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Quantitative Safety & Epidemiology

Erenumab

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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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Medicinal product	Aimovig 70 mg, 140 mg solution for injection in pre-filled pen
Product reference	Aimovig
Procedure number	EMEA/H/C/0004447
Marketing authorization holder	Novartis Europharm Ltd
Joint PASS	No
Research question and objectives	The primary objective was to describe utilization of erenumab among patients with migraine. The secondary objective was to identify potential comparators for a future erenumab PASS. The exploratory objectives were 1) to estimate rates of cardiovascular outcomes in patients initiating erenumab or other prophylactic migraine medication; and 2) to describe utilization of erenumab and outcomes in pregnancy
Country(-ies) of study	Denmark, Finland, Norway, Sweden
Main author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	[redacted]
MAH contact person	[redacted]

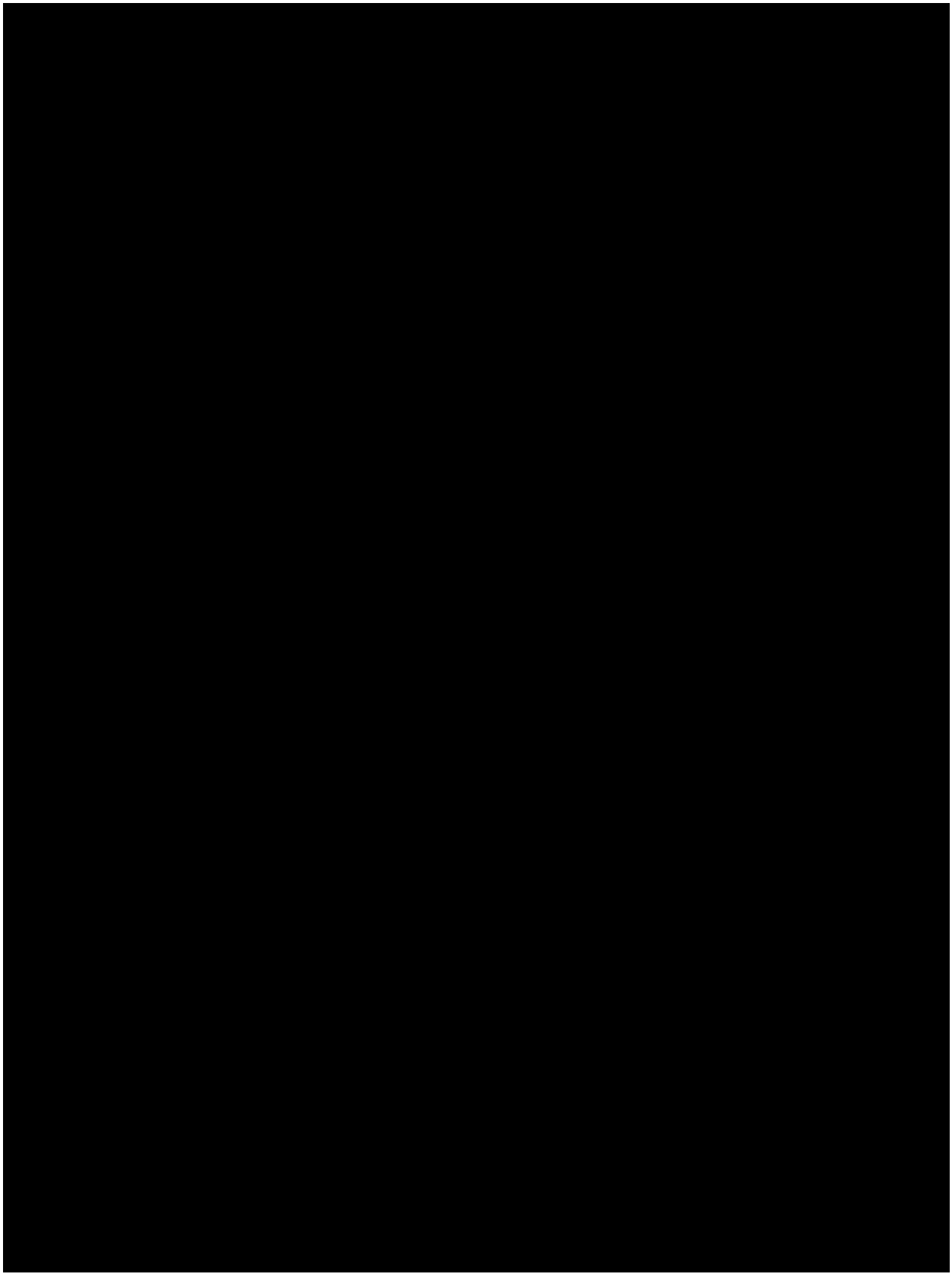


Table of Contents

1 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

Version 1.0, 31-MAR-2025

NIS Type

NIS with use of secondary health data

Name and affiliation of main author

[redacted]

Keywords

Cohort study, drug utilization study, epidemiology, migraine

Rationale and background

Erenumab was approved by the European Medicines Agency on 26-Jul-2018 for prophylaxis of migraine in adults with chronic migraine. For a drug with a novel mechanism of action, such as erenumab, a non-interventional study is needed to characterize use and outcomes in routine clinical practice, including patient characteristics, cardiovascular (CV) endpoints and use in pregnancy. Furthermore, this study was designed to help identify a suitable comparator for a potential future safety study of erenumab.

Research question and objectives

The primary objective of this study was to describe utilization of erenumab among patients with migraine.

The secondary objective was to identify potentially suitable comparators for a potential future postauthorization safety study.

The exploratory objectives were: 1) to estimate rates of pre-specified CV endpoints among patients with migraine initiating erenumab or other prophylactic migraine medications, overall, and stratified by age, sex, and history of CV morbidity; and 2) to characterize drug utilization and pregnancy/offspring outcomes in pregnant migraine patients exposed to erenumab or, other prophylactic migraine medications, as well as in pregnancies without treatment.

Study design

Cohort study, drug utilization study

Setting

This study was based on routinely collected health care data in Denmark, Finland, Norway and Sweden, which are welfare states with universal health care. The study population consisted of residents in each country with migraine. Patient inclusion period extended from 08-Aug-2018 to 30-Sep-2022. The follow-up was through 31-Dec-2022. The lookback period for patients' characteristics was up to 10 years.

Subjects and study size, including dropouts

The study population included all eligible migraine patients identified during the patient inclusion period in Denmark, Finland, Norway, and Sweden. In the main study population (adults with migraine ages 18 years or older), erenumab, other calcitonin gene-related peptide (CGRP) antagonists, botulinum toxin, or other prophylactic migraine medications defined the respective treatment cohorts. The pregnancy population, in addition to the above treatment cohorts, included migraine patients treated with acute migraine medications only and patients not receiving any migraine treatment.

Variables and data sources

Within each country, data were linked from several health and administrative registries of routinely collected data. Use of medication was assessed based on outpatient dispensings or hospital procedure codes. Other variables, including migraine, comorbidities and endpoints were defined using hospital diagnoses, treatment proxies, or procedures. Standard classifications were used.

Statistical methods

All analyses were descriptive. Appropriate summary descriptive statistics were used for categorical and continuous variables. Cumulative incidences were used to summarize utilization of erenumab. Rates and cumulative incidences were used to describe the CV endpoints during the follow-up.

