 8% of pregnant women remain affected (Sacco et al 2015, Tepper 2015). Not all prophylactic migraine treatments are suitable for use in pregnancy (Evers et al 2009, Käypä hoito 2015, Läkemedelsverket 2015, Sundhedsdatastyrelsen 2015, Norsk legemiddelhåndbok 2018). Furthermore, migraine itself, regardless of treatment, may be associated with adverse pregnancy outcomes (Skajaa et al 2019). Although RCTs have

demonstrated a favorable risk-benefit profile for erenumab, there are no adequate well-controlled studies on the use of erenumab in pregnancy. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development in monkeys receiving SC erenumab from organogenesis through parturition at exposures up to 16-fold exceeding the maximum monthly recommended human dose of 140 mg. CGRP level increases during pregnancy, and CGRP receptors are expressed in uterus, placenta, and fetus Yallampalli et al (2002). Theoretically, CGRP receptor blockage may have an effect in fetal growth or a potential risk of pre-eclampsia. This NIS is a commitment of Novartis to the EMA as a component of the erenumab EU risk management plan (RMP). The primary objective of this drug utilization study (DUS) is to characterize use of erenumab in post-marketing setting.

6 Research question and objectives

This DUS is a descriptive study and no hypothesis will be tested.

6.1 Primary objectives

The primary objective of this study is to describe utilization of erenumab among patients with migraine, as measured by:

- Number of migraine patients with a dispensing of erenumab (stratified by CV history)
- Calendar year of erenumab initiation;
- Patients' sex and age;
- Prescriber health sector;
- Prescriber specialty;
- Erenumab initiation type: add-on to vs. switching from another prophylactic migraine medication;
- Erenumab persistence,
- Erenumab discontinuation, re-starting, and patterns of switching among CGRP inhibitors;
- Erenumab duration of use and cumulative dose.

6.2 Secondary objectives

To identify potential suitable comparators for a formal comparative safety analysis in a future PASS by identifying patients initiating prophylactic migraine treatment other than erenumab who have similar demographic and clinical characteristics as patients initiating erenumab. To identify such comparator, the following characteristics will be assessed among patients initiating erenumab and patients initiating other prophylactic migraine medications:

- Calendar year of initiation;
- Patients' sex and age;
- Prescriber health sector;
- Prescriber specialty;
- History of CV morbidity (hypertension [including uncontrolled hypertension], unstable angina, MI, coronary artery revascularization by coronary artery bypass graft (CABG) or percutaneous intervention (PCI) (Cohen et al 2018), ischemic stroke (Sulo et al 2017), hemorrhagic stroke, transient ischemic attack [TIA]);

- History of conditions that are risk factors for CV morbidity that can be measured using available data sources (e.g. diabetes, hypercholesterolemia, kidney disease, rheumatic diseases, chronic obstructive pulmonary disease [COPD], obesity);
- History of other somatic or psychiatric morbidity (diseases that may be alternative indications for migraine medications [depression, epilepsy, cluster headache]; psychiatric and somatic morbidity that may affect migraine treatment decisions (Buse et al 2013, Minen et al 2016, Klenofsky et al 2019) [mood disorders, anxiety/stress disorders, substance abuse, chronic pain, sleep disorders]);
- Overall measure of comorbidity burden using Charlson Comorbidity Index and/or another population-suitable comorbidity measure (Charlson et al 1987, Romano et al 1993, Thygesen et al 2011, Yurkovich et al 2015);
- History of use of other specific and non-specific acute and prophylactic migraine medications;
- For patients with migraine initiating other prophylactic migraine medications: distribution of specific prophylactic migraine agents initiated during the study, especially number and proportion of patients treated with onabotulinumtoxin A;
- History of use of prescription medications indicative of comorbidities affecting CV risk or those used in migraine prophylaxis (oral contraceptives, lipid lowering agents, antiemetics, antithrombotics, antihypertensives, antidiabetics, antirheumatics, antidepressants, antiepileptics, antipsychotics, anxiolytics, medication used in substance abuse, pain medications, hypnotics);
- Indicators of overall medication use (number of different medication classes from among the above-listed classes);
- Indicators of health care utilization (number of hospitalizations, outpatient visits);
- Lifestyle indicators of CV risk (smoking, alcohol use, obesity);
- Socioeconomic indicators (education, income).

6.3 Exploratory objectives

This study will have two exploratory objectives.

1. To estimate rates of the following CV endpoints of interest among patients with migraine initiating erenumab or other prophylactic migraine medications, overall, and stratified by age, sex, and history of CV morbidity. The following endpoints will be assessed:
    - Hypertension;
    - Hospitalization for acute MI;
    - Coronary artery revascularization by CABG or PCI (Cohen et al 2018);
    - Hospitalization for ischemic stroke (Sulo et al 2017);
    - Hospitalization for hemorrhagic stroke;
    - CV death;
    - MACE, defined in this study as composite endpoint of non-fatal myocardial infarction, non-fatal stroke or CV death.

2. To characterize drug utilization and pregnancy outcomes in pregnant migraine patients exposed to erenumab, other prophylactic migraine medications, and without treatment. (Skajaa et al in press) as measured by:
    - Number and proportion of pregnancies with a dispensing of erenumab (overall, periconception, and in each trimester);
    - Number and proportion of pregnancies among women with migraine with a dispensing of other prophylactic migraine medications (overall, periconception, and in each trimester);
    - Number and proportion of pregnancies among women with untreated migraine;
    - Characteristics of the categories of pregnancies described above pregnancies with a dispensing of erenumab or other prophylactic migraine medications dispensing and in pregnancies with migraine, specifically:
        - Age at conception;
        - Parity;
        - Smoking in pregnancy;
        - Body mass index (BMI);
        - Comorbidities (preconception, same as specified in the primary objectives);
        - Comedications (preconception and during pregnancy, as specified in the primary objectives).
    - Number and prevalence of pregnancy complications in the groups of pregnancies described above:
        - Hypertensive disorders of pregnancy (hypertension, preeclampsia, eclampsia);
        - Placenta previa;
        - Premature separation of placenta [abruptio placentae].