Results

Between 08-Aug-2018 and 30-Sep-2022 (followed through 31-Dec-2022), there were 20,218 initiators of erenumab: 1,835 in Denmark, 4,949 in Finland, 8,276 in Norway, and 5,158 in Sweden. Erenumab was nearly exclusively prescribed in the secondary care (data on sector available in Denmark and Sweden), and primarily by neurologists. Overall, a large majority (17,129 (84.7%)) of the erenumab initiators were women and the median age at erenumab initiation was 43.7 years. Across all countries, 13,624 (67.4%) persons initiated erenumab as monotherapy. The type of initiation and type of initiation (monotherapy vs add-on) varied by country. In Sweden 93% initiated erenumab as monotherapy, in Norway 46% and in Denmark and Finland 74%. At three years of follow-up, persistence with erenumab was 17.8% (Denmark) / 20.7% (Finland) / 23.0% (Norway) / 10.4% (Sweden). At three years of follow-up, the proportion of patients switching to another CGRP antagonist was 23.3% (Denmark) / 37.5% (Finland) / 33.9% (Norway) / 37.0% (Sweden).

Across the four countries, 16,515 patients entered the CGRP antagonists treatment cohort, 16,648 botulinum toxin treatment cohort, and 227,389 other prophylactic migraine medications treatment cohort. The erenumab and other CGRP antagonist treatment cohort and the botulinum toxin treatment cohort had a greater prevalence of history of use of more than 2 different prophylactic migraine agents in the preceding 12 months than patients in the other prophylactic migraine medication cohort.

Hypertension was the most common CV endpoint. During the follow-up, the crude rates per 1000 person-years of hypertension regardless of previous history of hypertension in the treatment cohorts were 130 for the erenumab cohort, 161 in the other CGRP antagonists cohort, 259 in the botulinum toxin cohort, and 454 in the other prophylactic migraine medication treatment cohort. The rates varied by sex, age and CV history. The rates of the other CV endpoints were low, and many cohorts had zero events.

In Finland, Norway, and Sweden, there were 208 pregnancies with a record of erenumab use between 90 days preconception and pregnancy end. There were fewer than 5 pregnancies with a record of erenumab dispensing did not exceed the reportable minimum in Denmark.

Discussion

This study was based on routinely collected population-based secondary data in four Nordic countries; use of erenumab varied by country, with the largest number of users identified in Norway and the smallest in Denmark. Between 08-Aug-2018 and 30-Sep-2022, there were 20,218 initiators of erenumab: 1,835 in Denmark, 4,949 in Finland, 8,276 in Norway, and 5,158 in Sweden. Erenumab was nearly exclusively prescribed in the secondary care (data on sector available in Denmark and Sweden), and primarily by neurologists. Overall, 17,129 (84.7%) of the erenumab initiators were women and median age at erenumab initiation was 43.7 years. The type of initiation varied by country, with the largest proportion of add-on initiation observed in Norway. Persistence, switching and discontinuation varied by country, with some variation potentially related to differences in clinical practices and recording of use.

The erenumab initiators cohort exhibited demographic, clinical, socioeconomic and other relevant characteristics similar to those of users of other CGRP antagonists and of botulinum toxin, and were less similar to users of other prophylactic migraine medications, suggesting that the latter do not adequately represent erenumab-indicated population. This may be considered when designing a future potential safety study of erenumab. Use of more than one active comparator, from different drug classes is recommended, however, for treatments with indications other than migraine (such as botulinum toxin), steps should be taken to ensure inclusion of the relevant indicated population.

The most frequent CV endpoint was hypertension, and its rate varied by treatment cohort, age, sex and CV history. No comparative analysis by treatment was undertaken. There were few events and low rates of hospitalization for acute myocardial infarction, artery revascularization by CABG or PCI, hospitalization for ischemic stroke, hospitalization for hemorrhagic stroke, and of hospitalization for transient ischemic attack, CV death, and MACE among erenumab initiators. The low rates are expected in a relatively young population of migraine patients.

Few pregnancies were exposed to erenumab or other CGRP antagonists. Owing to the rather recent approval of these medications, this was also as expected.

Limitations include uncertainty about medication intake and its duration, lack of precise indication data for nonspecific agents, potential misclassification of health conditions in routinely collected data, and low precision of multiple estimates.

Conclusion

In nearly 4 years following approval of erenumab in the European Union, the uptake, persistence, and switching of erenumab varied in the four Nordic countries, despite generally similar setup of the underlying data sources and health care systems. Some of the variation may be explainable by country-specific differences in recording, prescribing, and reimbursement practices. As expected, majority of the erenumab initiators were young females, and erenumab was mainly prescribed by neurologists. The most common cardiovascular condition was hypertension. The rates of the other examined cardiovascular events and conditions were low, as expected in a younger population. By design, no formal comparative analysis by treatment was performed. In a potential comparative analysis, use of more than one active comparator, from different drug classes is recommended, and steps should be taken to ensure inclusion of the relevant indicated population. In the exploratory analysis in the pregnancy population, fewer than 5 pregnancies were exposed to erenumab in Denmark. In Finland, Norway and Sweden combined, 208 pregnancies had a record of erenumab dispensing. The results of this study may inform feasibility of potential future studies on overall and reproductive safety of novel migraine treatments. This descriptive study was not designed to assess the benefit-risk balance of erenumab.

Marketing Authorization Holder(s)

[redacted]

Name(s) and Affiliation(s) of Principal Investigator(s)

[redacted]

2 List of abbreviations

ATC	Anatomical Therapeutic Chemical
BOT	Botulinum toxin
CABG	Coronary artery bypass graft
CGRP	Calcitonin Gene-related Peptide
CI	Confidence interval
CV	Cardiovascular
DDD	Defined daily dose
DUS	Drug Utilization Study
EAA	European Economic Area
EMA	European Medicines Agency
ERE	Erenumab
EU	European Union
FDA	Food and Drug Administration
FDA FAERS	FDA Adverse Event Reporting System
ICD-10	The International Classification of Diseases, 10th Revision
ICPC-2	International Classification of Primary Care, 2nd Edition
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
LMP	Last menstrual period
MACE	Non-fatal MI, non-fatal stroke or CV death
MAH	Marketing Authorization Holder
MI	Myocardial infarction
NI	Non-interventional
NIS	Non-interventional Study
OCG	Other CGRP antagonists
OPM	Other prophylactic migraine medications
PASS	Post-authorization Safety Study
PCI	Percutaneous intervention
PI	Principal Investigator
PPC	Proportion of patients covered
RCT	Randomized Controlled Trial
RMP	Risk Management Plan
SAP	Statistical Analysis Plan

TIA	Transient ischemic attack
USA	United States of America

3 Investigators

Role	Person
Principal investigator (PI), report reviewer; legally responsible	[redacted]
Coordinating investigator (Denmark), main author of the protocol and the final study report	[redacted]
Coordinating investigator, report contributor, reviewer (Finland)	[redacted]
Coordinating investigator, report contributor, reviewer (Norway)	[redacted]
Coordinating investigator, report contributor, reviewer (Sweden)	[redacted]
Coordinating investigator, MAH	[redacted]

4 Other responsible parties

MAH contact person	[redacted]

5 Milestones

Study milestones are shown in Table 5-1.

Table 5-1 Study milestones

Milestone	Planned date	Actual date	Comments
Start of data collection for the final report (the date from which data extraction starts for the final report)	29-May-2024	29-May-2024	
End of data collection (date from which the analytical dataset was completely available)	28-Aug-2024	26-Sep-2024	
Interim results 1	20-Dec-2022	19-Dec-2022	Due to waiting times of the local data custodians in Finland and Norway, only data from Denmark and Sweden were available for this report
Interim results 2	20-Dec-2023	19-Dec-2023	
Final report of study results submitted to EMA (1 year after end of data collection)	30-May-2025	30-May-2025	

6 Rationale and background

Migraine is a leading contributor to burden of disease and to loss of disability-adjusted life-years (G. B. D. Disease Injury et al 2017, G. B. D. Neurological Disorders Collaborator Group 2017, Steiner et al 2020, Steinmetz et al 2024). Erenumab, a monoclonal antibody, is a human IgG_2 targeting the calcitonin gene-related peptide (CGRP) receptor (Bigal et al 2015). Erenumab was approved in the European Union/European Economic Area (EU/EAA) on 26-Jul-2018 for prophylaxis of migraine in adults who have at least 4 migraine days per month

(EMA 2018). Initial safety and efficacy of erenumab have been established in randomized controlled trials (RCTs) (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), including head-to head comparisons with topiramate (Ehrlich et al 2022, Reuter et al 2022). A synthesis of results of preapproval and postmarketing studies reported no increased risk of hypertension associated with erenumab use but noted need for further evidence (Dodick et al 2021). Another review of available evidence highlighted established long-term safety of onabotulinumtoxin A (botulinum toxin) and stressed the remaining need for such evidence for other preventive treatments for chronic migraine (Blumenfeld et al 2022). Open-label analyses of RCT patients (Ashina et al 2021, Noseda et al 2021), observational studies in routine clinical practice (Schenk et al 2022, Viudez-Martinez et al 2022, Cantarelli et al 2023) and systematic reviews (Bomtempo et al 2023, Reuter et al 2024) generally did not reveal new signals. However, some signals (*e.g.* cardiovascular and gastrointestinal events) were suggested by spontaneous reports disproportionality analyses of EudraVigilance and the US FDA Adverse Event Reporting System (FDA FAERS) (Sessa et al 2021, Liang et al 2022).

For a drug with a novel mechanism of action such as erenumab, a non-interventional study (NIS) from routine clinical practice is useful for characterizing the user population and the patterns of drug utilization. This characterization includes previous prophylactic treatments, comorbidities and concomitant medication. In addition, estimated rates of cardiovascular (CV) events and the availability of a suitable comparator treatment are essential for assessing the feasibility and designing a potential postauthorization safety study (PASS) with a comparative analysis, should one be required. The study population of a potential PASS would include erenumab-indicated population receiving either erenumab or a comparator treatment. Potential suitable comparator treatments for a PASS are treatments with indications similar to those of erenumab. CGRP antagonists other than erenumab represent such treatments. However, similarly to erenumab, other CGRP antagonists are also treatments new to the market, without own established long-term safety profile. Furthermore, all CGRP antagonists may be subject to a class effect in a comparative analysis (Soares et al 2002). Therefore, botulinum toxin was also considered as potential comparator given its established safety profile from being marketed for migraine the last decade (Blumenfeld et al 2022) and given that the reimbursement indications for migraine are similar to those of erenumab in the Nordic countries that participate in this study (Käypä_hoito 2015, Legemiddelverket 2019, Medicinrådet 2019, REFERENCEPROGRAM 2020, Medicinrådet 2021, Nevrologi.legehandboka.no 2022, Sundhedsstyrelsen 2022, Sundhed.dk 2023, Käypä hoito 2024). Table 6-1 lists per-label indications of the relevant erenumab, fremanezumab, galcanezumab, eptinezumab, and botulinum toxin. Finally, other prophylactic migraine medications were considered based on the current guidelines for migraine treatment (Ashina 2020).

Table 6-1 Therapeutic indications and dosing for the CGRP antagonists and botulinum toxin in treatment of migraine

Agent	Label/recommended indication	Recommended migraine dosing
Erenumab	Prophylaxis of migraine in adults who have at least 4 migraine days per month (EMA 2018)	70 mg every 4 weeks or 140 mg every 4 weeks for some patients. Each 140 mg dose is given either as one subcutaneous injection of 140 mg or as two subcutaneous injections of 70 mg (EMA 2018).
Fremanezumab	Prophylaxis of migraine in adults who have at least 4 migraine days per month (EMA 2019a)	225 mg once monthly (monthly dosing) or 675 mg every 3 months (quarterly dosing) (EMA 2019a)
Galcanezumab	Prophylaxis of migraine in adults who have at least 4 migraine days per month (EMA 2019b)	120 mg once monthly, with a 240 mg loading dose as the initial dose (EMA 2019b)
Eptinezumab	Prophylaxis of migraine in adults who have at least 4 migraine days per month (EMA 2022)	100 mg administered by intravenous infusion every 12 weeks. Some patients may benefit from a dosage of 300 mg administered by intravenous infusion every 12 weeks (EMA 2022)
Botulinum toxin	Prophylaxis of migraine in patients with chronic migraine (Bendtsen et al 2018)	155 U–195 U every 12-weeks (Bendtsen et al 2018)

Most of the migraine patients using preventive medication are persons of childbearing potential (Thomsen et al 2019), while the evidence remains limited on the use and safety of erenumab in pregnancy. Most current evidence comes from examination of spontaneous reports or case reports (Noseda et al 2021, Bonifacio et al 2022, Vig et al 2022, Noseda et al 2023). The current drug utilization study (DUS) therefore also aimed to describe the use of erenumab in pregnant migraine patients.

This NIS is a DUS that is a post-approval commitment to the European Medicines Agency (EMA), listed as a required additional pharmacovigilance activity (PASS Category 3) in the erenumab EU Risk Management Plan (RMP) (EMA 2018). The study period for this report is 08-Aug-2018 to 31-Dec-2022. This is the final report for this study (CAMG334A2023). This study has been registered and the protocol has been published in the HMA-EMA Catalogues of real-world data sources and studies (EUPAS36014 https://catalogues.ema.europa.eu/node/3619/administrative-details#darwin-study-protocol).

7 Research question and objectives

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

7.1 Primary objectives

The primary objective of this study is to describe utilization of erenumab among patients with migraine (for details see protocol Section 6.1).

7.2 Secondary objectives

The secondary objective is to identify potential suitable comparators for a formal potential 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 potential comparator, multiple clinical and sociodemographic characteristics were assessed among patients with migraine initiating erenumab and patients with migraine initiating other prophylactic migraine medications (for details see protocol Section 6.2).

7.3 Exploratory objectives

This study has two exploratory objectives:

1. To estimate rates of the protocol-specified 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.
2. To characterize drug utilization and pregnancy/offspring outcomes in pregnant migraine patients exposed to erenumab, other prophylactic migraine medications, and without treatment.

8 Amendments and updates to the protocol

None.

This report was prepared according to the protocol V02, dated 12-Sep-2019 (Appendix 1 – List of stand-alone documents). https://catalogues.ema.europa.eu/node/3619/administrative-details#darwin-study-protocol).

9 Research methods

9.1 Study design

This study was a population-based cohort study with elements of the prevalent new user approach (Gagne 2017, Suissa et al 2017). This was a multinational multidatabase postmarketing NIS/DUS, based on secondary health care data in Denmark, Finland, Norway, and Sweden. The study population comprised adults with migraine who initiate erenumab, other CGRP antagonists, botulinum toxin, or other prophylactic migraine medications during the patient inclusion period.

The study start date was 08-Aug-2018 (the date of the initial RMP publication). The patient inclusion period started on the study start date and ended on 30-Sep-2022, to allow four years' accumulation of treatment data and a minimum 3-month follow-up. The latest date of follow-up end was 31-Dec-2022, the date of administrative censoring for the data extraction. The lookback period for patients' characteristics was up to 10 years.