7 Research methods

7.1 Study design

This will be a cohort study using elements of prevalent new user (PNU) approach (Gagne 2017, Suissa et al 2017), which has been proposed for settings when no ideal contemporaneous comparator is available for newly a marketed medicine, while initiation of the newly marketed medication represents either a switch from or add-on to the older therapy.

7.2 Setting and study population

This study, based on secondary data collection, will be a population-based study based on routinely and prospectively collected data in four Nordic countries: Denmark, Finland, Norway, and Sweden (listed alphabetically). Each country has tax-funded, universal access to health care (Schmidt et al 2019) and a vast network of interlinkable health and administrative registries (Rosen 2002, Wettermark et al 2013, Langhoff-Roos et al 2014). Thanks to unique personal identifiers, used in all countries for linkage and tracking of vital status and migrations, the population of each Nordic country is an open cohort with reliable ascertainment of cohort entry (birth, immigration) and exit (death, emigration) dates. Feasibility of this approach has been established previously: identification of diagnoses of migraine and migraine medications, as well as comorbidities, comedications, pregnancies, and endpoints is possible using the proposed data sources (Adelborg et al 2018, Thomsen et al 2019).

The source population of this study will be residents of each participating country aged 18 years or older on the study start date. The study population will be patients with migraine initiating erenumab or another prophylactic migraine medication. The study start date will be 08 August 2018 (the earliest date of erenumab market release) and the study end date will be 31 December 2022. The patient inclusion period will extend from 08 August 2018 until 30 September 2022 (inclusive), allowing a minimum of 3 months of follow-up for all patients. Presence of migraine will be established, as previously described (Thomsen et al 2019), during a period extending from up to 10 years before the study start date and throughout the inclusion period. To be classified as having migraine, patients in the source population will need to fulfill at least one of the following criteria:

- Have a diagnosis of migraine (an inpatient or outpatient hospital diagnosis [all countries] or a diagnosis made in primary care[1] [Finland and Norway]);
- Have ≥2 outpatient dispensings of a migraine-specific acute medication (same or different agents) (Table 7-1);
- Have ≥1 outpatient dispensing of a CGRP inhibitor (erenumab, galcanezumab, fremanezumab, or eptinezumab [as available during the patient inclusion period]).

Migraine date for each patient will be the earliest date the patient fulfills one of the above criteria (migraine diagnosis; second dispensing for a migraine-specific acute medication; or first dispensing of a CGRP inhibitor). The global index date for each eligible patient will be the date of the first dispensing of a prophylactic migraine medication during the patient inclusion period.

7.2.1 Inclusion criteria

Patients in the source population will be required to fulfill the following criteria to be included in the study:

- Fulfill the criteria for migraine between 08 August 2008 and 30 September 2022;
- Have a dispensing a prophylactic migraine medication during the patient inclusion period (between 08 August 2018 and 30 September 2022); the qualifying dispensing must occur on or after the date of fulfilling the criteria for migraine (Table 7-2 and Table 7-3);

7.2.2 Exclusion criteria

Patients fulfilling any of the following criteria will be excluded:

- Age <18 years on the study entry date (the global index cate);
- Less than 12 months' continuous residence in a country of analysis before the study entry date (global index date);
- For patients initiating non-specific prophylactic migraine medication, a dispensing of the same non-specific prophylactic agent in 12 months before the study entry date (global index date).

[1] Use of primary care databases is relatively new and the validity of migraine diagnoses is unknown. It will be determined in the course of the study in consultation with database holders and clinicians whether 1 or 2 records of migraine diagnosis should be indicative of true migraine with sufficient accuracy.

7.3 Variables

7.3.1 Identification of migraine

Migraine will be identified using hospital diagnostic codes in the International Classification of Diseases, 10th Revision (ICD-10) or via medication codes using the Anatomical Therapeutic Chemical (ATC) classification in all countries. Additionally, in Finland and Norway, primary care diagnostic codes in the International Classification of Primary Health Care (ICPC)-2 will be used to identify diagnoses; in Denmark, hospital procedure codes may be used to identify migraine medication (Table 7-1).

Table 7-1 Diagnostic and medication codes used to identify patients with migraine

Migraine cohort defining events	ICD-10 code	ICPC-2 code (Finland, Norway)	ATC code	Hospital procedure code (Denmark)
Migraine diagnosis (primary, secondary, inpatient, outpatient, hospital care, primary care)	G43.0-G43.9	N89		
Specific migraine treatment				
Triptans			N02CC	
Ergots			N02CA	
Erenumab			N02CX07	BOHJ19M1
Galcanezumab			N02CX08	To be added as becomes available
Fremanezumab			N02CX09	To be added as becomes available
Eptinezumab			To be added if becomes available	To be added as becomes available

7.3.2 Exposure

Based on the dispensing on the global index date, patients will be classified into one of the two treatment cohorts:

- Erenumab cohort (sub-classified as switch/add-on);
- Other prophylactic migraine medication cohort (Table 7-2 and Table 7-3).

A third – onabotulinumtoxin A – treatment cohort will be identified if feasible from the available data sources based on record-generating mechanisms.