9.2 Setting

Nordic countries have single-payer universal tax-funded health care. Since 1950s-1990s, the Nordic countries have maintained population-based national administrative and health registries of routinely collected data. National personal identifiers enable exact individual-level linkage of data from all registries, including tracking of vital status and migrations. Thus, the population of each Nordic country is an open cohort with reliable ascertainment of cohort entry (birth, immigration) and exit (death, emigration) dates (Laugesen et al 2021). In each country, protocol-based access to pseudonymized data for research is granted by government data custodians.

This study received all required country-specific approvals. In Denmark, an approval from the Danish Data Protection Agency was obtained (2016-051-000001, serial number 603) and registered at Aarhus University. In Finland, the study was approved by the Finnish Social and Health Data Permit Authority (THL/259/14.02.00/2022, THL/3361/14.06.00/2023, THL/6210/14.06.00/2023) and Statistics Finland (TK/1592/07.03.00/2021, TK/2121/07.03.00/2023, TK/1114/07.03.00/2024). In Norway, the study was approved by the Regional Committee for Medical and Health Research Ethics (REK-198928). In Sweden, an Independent Ethics Committee (IEC) approval was obtained from the Swedish Ethical Review Authority (reference number 2021-01911).

9.3 Subjects

9.3.1 Source population

The source population were adult (age 18 years or older) residents of the participating countries satisfying the operational definition of migraine during the patient inclusion period (08-Aug-2018 – 30-Sep-2022). Presence of migraine was defined during a period extending from up to 10 years before the study start date and throughout the inclusion period. Migraine date for each patient was the earliest date between 08-Aug-2008 and 30-Sep-2022 on which the patient fulfilled one of the following migraine criteria.

- At least one inpatient or at least two outpatient (but not emergency-room) hospital diagnoses of migraine in primary or secondary position (in Finland only diagnoses in the primary position were used)
- Two or more outpatient dispensings of a migraine-specific medication other than erenumab, galcanezumab, fremanezumab, or eptinezumab (same or different agents on separate dates)
- At least one dispensing of erenumab, galcanezumab, fremanezumab, or eptinezumab

- Two or more diagnoses of migraine made in primary care on separate dates (Norway and Finland only)

- Two or more outpatient dispensings of a non-specific guideline-recommended migraine medication with migraine listed as the reimbursement code (Norway only)

From the source population, two distinct analysis populations were defined: the Main Analysis Population and the Pregnancy Population.

9.3.2 Main Analysis Population and treatment cohorts

The Main Analysis Population included migraine patients who were new users of erenumab or new users of other prophylactic migraine medications during the patient inclusion period. The following treatment cohorts were defined: 1) Erenumab cohort (ERE) 2) Non-erenumab CGRP antagonists cohort (OCG); 3) Botulinum toxin cohort (BOT); 4) Other prophylactic migraine medication cohort (OPM).

Patients entering the study in one treatment cohort could subsequently contribute to a different treatment cohort as long as they fulfilled the inclusion and exclusion criteria for that cohort, however, patients were not allowed to re-enter the same treatment cohort. Patients in the ERE treatment cohort who discontinued and subsequently restarted erenumab were included in the primary objective analyses of erenumab restarting and cumulative dose and duration.

9.3.2.1 Erenumab cohort

9.3.2.1.1 Inclusion criteria

Patients with a dispensing of erenumab during the patient inclusion period (08-Aug-2018 to 30-Sep 2022) were included in the ERE cohort.

9.3.2.1.2 Exclusion criteria

Patients were excluded from the erenumab treatment cohort if they fulfilled any of the following exclusion criteria:

- A dispensing of erenumab before the study start date, 08-Aug-2018
- Age <18 full years on the date of the first dispensing of erenumab in the inclusion period
- Lack of continuous residence in the country of analysis in the 365 days preceding the date of the first dispensing of erenumab in the inclusion period

9.3.2.1.3 Index date

For patients in the erenumab cohort, the index date was the date of the first dispensing of erenumab in the inclusion period. Due to the first exclusion criterion, the index date was the first-ever dispensing of erenumab.

9.3.2.2 Other CGRP cohort

9.3.2.2.1 Inclusion criteria

Patients with a dispensing of fremanezumab, galcanezumab, or eptinezumab during the patient inclusion period were included in the OCG cohort.

9.3.2.2.2 Exclusion criteria

A dispensing of a cohort-qualifying medication for the OCG cohort in the inclusion period was eligible as potential index dispensing unless any of the following criteria were true:

- Age <18 full years on the date of dispensing
- Lack of continuous residence in the country of analysis in the 365 days preceding the date of dispensing
- A dispensing of erenumab on the same date as dispensing of another CGRP antagonist
- A dispensing of galcanezumab, fremanezumab, or eptinezumab 365 days before the date of dispensing

Patients without any eligible dispensings were excluded from the OCG cohort.

9.3.2.2.3 Index date

The first eligible dispensing within the OCG cohort was the index dispensing of the OCG cohort. The index date in the OCG cohort was the date of the index dispensing. In this way, the patients in OCG cohort were not required to be first-ever users.

9.3.2.3 Botulinum toxin cohort

9.3.2.3.1 Inclusion criteria

Patients with a dispensing of botulinum toxin during the patient inclusion period at or after the migraine date were included in the BOT cohort. To reduce misclassification of the BOT cohort by indications other than migraine, the following restrictions were applied for the BOT-cohort qualifying dispensings/administrations:

- In Denmark (hospital administrations only): only BOT administrations from departments of neurology were counted in the BOT cohort.
- In Norway (hospital administrations and outpatient dispensings): for hospital administrations only BOT administrations with a primary diagnosis of migraine at the same encounter were counted in the BOT cohort.
- In Sweden (hospital administrations and outpatient dispensings): for hospital administrations BOT administrations with a primary diagnosis of migraine at the same encounter were counted in the BOT cohort.
- In Finland (outpatient dispensings only): no restrictions were applied, since indication is not recorded, while information on prescriber specialty was missing for more than 90% of dispensings.

Once a patient entered the BOT cohort, the subsequent BOT dispensings used for deriving continuous use were counted without restrictions regarding hospital department or presence of migraine diagnosis.

9.3.2.3.2 Exclusion criteria

A dispensing of botulinum toxin in the inclusion period on or after the migraine date meeting the listed conditions in the inclusion step were eligible as potential index dispensing in the BOT cohort unless any of the following criteria were true:

- Age <18 full years on the date of dispensing
- Lack of continuous residence in the country of analysis in the 365 days preceding the date of dispensing
- The dispensing occurred during periods of use of erenumab or other CGRPs
- A dispensing of botulinum toxin 365 days before date of dispensing

For definition of periods of use of erenumab and other CGRP, see Section 9.9.2. For the exclusion step, periods of use were derived from all dispensings of erenumab and other CGRPs in the inclusion period starting with the first dispensing in the period.

9.3.2.3.3 Index date

The first eligible dispensing within the BOT cohort was the index dispensing of the BOT cohort. The index date in the BOT cohort was the date of the index dispensing.

9.3.2.4 Other prophylactic migraine medication cohort

9.3.2.4.1 Inclusion criteria

Patients with a dispensing of a cohort-qualifying country-specific other prophylactic migraine medication during the patient inclusion period at or after the migraine date were included in the OPM cohort. In Sweden, membership in this cohort was based on diagnoses and dispensings from 2018-2022, based on available data permits. Table 9-1 lists the medications defining the OPM cohort in each country, per guidelines (Käypä_hoito 2015, Legemiddelverket 2019, Medicinrådet 2019, REFERENCEPROGRAM 2020, Medicinrådet 2021, Nevrologi.legehandboka.no 2022, Sundhedsstyrelsen 2022, Sundhed.dk 2023, Käypä hoito 2024).