Table 7-2 Codes to identify specific prophylactic migraine medications (erenumab and other CGRP inhibitors)

Treatment cohort	Drug class	Active substance	ATC code	Hospital procedure code (Denmark)

Erenumab treatment cohort	Other antimigraine preparations	erenumab	N02CX07	BOHJ19M1
Other prophylactic migraine medication treatment cohort	Other antimigraine preparations	galcanezumab	N02CX08	To be added as becomes available
	Other antimigraine preparations	fremanezumab	N02CX09	To be added as becomes available
	Other antimigraine preparations	eptinezumab	To be added if becomes available	To be added as becomes available

Country-specific guidelines (Käypä_hoito 2015, Läkemedelsverket 2015, Sundhedsdatastyrelsen 2015, Norsk_legemiddelhåndbok 2018) differ somewhat with respect to the recommended type of non-specific prophylactic migraine treatments (Table 7-3). Because most erenumab initiators will have tried and failed other treatment options, the initial definition of the prophylactic migraine medication treatment cohort will be broad, i.e., will include all candidate agents and may be narrowed based on the observed patients' characteristics. Onabotulinumtoxin A has been proposed as a potentially suitable comparator for erenumab in a future PASS. However, onabotulinumtoxin AA may be primarily administered in hospitals, while treatments administered in hospitals generally do not generate records in prescription registries.

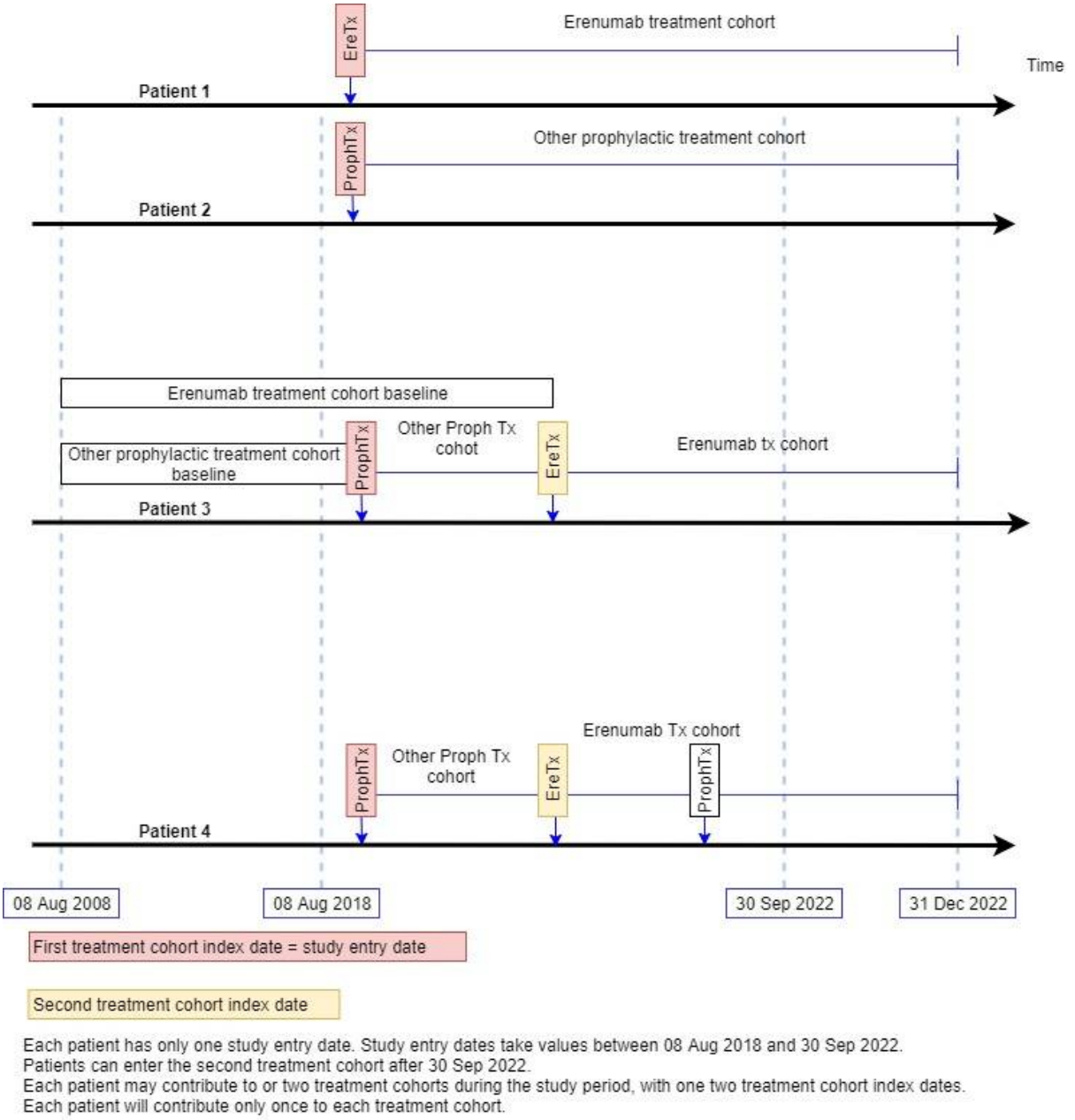
Table 7-3 Codes for non-specific prophylactic migraine medications listed in country-specific guidelines and recommendations

Drug class	**Active substance**	**ATC code**	**Listed in guidelines for prophylactic treatment**			
			Denmark (Sundhedsdatastyrelsen 2015)	**Finland** (Käypä_hoito 2015)	**Norway** (Norsk_legemiddelhåndbok 2018)	**Sweden** (Läkemedelsverket 2015)
Other antimigraine preparations	methysergide	N02CA04				
	pizotifen	N02CX01	x			x
	clonidine	N02CX02				
Beta-blockers	propranolol	C07AA05	x	x	x	x
	timolol	C07AA06			x	
	metoprolol	C07AB02	x	x	x	x
	atenolol	C07AB03		x	x	
	bisoprolol	C07AB07		x		
Calcium channel blockers	verapamil	C08DA01		x		
	flunarizine	N07CA03	x			x
Antidepressants	amitriptyline	N06AA09	x	x	x	x

Drug class	Active substance	ATC code	Listed in guidelines for prophylactic treatment			
			Denmark (Sundhedsdatastyrelsen 2015)	**Finland** (Käypä_hoito 2015)	**Norway** (Norsk_legemiddelhåndbok 2018)	**Sweden** (Läkemedelsverket 2015)
	nortriptyline	N06AA10		x		
	venlafaxine	N06AX16		x		
	fluvoxamine	N06AB08				x
Anticonvulsants	valproate	N03AG01	x	x	x	x
	topiramate	N03AX11	x	x	x	x
Antihypertensives	lisinopril	C09AA03	x	x	x	
	candesartan	C09CA06	x	x	x	x
Other	riboflavin	A11HA04	x			
	estrogen patch	G03CA03				x
	naproxen	M01AE02	x			x
	onabotulinumtoxin A	M03AX01 +hospital procedure codes whenever available	x	x		x

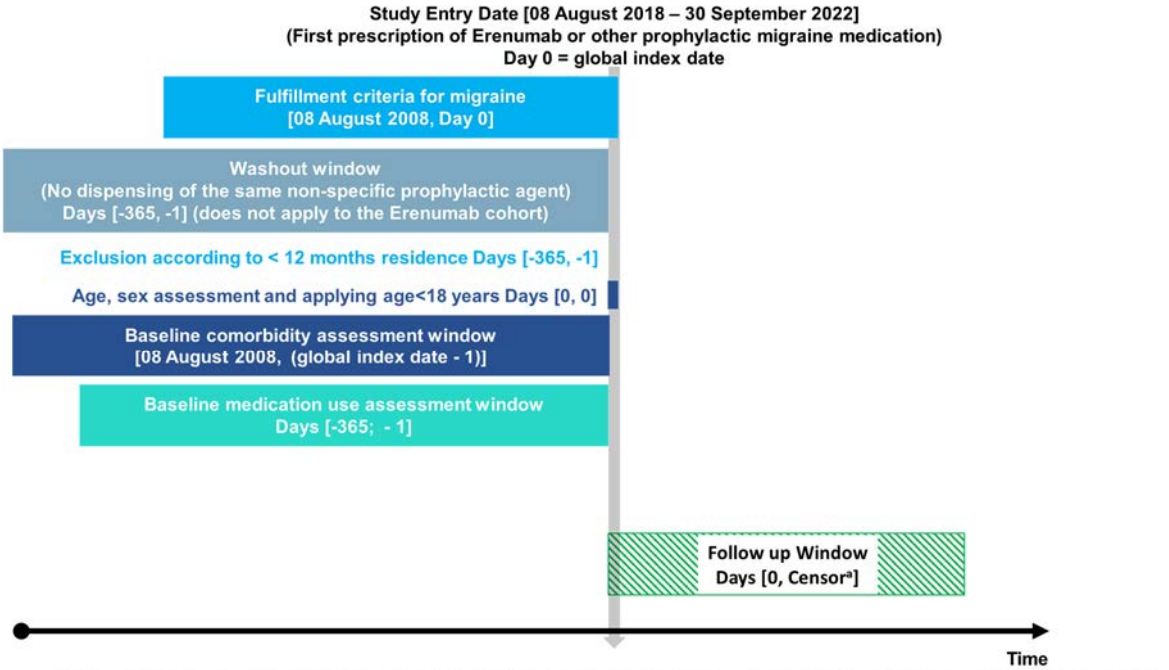
Patients will remain in the initial treatment cohort (the treatment cohort entered on the global index date) until the earliest of initiation of a prophylactic migraine medication qualifying for membership in a different treatment cohort; discontinuation of the prophylactic migraine medication; death; emigration; or the study end date (31 December 2022). On the date of dispensing of a prophylactic migraine medication qualifying for membership in different treatment cohort, a patient will stop membership in the original treatment cohort and start membership in a second treatment cohort, with its own treatment cohort index date, and treatment cohort baseline (Figure 7-1, Figure 7-2) (Schneeweiss et al 2019).

Figure 7-1 Hypothetical scenarios for patients' classification into treatment cohorts



Each patient has only one study entry date. Study entry dates take values between 08 Aug 2018 and 30 Sep 2022.
Patients can enter the second treatment cohort after 30 Sep 2022.
Each patient may contribute to or two treatment cohorts during the study period, with one two treatment cohort index dates.
Each patient will contribute only once to each treatment cohort.

Figure 7-2 Study schema as applied to each individual patients



a. Earliest of: outcome of interest, discontinuation switching to another treatment cohort, death, emigration, end of the study period.

7.3.3 Endpoints

The following section lists primary, secondary and exploratory endpoints according to the corresponding study objectives, with brief definitions of each endpoint. Full operational definitions of the study variables will be developed in consultation with clinical experts and provided in the Statistical Analysis Plan (SAP).

7.3.3.1 Primary endpoints

Primary endpoints will be the appropriate descriptive statistics for the characterization of the patients initiating erenumab.

- Number of migraine patients with a dispensing of erenumab (stratified by CV history)
- Calendar year of erenumab initiation (2018…2022);
- Sex (male/female, as reported in the registries);
- Age at erenumab initiation date (in years, as reported in the registries);
- Prescriber health sector (primary/secondary [hospital]) (Denmark, Sweden) (as identifiable by standard coding in the prescription registries);
- Prescriber specialty (all countries) (neurology, internal medicine.. etc., as identifiable by standard coding in the prescription registries);
- Erenumab initiation type: add-on to vs. switching from another prophylactic migraine medication;
- Erenumab persistence, defined, using published methods, suitable for injectables (Campagna et al 2014, Meid et al 2016), based on dispensing amounts combined with defined daily doses (DDDs); furthermore, persistence will be assessed comparing the

number of dispensings over 1, 2, or 3 years with the yearly number of expected dispensings i.e. 12;

- Erenumab discontinuation, re-starting, and patterns of switching among CGRP inhibitors;
- Erenumab duration of use and cumulative dose received will be expressed in mg and in the number of monthly injections.