Table 9-1 Non-specific prophylactic migraine medications used in each country with assumed migraine daily doses

	Assumed migraine-specific daily dose, per country guidelines			
Active substance, alphabetically	Denmark	Finland	Norway	Sweden
Amitriptyline	50 mg	20 mg	30 mg	40 mg
Atenolol	Not used	50 mg	Not used	Not used
Bisoprolol	Not used	5 mg	Not used	Not used
Candesartan	16 mg	16 mg	16 mg	24 mg
Clonidine	Not used	Not used	0.1 mg	Not used
Flunarizine	10 mg	5 mg	7.1 mg	10 mg
Lisinopril	20 mg	10 mg	15 mg	Not used

	Assumed migraine-specific daily dose, per country guidelines			
Active substance, alphabetically	Denmark	Finland	Norway	Sweden
Metoprolol	100 mg	47.5 mg	100 mg	150 mg
Nortriptyline	Not used	30 mg	Not used	Not used
Pizotifen	1.5 mg	1.5 mg	1.5 mg	1.5 mg
Propranolol	160 mg	80 mg	160 mg	120 mg
Riboflavin	Not captured	400 mg	Not captured	Not used
Topiramate	100 mg	75 mg	75 mg	200 mg
Valproate	1000 mg	600 mg	750 mg	150 mg
Venlafaxine	Not used	75 mg	75 mg	Not used

9.3.2.4.2 Exclusion criteria

A dispensing of a country-specific cohort-qualifying medication for the OPM cohort in the inclusion period on or after the migraine date was eligible as potential index dispensing unless any of the following criteria were true:

- Age <18 full years on the date of dispensing
- Lack of continuous residence in the country of analysis in the 365 days preceding the date of dispensing
- The dispensing occurred during periods of use of erenumab, other CGRPs, or botulinum toxin
- A dispensing of more than one country-specific OPM cohort-qualifying medication on the date of dispensing
- A dispensing of the same treatment cohort-qualifying agent in 365 days before the date of the dispensing

9.3.2.4.3 Index date

The first eligible dispensing within the OPM cohort was the index dispensing of the OPM cohort. The index date in the OPM cohort was the date of the index dispensing.

The study schema as applied to each study population individual patient is presented in Figure 9-1 (Schneeweiss et al 2019).

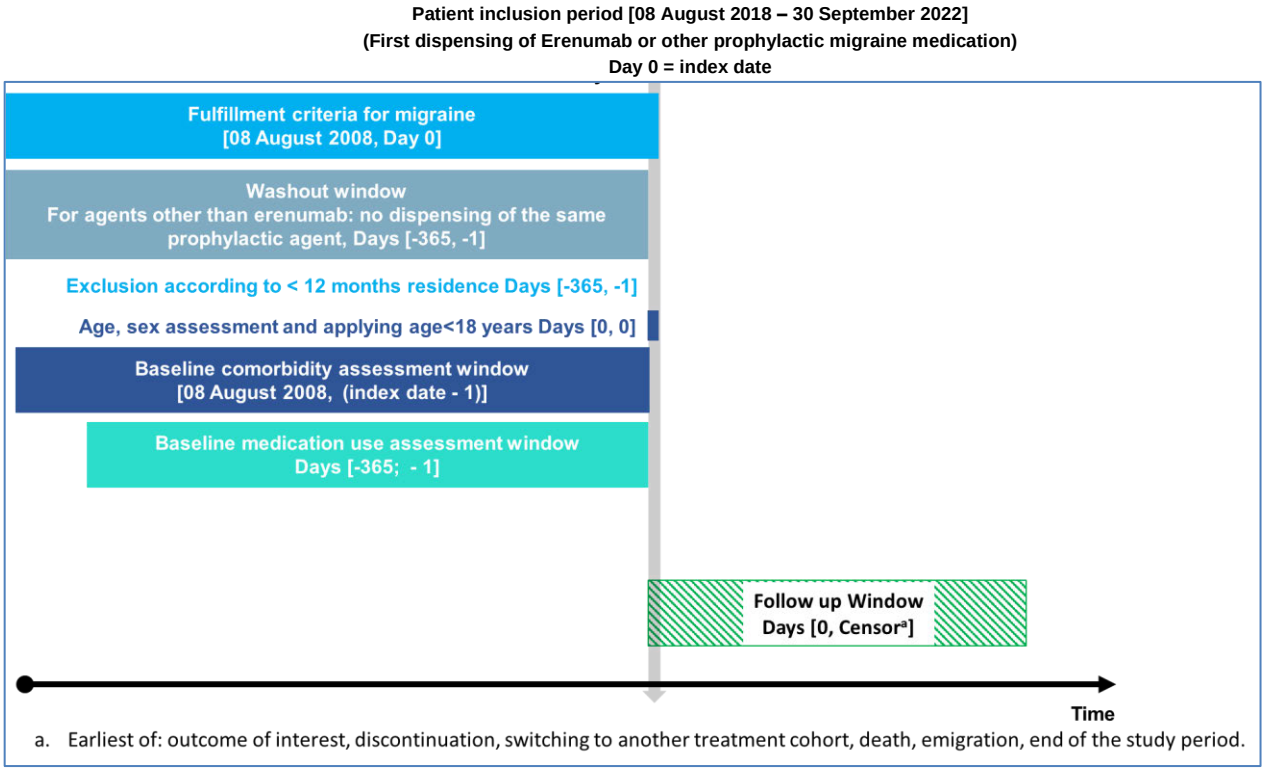


Figure 9-1 Study schema as applied to individual patients at treatment cohort entry in the second interim report

9.3.3 Pregnancy Population

The Pregnancy Population was identified from each country's birth registry as deliveries of live born or stillborn infants between 08-Sep-2018 and 30-Sep-2022 by women with migraine. In Denmark and Sweden, the birth registries contain records of births of fetuses where the gestational age is 22+0 weeks or more. In Finland, the birth registry includes records of live and still births of fetuses with a birth weight of at least 500g or with a gestational age of at least 22 weeks. In Norway, the birth registry additionally contains records of abortions from week 12 onwards. All pregnancies recorded in these registries, including those ending in abortion from Norway, were included in the study. One woman could contribute one or more deliveries to the Pregnancy Population. Women with migraine originated from the source population and needed to fulfill the criteria for migraine as described in Section 9.3.1 between 08-Aug-2008 and the date of delivery. Pregnancies with missing gestational age were excluded.

9.3.3.1 Treatment categories for the Pregnancy Population

In the Pregnancy Population, treatment categories were defined based on dispensings/hospital administrations recorded between 90 days before and including the date of the last menstrual period (LMP) and the date of delivery (excluded). Each pregnancy was classified into one treatment category and different pregnancies of the same person were classified independently.