7.3.3.2 Secondary endpoints

The following secondary endpoints will be reported as frequencies and percent in each cohort with appropriate baseline as of the global index date (Figure 7-2) (ICD-10 and procedure codes will be used as appropriate in all definitions):

- Calendar year of global index date (2018..2022);
- Sex (male/female, as reported in the registries);
- Age at global index date (in years, as reported in the registries);
- Prescriber health sector (primary/secondary [hospital]) (Denmark, Sweden) (as identifiable by standard coding in the prescription registries);
- Prescriber specialty (all countries) (neurology, internal medicine.. etc., as identifiable by standard coding in the prescription registries);
- Number and proportion of patients with baseline history of each CV morbidity (hypertension [including uncontrolled hypertension], unstable angina MI, CABG or percutaneous intervention PCI, ischemic stroke, hemorrhagic stroke, TIA) (uncontrolled hypertension will be approximated stratification on severity, based on combination of hospital diagnoses, primary care diagnoses [whenever available] and treatment proxies; specifically, diagnostic codes indicating end-organ damage will be considered in the definition);
- Number and proportion of patients with baseline history of each condition that is a risk factor for CV morbidity (diabetes, hypercholesterolemia, kidney disease, rheumatic diseases, COPD] obesity, IBD, psoriasis);
- Number and proportion of patients with baseline history of each specified other somatic or psychiatric morbidity (depression, epilepsy, cluster headache, mood disorders, anxiety/stress disorders, substance abuse, chronic pain, sleep disorders);
- Number and proportion of patients in each category of Charlson Comorbidity Index or another comorbidity measure if deemed appropriate (no comorbidity, low comorbidity, high comorbidity);
- Number and proportion of patients with baseline history of use of each specific and non-specific acute and prophylactic migraine medication;
- For patients with migraine initiating other prophylactic migraine medications: distribution of specific prophylactic migraine agents initiated, especially number and proportion of patients treated with onabotulinumtoxin A;
- Number and proportion of patients with baseline history of use of oral contraceptives, lipid lowering agents, antiemetics, antithrombotics, antihypertensives, antidiabetics, antirheumatics, antidepressants, antiepileptics, antipsychotics, anxiolytics, medication used in substance abuse, pain medications, hypnotics;

- Number and proportion of patients according to categories of number of different medication classes from among the above-listed classes, categories to be specified in the SAP;
- Number and proportion of patients according to categories of health care utilization indicators (number of hospitalizations, outpatient visits), categories to be specified in the SAP;
- Number and proportion of patients with a recorded baseline history of smoking and alcohol use (to the extent recorded in the available data sources);
- Number and proportion of patients according to socioeconomic indicators (highest achieved education, quantiles income), categories to be specified in the SAP.

The maximum baseline period for ascertaining the above characteristics will extend from the day before the appropriate index date (global index date or treatment cohort index date) to 08 August 2008 (10 years before the study start date). A different baseline may be defined for specific characteristics (e.g., medications, ascertainment of the new user status, or income). The length of baseline period for each variable will be specified in the SAP, based on clinical relevance (Figure 7-2).

Based on the distribution of the baseline characteristics of the treatment cohorts, an assessment will be made about the appropriate comparator for a potential erenumab PASS.

7.3.3.3 Exploratory endpoints

The following exploratory endpoints will be measured during the follow-up in each treatment cohort:

- Hypertension (ICD-10/ICPC-2 diagnostic codes, ATC codes for medication proxies);
- Hospitalization for acute MI (ICD-10 codes);
- Coronary artery revascularization by CABG or PCI (NSCP procedure codes);
- Hospitalization for ischemic stroke (ICD-10 codes);
- Hospitalization for hemorrhagic stroke (ICD-10 codes);
- CV death (ICD-10 codes);
- MACE (ICD-10 codes).

The following characteristics will be reported descriptively among the included pregnancies ending in live or still birth, identified in each country's birth registry:

- Number and proportion of pregnancies with a dispensing of erenumab during the study period, overall, periconception and in each trimester (dispensings/ATC codes);
- Number and proportion of pregnancies among women with migraine with a dispensing of other prophylactic migraine medications, overall, periconception, and in each trimester;
- Number and proportion of pregnancies among women with untreated migraine;
- Age at conception (in years, as recorded, categories to be specified in the SAP);
- Number and proportion of pregnancies according to parity categories (as recorded in the birth registries, categories to be specified in the SAP);
- Number and proportion of pregnancies with smoking in pregnancy (yes/no, as recorded in the birth registries);

- Number and proportion of pregnancies in categories of BMI (as recorded in the birth registries);
- Number and proportion of pregnancies with hypertensive disorders of pregnancy (hypertension, preeclampsia, eclampsia) (ICD-10 codes or self-report if available [e.g., in Sweden]);
- Number and proportion of pregnancies with placenta previa (ICD-10 codes);
- Number and proportion of pregnancies with premature separation of placenta [abruptio placentae] (ICD-10 codes);
- Number and proportion of pregnancies with chronic comorbidities (preconception, as specified in the secondary objectives) (ICD-10 codes);
- Number and proportion of pregnancies with (preconception and during pregnancy, as specified in the secondary objectives, as well as antiemetics) (ATC codes).

7.3.4 Other variables

All analyses, except for the pregnancy analyses, will be reported overall and stratified by:

- Country (Denmark, Finland, Norway, Sweden);
- Age at index date (<20 years, 20-35 years; >35 years);
- Sex (if applicable).

Pregnancy analyses will be stratified by country and age group (<20 years [if sufficient size], 20-35 years; >35 years).