Pregnancies qualifying for multiple treatment categories, were counted only in one treatment category according to the following hierarchy, to achieve mutually-exclusive all-inclusive treatment categories:

- Erenumab: at least one dispensing/hospital administration of erenumab regardless of any other migraine medication
- Non-erenumab CGRP antagonists: at least one dispensing/hospital administration of galcanezumab, fremanezumab, or eptinezumab regardless of other migraine medications
- Botulinum toxin: at least one dispensing/hospital administration of botulinum toxin regardless of other migraine medications with following restrictions applied:
  - In Denmark (hospital administrations only): only BOT administrations from departments of neurology were counted in the BOT cohort.
  - In Norway (hospital administrations and outpatient dispensings): for hospital administrations only BOT administrations with a primary diagnosis of migraine at the same encounter were counted in the BOT cohort.
  - In Sweden (hospital administrations and outpatient dispensings): for hospital administrations BOT administrations with a primary diagnosis of migraine at the same encounter were counted in the BOT cohort.
  - In Finland, no restrictions were applied.
- Other prophylactic migraine medications: at least one dispensing of country specific cohort-qualifying prophylactic migraine medication other than CGRP antagonists or botulinum toxin regardless of acute migraine medications
- Acute migraine treatment only: at least one dispensing of any specific or non-specific acute migraine medication
- Untreated migraine: no record of migraine medication

Analyses in the pregnancy population were not conducted in countries where the number of pregnancies exposed to erenumab was either zero or had to be masked due to data protection rules.

9.4 Variables

For each data source, local operational definitions were developed in consultations with the clinical and epidemiology experts and further refined based on observed utilization patterns (described in Section 9.9.5 if relevant). These are documented in the Statistical Analysis Plan (SAP), Appendix 1 – List of stand-alone documents, Section 15.1.6.

9.4.1 Migraine identification

Migraine was identified in all countries using hospital diagnosis codes according to the International Classification of Diseases, 10th Revision (ICD-10) or via migraine treatment from outpatient dispensings according to the Anatomical Therapeutic Chemical (ATC) classification. In Norway, migraine was also identified using primary care diagnostic codes using the International Classification of Primary Care, 2nd Edition (ICPC-2). Relevant ATC, procedure, or injection codes were used to identify hospital-administered migraine treatment in Denmark, Norway, and Sweden.

9.4.2 Exposure

Since the indicated population may differ by agent and guidelines, the cohort of new users of other prophylactic migraine medications was subcategorized according to the type of the initiated prophylactic agent. Thus, patients with migraine were classified into one of the following treatment cohorts, according to the initiated treatment:

- Erenumab cohort, referred to as "ERE" (sub-classified as monotherapy/add-on);
- Other CGRP antagonists cohort, referred to as "OCG"
- Botulinum toxin cohort, referred to as "BOT"
- Other prophylactic migraine medication cohort, referred to as "OPM" (specific and non-specific prophylactic migraine medications used according to each country's clinical guidelines, see Table 9-1)

The list of non-specific prophylactic migraine medications qualifying patients for the OPM cohort membership was based on consultation with local clinicians and local guidelines (Käypä_hoito 2015, Legemiddelverket 2019, Medicinrådet 2019, REFERENCEPROGRAM 2020, Medicinrådet 2021, Nevrologi.legehandboka.no 2022, Sundhedsstyrelsen 2022, Sundhed.dk 2023, Käypä hoito 2024).

9.4.3 Endpoints

The following sections list primary, secondary and exploratory endpoints.

9.4.3.1 Primary endpoints

Given the stated objectives, the following summary descriptive statistics for the characterization of the patients initiating erenumab.

- Number of migraine patients with a dispensing of erenumab (overall and stratified by CV history)
- Calendar year of erenumab initiation
- Sex
- Age at erenumab initiation date
- Prescriber health sector
- Prescriber specialty
- Erenumab initiation type: add-on to vs switching from another prophylactic migraine medication (monotherapy)
- Erenumab persistence
- Erenumab discontinuation, restarting, and patterns of switching among CGRP antagonists
- Erenumab duration of use and cumulative dose received were expressed in mg and in the number of monthly injections
- Erenumab package strength at the initial dispensing

9.4.3.2 Secondary endpoints

For the secondary objectives, the following variables were summarized as frequencies and percent in each treatment cohort with predefined baseline as of the index date as well as lookback period:

- Calendar year of index date
- Sex
- Age at index date in years
- Prescriber health sector
- Prescriber specialty
- Baseline history of each protocol-defined CV morbidity
- Baseline history of each protocol-defined condition that was a risk factor for CV morbidity
- Baseline history of each specified other somatic or psychiatric morbidity
- Baseline distribution of the Charlson Comorbidity Index score categories
- 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 botulinum toxin
- Baseline history of use of protocol-specified other medications
- Distribution of the number of different medication classes from among the above-listed classes
- Health care utilization indicators (number of hospitalizations, outpatient visits)
- Number and proportion of patients according to socioeconomic indicators (highest achieved education, quantiles income)
- Number and proportion of patients with COVID-19 related diagnoses and medication recommended for COVID-19 treatment

9.4.3.3 Exploratory endpoints

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

- Hypertension
- Hospitalization for acute myocardial infarction (MI)
- Coronary artery revascularization by coronary artery bypass graft (CABG) or percutaneous intervention (PCI)
- Hospitalization for ischemic stroke
- Hospitalization for hemorrhagic stroke
- Hospitalization for transient ischemic attack (TIA)
- CV death
- MACE (defined in this study as composite endpoint of non-fatal myocardial infarction, non-fatal stroke or CV death)

9.4.3.4 Exploratory endpoints in the Pregnancy Population

The following exploratory endpoints were measured in the Pregnancy Population, overall and in the treatment categories:

Pregnancy characteristics

- Number of pregnancies
- Calendar year of delivery
- Maternal age
- Parity
- Smoking in pregnancy
- Maternal pre-pregnancy BMI
- Gestational diabetes
- Comorbidities
- Medications used between 90 days before LMP and during pregnancy
- Use of known teratogens preconception or in the first trimester

Reproductive history:

- Hypertensive disorders of pregnancy
- Cesarean section
- Spontaneous abortion
- Stillbirth
- Induced abortion

Pregnancy complications and birth outcomes:

- Hypertensive disorders of pregnancy
- Gestational diabetes
- Placenta previa
- Premature separation of placenta
- Cesarean delivery
- Multifetal gestation
- Preterm delivery (<37 weeks)
- Gestational age
- Stillbirth
- Low birth weight (<2500 grams)
- Birth weight in grams
- Small for gestational age (birthweight <10^{th} percentile)

9.4.3.5 Subgroups for the primary objectives

The following subgroups were defined for the primary endpoints:

- Age in years (in categories 18 - <30, 30 - <40, 40 - <50, 50 - <60, 60 and older)

- Sex (Male, female)
- Patients with and without history of CV morbidity (including hypertension, unstable angina, MI, CABG or PCI, ischemic stroke, hemorrhagic stroke, TIA)
- Number of different prophylactic migraine agents dispensed between the date of qualifying for the migraine population and before the index date (0-1, ≥2).

9.4.4 Other variables

Analyses of the exploratory objective related to rates of CV outcome were reported by country and, according to the extent the data allowed, stratified by age, sex, and history of CV morbidity.

9.5 Data sources and measurement

Within each country, data from that country's routinely collected and government-agency maintained registries were linked at an individual level using a pseudonymized individual national identifier. The specific data sources and the associated coding systems and contents were described in the Study Protocol (Appendix 1 – List of stand-alone documents, Section 15.1.1) and in the associated SAP (Appendix 1 – List of stand-alone documents, Section 15.1.6).