Analyses of the exploratory objective related to rates of CV outcome will be reported overall and additionally stratified by:

- History of any CV morbidity (hypertension [including uncontrolled hypertension], unstable angina, MI, CABG or percutaneous intervention PCI, ischemic stroke, hemorrhagic stroke, TIA);
- History of each specific CV morbidity listed above;
- History of diseases that are alternative indications for non-specific prophylactic migraine medication (hypertension, depression, epilepsy);
- Number of different prophylactic migraine agents dispensed before treatment cohort index date (categories: 1, 2, ≥3).

7.4 Data sources

Data for this study will be linked, within each country, from that country's routinely collected and government-agency maintained registries. Data from all registries within each country are linkable via individual national identifier. Table 7-4 summarizes the data sources and variables used from each data source.

Table 7-4 National registries in Denmark, Finland, Norway and Sweden and type of data available from each registry

Role in the analysis	Type of data	Data sources	Relevant variables	Coding system used
Linkage, residence, outcome (all-cause death)	Unique personal identifier for data linkage	Danish Civil Danish Civil Registration System (Schmidt et al 2014) Finnish National Institute of Health and Welfare (THL) Finnish Population Register Centre (Väestörekisterikeskus 2019) National Registry of Norway Swedish Total Population Register (Ludvigsson et al 2009)	Unique personal identifier for data linkage, dates of birth, migration, death of any cause	None
Identification of migraine diagnoses in hospital care (study population) Identification of hospital treatment with erenumab (exposure, Denmark only)	Administrative record of all hospital encounters (inpatient, outpatient, emergency)	Danish National Patient Registry (Schmidt et al 2015) Finnish Care Register for Health Care (HILMO) (National Institute for Health and Welfare 2019a) Norwegian Patient Registry (Helsedirektoratet 2019b) Swedish National Patient Register (Ludvigsson et al 2011, Socialstyrelsenregister)	Dates of admissions and discharge, surgeries, diagnoses (primary and secondary), treating department, diagnostic procedures (without result), some in-hospital medications (Denmark only)	ICD-10* for diagnoses Nordic Medical Statistical Committee Classification of Surgical Procedures (NCSP) for procedures Local codes for in-hospital medications
Identification of migraine diagnoses in primary care (study population)	Primary care diagnoses	Finnish Register of Primary Health Care visits (AvoHILMO) (since 2011) (National Institute for Health and Welfare 2019b) Health Checks and Payments (KUHR) database, Norway (since 2006/complete from 2011) (Helsedirektoratet 2019a)	Primary care diagnoses	International Classification of Primary Health Care V. 2 (ICPC-2) codes
Identification of endpoints	Administrative record of all hospital encounters (inpatient, outpatient, emergency) or primary care diagnoses (Finland, Norway)	Danish National Patient Registry (Schmidt et al 2015) Finnish Care Register for Health Care (HILMO) Finnish Register of Primary Health Care visits (AvoHILMO) (since 2011) (National Institute for Health and Welfare 2019b) Norwegian Patient Registry (Helsedirektoratet 2019b) Health Checks and Payments (KUHR) database, Norway (since 2017) (Helsedirektoratet 2019a) Swedish National Patient Register (Ludvigsson et al 2011, Socialstyrelsenregister)	Dates of admissions and discharge, surgeries, diagnoses (primary and secondary), treating department, diagnostic procedures (without result), some in-hospital medications (Denmark only)	ICD-10* for diagnoses NCSP for procedures

Role in the analysis	Type of data	Data sources	Relevant variables	Coding system used
Identification of exposure to erenumab and other prophylactic medications Identification of treatment proxies for endpoints and baseline comorbidities Identification of concomitant medications	Outpatient dispensings of prescribed medicines	Danish National Health Services Prescription Database** (Johannesdottir et al 2012, Wettermark et al 2013) Danish National Prescription Registry 11 References (Pottegard et al 2017) Finnish Prescription Register (Wettermark et al 2013)** Finnish e-prescription Register (Kanta 2019) Norwegian Prescription Database (Wettermark et al 2013) Swedish Prescribed Drug Register (Wettermark et al 2013)	Date of dispensing Active substance Amount dispensed Pill strength Prescriber specialty and prescriber type (whenever available)	ATC
Identification of pregnancies	Pregnancies ending in live or still birth at 22+ weeks of gestation	Danish Medical Birth Register (Langhoff-Roos et al 2014, Bliddal et al 2018) Finnish Medical Birth Register (Langhoff-Roos et al 2014) Medical Birth Registry of Norway (Langhoff-Roos et al 2014) Swedish Medical Birth Register (Langhoff-Roos et al 2014)	Mother's unique identifier Dates of conception and/or last menstrual period (LMP) and delivery Gestational age at delivery, hypertensive disorders of pregnancy Parity	Structured data using local coding conventions
Cause of death (CV mortality in the MACE endpoint)	Cause of death	Danish Register of Causes of Death (Helweg-Larsen 2011) Finnish Causes of Death Register (Tilastokeskus 2017) Swedish Cause of Death Register (Brooke et al 2017) Norwegian Cause of Death Register	Immediate and underlying cause of death	ICD-10*
Education	Patient characteristic	Statistics Denmark (Jensen et al 2011) Statistics Finland (Statistics_Finland 2019) Statistics Norway Statistics Sweden	Highest completed/ongoing education using the International Standard Classification of Education (EUROSTAT 2019)	Structured data using local coding conventions and/or international classifications

* The International Classification of Diseases, 11th Revision (ICD-11) is scheduled to be implemented by the EU Member States in January 2022 [https://www.who.int/classifications/icd/revision/timeline/en/]. If relevant, ICD-10 diagnostic codes will be mapped to ICD-11 codes.