9.6 Bias

An important source of bias in this study is potential misclassification in identifying the erenumab-indicated population when assembling potential comparator treatment cohorts. While treatment cohorts of other CGRP antagonists have the same on-label and reimbursement indications as erenumab, other proposed treatment cohorts may include patients not receiving the medication to treat migraine but to treat other conditions. While CGRP antagonists themselves qualify patients for the migraine population, for patients in the non-CGRP treatment cohorts there is an additional inclusion criterion of previous evidence of migraine. The list of non-specific prophylactic migraine medications that qualify in the OPM cohort membership is based on consultation with local clinicians and local guidelines (Käypä_hoito 2015, Legemiddelverket 2019, Medicinrådet 2019, REFERENCEPROGRAM 2020, Medicinrådet 2021, Nevrologi.legehandboka.no 2022, Sundhedsstyrelsen 2022) Some of the most common OPM medications are antihypertensives. This could mean including persons with migraine into OPM cohort who received the OPM medication not as a prophylactic migraine medication but rather as an antihypertensive treatment. Furthermore, hypertension may in some instances be recorded as the indication despite the drug being used solely or partly for migraine. Such misclassification could lead to overestimation of the rates of hypertension. Furthermore, specific indication criteria (number of monthly migraine days) are not recorded in the available data. Despite identification of the BOT cohort in the migraine population, misclassification of the indication cannot be ruled out, especially in Finland, where prescriber specialty for the index botulinum toxin dispensing was found missing for over 90% of the patients.

Another source of bias is potential misclassification of the erenumab treatment duration, with the resulting misclassification of discontinuation and switching. Sensitivity analyses with an extended grace period were designed to examine the impact of this bias.

Further, there is inevitable misclassification of the patients' characteristics and endpoints with the use of routinely collected data. Specifically in relation to the results from Denmark and

Sweden, diagnoses originate from hospitalizations or outpatient specialist clinic encounters, whereas diagnoses from primary care are unavailable. For some conditions, such as hypertension, a treatment proxy is used to compensate for lack of primary care diagnoses, however, underascertainment cannot be ruled out. Generally, in the routinely collected health data, only symptomatic or treated conditions that lead to a contact to health care are identifiable. Data on lifestyle markers are either under-recorded (e.g., body mass index) or unavailable in all countries (e.g. smoking or alcohol intake).

9.7 Study size

In this descriptive observational NIS based on routinely collected secondary health care data, all eligible patients identified in the participating countries during the patient inclusion period were included.

9.8 Data transformation

Data were accessed, managed, and analyzed locally by each country's investigator according to the common protocol (Appendix 1 – List of stand-alone documents, Section 15.1.1) Source data from the registries were linked using each country pseudonymized personal identifier. Data were managed and coded according to the country-specific variable definitions and availability, as detailed in the SAP, Appendix 1 – List of stand-alone documents, Section 15.1.6.

Aarhus University was the coordinating investigator. Investigators in the participating countries transferred the aggregated results for reporting. The main study statistician at Aarhus University provided the research partners in the other countries with a template guiding the contents of the format of the aggregated data to be transferred. Based on those data, the final study output was prepared by Aarhus University for review by all research partners and the Sponsor.

9.9 Statistical methods

In Norway, data management and analysis were performed using R software version 4.3.0 (The R Foundation for Statistical Computing, R: The R Project for Statistical Computing (r-project.org)) and STATA SE statistical software package version 18 (StataCorp, TX, USA). In Finland, R version 4.2.2 was used. In Denmark and Sweden, data management and analysis were conducted using SAS software, version 9.4 (Cary, NC, USA). The data cut for the final report was 31-Dec-2022.

9.9.1 Main summary measures

Categorical variables and categorized continuous variables were summarized using frequencies and proportions (expressed in %). Continuous variables (e.g., age) were summarized using means with standard deviations and/or medians with interquartile ranges (IQRs).

Values that could allow re-identification of individuals were reported in accordance with the local data protection regulations. In Denmark and in Finland, potentially identifiable personal data, which are therefore not reportable, include cell counts containing 1 to 4 observations and maxima and minima of continuous variables. (Maxima and minima for cumulative dose and duration of treatment were reportable in Denmark. Instead of minima and maxima, the 5^{th} and 95^{th} percentiles were reported for continuous variables in Finland). Cell counts between 1 and 4 were masked and reported as <5. In addition, potentially identifiable data are counts of 1-4

observations that could be recomputed from the surrounding data, e.g., variables with mutually exclusive and all-inclusive categories. Presence of such implicit counts necessitates masking of selected additional cells even if their counts exceed 4. Masking of other values was accomplished by reporting ranges whenever necessary. Because of small counts of endpoints of exploratory objectives, most stratified analyses were not possible in Denmark. In those cases, only overall results were presented. In Norway, investigators are responsible for evaluating whether small numbers may risk revealing personal data and thereby whether these can be reported for regulatory purposes. In Sweden, the data protection regulations do not formally require masking for regulatory reporting, but the investigator may decide to do so if necessary.

9.9.2 Main statistical methods

9.9.2.1 Duration of prophylactic migraine treatment

Based on the Summary of Product Characteristics (EMA 2018), each package of erenumab, regardless of dosage (70 mg or 140 mg), was assumed to have the duration of 28 days (Table 9-2). For galcanezumab, each 120 mg dose was assumed to have a duration of 28 days. For fremanezumab, each 225 mg dose was assumed to have a duration of 28 days. The number of packages and package size are not available from the data source supplying information about hospital medication use in Denmark. Therefore, these agents were identified based on procedure codes. Therefore, based on clinical practice, in Denmark, the first and second erenumab dispensing was assumed to have a duration of 84 days. Dispensings thereafter were assumed to have a duration of 168 days.

Table 9-2 Illustration of relation between package strength, dispensed amount, and duration for 5 hypothetical patients initiating erenumab on 01-Apr-2019

Patient number	Dispensing date	Package strength	Packages dispensed	Amount dispensed	Duration of package	Duration of dispensing
1	01-Apr-2019	70 mg	1	70 mg	28 days	28 days
2	01-Apr-2019	70 mg	2	70 mg	28 days	56 days
3	01-Apr-2019	140 mg	1	140 mg	28 days	28 days
4	01-Apr-2019	140 mg	2	140 mg	28 days	56 days
5	01-Apr-2019	70 mg	1	210 mg	28 days	56 days
		140 mg	1		28 days	

For prophylactic migraine medications other than CGRP antagonists, duration of each dispensing was computed by dividing the total amount dispensed by the assumed daily dose. The assumed daily dose for specific migraine medication was equal to the defined daily dose (DDD), which is the standard daily dose for the main indication. The assumed daily dose for non-specific prophylactic migraine medications was equal the migraine-specific daily dose per local guidelines, if defined, otherwise was equal the DDD (Table 9-1). Total amount dispensed was the sum of the amount dispensed from all packages. The amount dispensed in a package of

orally administered medications was the product of the package-specific unit strength and the number of units.

$$Package\ quantity\ dispensed\ (mg) = number\ of\ units\ per\ package\ \times unit\ strength$$

$$Duration\ of\ dispensing\ (days) = \frac{Total\ amount\ dispensed\ in\ all\ packages\ (mg)}{Assumed\ daily\ dose\ (mg/day)}$$

For botulinum toxin, all dispensings were assumed to have a duration of 12 weeks regardless of origin. Dispensings of medications in the same treatment cohort (including different agents in the "Other prophylactic migraine medications" cohort) occurring before expiration of an ongoing dispensings was 'stacked', i.e., it was assumed that a patient used up the ongoing dispensing before starting a new one. However, based on data flow and prescribing practices, it was assumed that the maximum stock equaled 9 months' worth of medication in Denmark and Norway and 3 months' worth of medication in Sweden and Finland.

A grace period of maximum of 30 days was allowed between consecutive dispensings qualifying patients for the same treatment cohort to allow for irregularities in prescription fills and stockpiling (Nielsen et al 2008).