** Reimbursed medicines

7.5 Study size/power calculation

Not applicable. All initiators of erenumab during the study period will be included in the study; however, no comparative analysis will be conducted.

7.6 Data management

Data retrieval and management will be conducted separately in each country. The coordinating investigator in each country will obtain all necessary permissions and prepare a data application

to its country-specific data custodian. A data manager in each country will ensure correctness of the delivered raw data before data management start. Pseudo-anonymous records from different registries will be linked by unique personal identifier or its pseudonym. Real identifiers are replaced by study identifiers. Data will be cleaned and coded, and harmonized analytic datasets will be prepared according to the specifications provided in the SAP. Patient-level data will be kept on secure servers within each respective country. For the purposes of the report, aggregated data will be shared. Patient-level data will not be made available to the MAH.

7.7 Data analysis

Department of Clinical Epidemiology, Aarhus University, Denmark, will develop a common SAP and coordinate the analyses. The coordinating investigator in each country will be responsible for his or her the country-specific analysis according to the protocol and the SAP. All steps of the country-specific data analyses will be conducted separately in each participating country by a trained statistician at each coordinating investigator's institution and supplied to Aarhus University for the purpose of preparation of the interim and the final reports. Country-specific results will be presented. Combining of the aggregated results in the four countries may be considered for the final study report, in which case, results will be combined at Aarhus University and reported with appropriate measures of heterogeneity (Higgins et al 2002, Barendregt et al 2013, Borenstein et al 2017).

For the primary and secondary objectives, class descriptive characteristics will be summarized using frequencies and proportions. Continuous variables (e.g., age, BMI) may be summarized using means with standard deviations and/or medians with interquartile ranges, and ranges. Continuous variables may be additionally categorized as appropriate clinically.

For the exploratory objective related to rates of CV endpoints, rates of the endpoints will be computed as the number of first events during the follow-up divided by the total person-time at risk. In each treatment cohort, the follow-up for each patient will begin on the treatment cohort index date and will end on the date of a given endpoint, switch to a new treatment cohort, treatment discontinuation, emigration, death, or 31 December 2022, whichever comes first. The endpoints will not be considered as competing endpoint i.e. the occurrence of one endpoint will not censor the observation time for another endpoint. For each rate, a 95% CI will be computed assuming that rates follow Poisson distribution. Assumptions about length of the risk period attributable to a discontinued treatment following discontinuation will be explored in sensitivity analyses.

For the exploratory objective related to pregnancy, number and prevalence of pregnancies with a dispensing of erenumab and pregnancies with dispensing of other prophylactic migraine medications will be reported, overall and by trimester of dispensing, in not mutually exclusive categories. First trimester/preconception will be defined from the first day of the last menstrual period (LMP)-90 days to LMP+97 days (both dates inclusive); second trimester will be defined from LMP+98 days to LMP+202 days (both dates inclusive); third trimester will be defined from LMP+203 days (inclusive) until date of delivery (not included).

Among pregnant women with migraine dispensing of erenumab and pregnant women with migraine dispensing of other prophylactic migraine medications, woman's age will be summarized using mean with standard deviation, median with interquartile range and range;

and in age categories. Parity and prevalence of the exploratory endpoints, will be summarized using frequencies and proportions with 95% CIs.

For data management and analyses, SAS software version 9.3 or later or R software version 3.1.1 or later will be used.

7.8 Quality control

Data in the Nordic registries are generally of high quality (Wettermark et al 2013, Schmidt et al 2015). Register records for many medical events, including those used in the current study have been validated in the Nordic countries (Sund 2012, Langhoff-Roos et al 2014), including stroke (Tolonen et al 2007, Varmdal et al 2016, Luhdorf et al 2017, Oie et al 2018), hypertensive disorders of pregnancy (Thomsen et al 2013, Luef et al 2016), and other cardiovascular events and procedures (Stegmayr et al 1992, Lindblad et al 1993, Linnersjo et al 2000, Hammar et al 2001, Adelborg et al 2016, Malmo et al 2016, Sundboll et al 2016, Govatsmark et al 2018). Linkage of data from different data sources is exact via a unique identifier. Dispensing records, although not perfect measures of medication intake, are considered superior to any other method. Furthermore, dispensings (used in this study) are superior to prescriptions, as they represent primary compliance, i.e., indicate a medication sale to a patient.

Data storage, management and analyses will be conducted according to each institution's standard procedures. At a minimum, all study documents (protocol, report, publications) will be reviewed by the entire research team. A senior epidemiologist in each institution will review the report before submission to the sponsor. Clinical expertise is available for development of setting-appropriate variable definition and interpretation of the results. At the start of the project, a kick-off meeting will establish a regular communication plan (via e-mail and regular teleconferences); and internal timelines will be established to allow review and quality control before submitting each deliverable. Each institution will also follow its internal standard quality control procedures and will ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations and will obtain all permission necessary to conduct this study.

7.9 Limitations of the research methods

Several limitations of the data sources must be considered when interpreting the results of this study.

First, patients with migraine diagnosed exclusively in primary care and treated exclusively with over-the-counter and non-specific migraine medications will not be captured in any data source in Denmark and in Sweden. Patients diagnosed with migraine in primary care will be identifiable in Finland and Norway through primary care databases. In Finland, patients diagnosed exclusively at private clinics and not identifiable via e.g., treatment proxy, will likewise not be captured since private clinics do not report to the Finnish Register of Primary Health Care visits. Furthermore, diagnoses of migraine might have variable validity depending on whether made in specialist care or in general practice. Hospital diagnoses, used in identifying indications, typically have high positive predictive values, but may capture only the more severe cases of a given condition, including migraine. Hospital dispensings (i.e., bypassing a pharmacy dispensing) will not be identifiable, which, depending on country-specific patterns of care, may affect none, the first, or all dispensings. Specifically, CGRP inhibitors and onabotulinumtoxin

A dispensings may be affected. Some hospital dispensings may be identifiable in Denmark thorough hospital treatment codes.

Second, indication for medication use is not explicitly recorded in the available data sources. Therefore, for patients treated with prophylactic migraine medication, there will be uncertainty about whether a given prophylactic medication was given for migraine or for another indication. A stratified analysis is planned to assess the extent of this limitation. In Sweden, it may be possible to text mine prescription data for indication, provided a permission is granted by the Swedish National Board of Health and Welfare.

Third, although dispensings (vis-à-vis prescriptions) represent 'primary compliance', dispensing records still may not accurately represent the actual amount and timing of medication intake (exposure misclassification).

Fourth, the risk of the CV endpoints in the study population is expected to be low, potentially precluding meaningful assessment of CV safety of erenumab in a future PASS. Challenge of separating CV risk from migraine itself from that of the medication is another limitation. Some medications may be selectively non-prescribed to migraine patients with CV risk factors.

Fifth with regard to CV risk factors, data on uncontrolled hypertension is not directly recorded in the respective data sources because there are no measurements of blood pressure. Instead uncontrolled hypertension proxy will be developed, in collaboration with local clinicians familiar with recording practices, based on severity. Severity will be defined using a combination of hospital diagnoses (with different weights given to diagnoses recorded in primary and secondary positions), primary care diagnoses [whenever available] and treatment proxies, as well as codes indicative of hypertension with end organ damage. The limitation remains that patients hospitalized with hypertension most likely represent the most severe cases and may not be representative of the population with uncontrolled hypertension.

Sixth, limitations of composite endpoints, and specifically MACE, are its treatment of death and non-fatal events as equally severe outcomes, and not taking into consideration competing risks (Shen et al 1998). Furthermore, if only some components of a composite endpoint relate to exposure, the precision may be reduced via dilution of the estimates by the null association of non-relevant components (Freemantle et al 2003, Prieto-Merino et al 2013).

7.10 Other aspects

Not applicable.

8 Protection of human subjects

Register-based studies in the Nordic countries do not require patient consent, but may need approvals by each country's relevant authority (Data Protection Agency and/or Ethics Committees) (Rosen 2002, Ludvigsson et al 2015). Investigators in each of the four countries will be responsible for obtaining all required approvals and compliance with all relevant local laws. Investigators will not have access to the personal identification numbers since those will be transferred to study-specific dummy-IDs by the data holders. Informed consent is not required for studies based exclusively on routinely collected data (Ludvigsson et al 2015).

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki. This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (EMA 2018b).

9 Management and reporting of adverse events/adverse reactions

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety relevant result, will be provided on an aggregate level only; no reporting on an individual case level to Novartis is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions will be summarized in the study report, i.e. the overall association between an exposure and an outcome will be presented. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to Health Authorities.

10 Plans of disseminating and communicating study results

Results of the interim analyses will be included in PSURs. The following will be reported in the interim reports:

- Number of patients with a dispensing erenumab during the reporting period (with and without history of CV morbidity);
- Distribution of patients' characteristics of the treatment cohorts listed as "Secondary endpoints"
- Rates of CV endpoints not requiring data on cause of death (due to longer data lags) among patients treated with erenumab and patients treated with other prophylactic migraine medications listed in the first exploratory objective;
- Number of pregnancies ending in live or still birth in women with a dispensing of erenumab (reporting to the extent allowed by data lags).

Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication and/or posted in a publicly accessible database of results. Preparation of publications in peer reviewed journals will be done in compliance with the International Committee of Medical Journal Editors (ICMJE) guidelines.

The final study report will be submitted to EMA one year after the end of data collection.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

None

12.2 Annex 2 – ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Study title:
A non-interventional study to examine patient characteristics and drug utilization patterns in migraine patients treated with prophylactic drugs in Nordic countries

EU PAS Register® number:
Study reference number (if applicable): CAMG334A2023

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	Section 4
1.1.2 End of data collection[3]	☒	☐	☐	Section 4
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	Section 4
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Section 4
1.1.6 Final report of study results.	☒	☐	☐	Section 4

Comments:

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[3] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	Section 6
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Section 5 Section 6
2.1.2 The objective(s) of the study?	☒	☐	☐	Section 6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section 5 Section 7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	Section 7.5

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	Section 7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 7.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	Section 7.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	Section 9

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	Section 7.2
4.2 Is the planned study population defined in terms of: 4.2.1 Study time period	☒	☐	☐	Section 7.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.2 Age and sex	☒	☐	☐	Section 7.3
4.2.3 Country of origin	☒	☐	☐	Section 7.3
4.2.4 Disease/indication	☒	☐	☐	Section 7.2
4.2.5 Duration of follow-up	☒	☐	☐	Section 7.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Section 7.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	Section 7.3.2 Section 7.3.4
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	Section 7.9
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section 7.3.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Identification of comparators and categorization of proper categorization of exposure are objectives of this study.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	Section 7.3.3

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Section 7.3.3 Section 7.3.4
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	Section 7.8
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	Section 7.3.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	Section 7.9

Comments:

Sources of bias will be explored for a potential future PASS, but are not relevant for this descriptive study

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	Section 7.3.4

Comments:

This descriptive study proposes stratification of variables that may be effect modifiers in a potential future PASS.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	Section 7.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Section 7.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	Section 7.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 7.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 7.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Section 7.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Section 7.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Section 7.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	Section 7.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	Section 7.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	Section 7.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	Section 7.4
10.4 Are stratified analyses included?	☒	☐	☐	Section 7.4
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	Section 7.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Section 7.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section 7.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	Section 10

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	Section 5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	Section 8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Section 5

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Section 3

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	Section 10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 10

Comments:

Name of the main author of the protocol: [redacted]

Date: 12/April/2019