9.9.2.2 Continuous use, discontinuation/switch of prophylactic migraine treatment

Continuous use in a given treatment cohort started on the index date and continued until discontinuation, switch to another treatment cohort (for ERE and OCG cohorts only), emigration, death or administrative censoring on 31-Dec-2022. Discontinuation was defined as absence of a new dispensing within the estimated duration of the last dispensing plus the 30-day grace period. The estimated duration of the last dispensing here included potential stock from previous dispensing. Date of discontinuation was the date of first dispensing + duration of all dispensings + potential gaps from grace periods between dispensings + 31 days. Continuous use, discontinuation, and restarting in a given treatment cohort are shown in Figure 9-2.

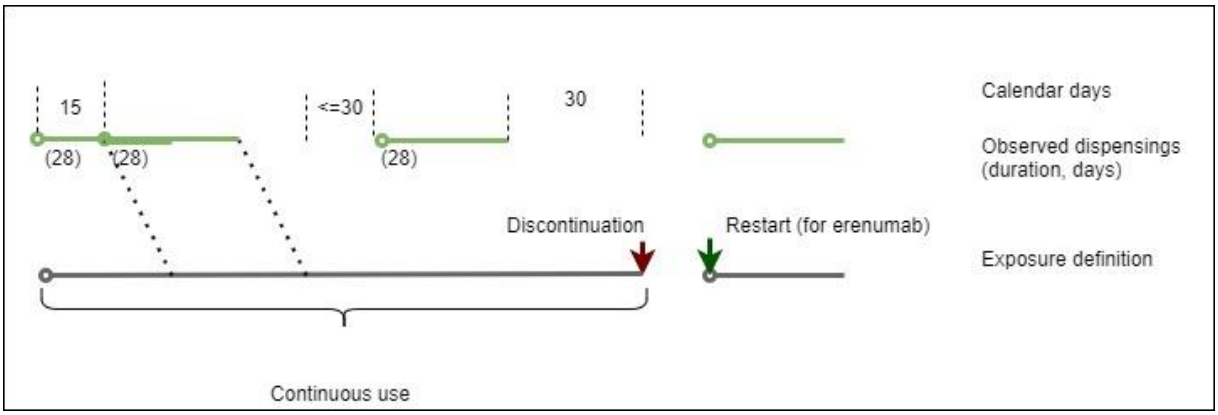


Figure 9-2 Continuous use, discontinuation and restarting in a given treatment cohort based on observed dispensing patterns

A switch from erenumab to other CGRP antagonists was defined by a dispensing of galcanezumab, fremanezumab or eptinezumab, which occurred before the date of discontinuation of erenumab as defined in the previous section. The date of the other CGRP antagonist dispensing was date of the switch (i.e., the patient was assumed to have given up the remaining daily doses on the date of the new dispensing, Figure 9-3). The date of discontinuation of erenumab was the date of the switch, and if inclusion and exclusion criteria were satisfied for entering the OCG cohort on the date of the switch, the switch date was the index date in the OCG cohort. A switch from other CGRP antagonists to erenumab was defined in the same way. Switch was not defined for botulinum toxin and other prophylactic migraine medications as these were considered add-ons.

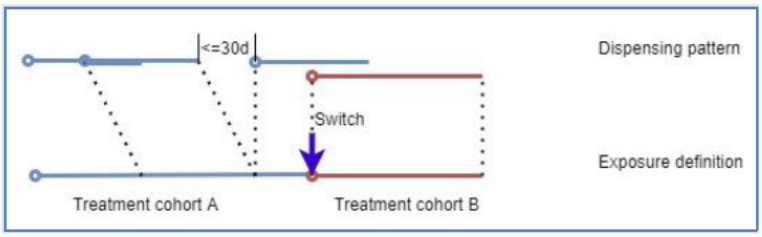


Figure 9-3 Defining switching from one prophylactic migraine medication to another based on observed dispensing patterns

In all analyses, follow-up was censored by death, emigration, or administrative censoring on 31-Dec-2022.

9.9.2.3 Erenumab utilization measures

The following drug utilization measures were examined only among initiators of erenumab and are described below: initiation type; persistence; switching to other CGRP antagonists; restarting; cumulative duration and cumulative dose. Cumulative duration and dose, as measures of utilization, were computed across all dispensings initiated during the study period regardless of switching or censoring.

9.9.2.3.1 Erenumab initiation type

Patients in the erenumab cohort were subclassified into whether erenumab was added to another prophylactic migraine medication or initiated as monotherapy. If patient's prior dispensing of a prophylactic migraine medication within previous 12 months included that patient's erenumab cohort index date, erenumab initiation was assumed to be as add-on. Otherwise erenumab initiation was classified as monotherapy.

9.9.2.3.2 Erenumab persistence

For the purposes of the analysis the duration of 6 months was set at 183 days; 1 year 365 days; 2 years 730 days; 3 years 1095 days; and 4 years, 1461 days. Persistence with erenumab was estimated as the proportion of patients who remained continuous users of erenumab (i.e., did not discontinue or switch from erenumab) following their first dispensing of erenumab.

Persistence was reported at 6 months, 1, 2, 3, and 4 years following first dispensing of erenumab, using the Kaplan-Meier approach as time to erenumab treatment discontinuation/switch (Campagna et al 2014, Meid et al 2016). In addition, cumulative incidence of erenumab initiators who filled at least 80% of the monthly prescriptions over 1, 2, 3, and 4 years of follow-up were computed. The 80% criterion was defined by at least 10 pens in the first full year following the erenumab first dispensing date, at least 20 pens in in the two full years etc. In Denmark, cumulative incidence of erenumab initiators who filled at least 50% of the prescriptions was used, to compensate the lack of information about the amount delivered at each administration based on dispensing amounts combined with defined daily doses (DDDs). The criterion was defined as at least two erenumab hospital records in the first year, at least three records in the first two years, at least 4 records in the first three years and at least five records in the first four years. Further, proportion of patients covered (PPC) were calculated (Rasmussen et al 2018) to account for restart and discontinuation of erenumab following first-time discontinuation.

9.9.2.3.3 Switching from erenumab to other CGRP antagonists

Switching from erenumab to another CGRP antagonist (galcanezumab, fremanezumab, eptinezumab) was reported as cumulative incidence of patients in the erenumab cohort who switch to another CGRP antagonist during the follow-up. Only the first episode of switch to another CGRP antagonist was considered. Cumulative incidence of switching from erenumab to another CGRP antagonist was reported over 6 months, 1 year, 2 years, 3 years, and 4 years of follow-up.

9.9.2.3.4 Restarting erenumab

Restarting of erenumab was defined as a new dispensing of erenumab after being recorded with erenumab discontinuation or with a switch from erenumab cohort to another treatment cohort. Patients who discontinue erenumab or switch from erenumab to another treatment cohort enter the at-risk population for restarting on the day of discontinuation or switch. Only the first episode of erenumab restarting was considered in the analysis. Cumulative incidences of restarting were estimated for the overall follow-up and for 6 months, and 1 year following the date of becoming at risk for restarting.

9.9.2.3.5 Erenumab cumulative duration of and cumulative dose

For the patients in the erenumab cohort, cumulative dispensed duration (in days) and cumulative dispensed dose (in mg) were continuous variables computed disregarding switches and discontinuation. Cumulative dispensed duration was the cumulative number of days summed across all 70 mg or 140 mg erenumab dispensings during follow-up, including the first episode of erenumab use and all subsequent episodes among patients initiating and restarting erenumab regardless of switching or censoring. The cumulative dose was the number of milligrams in the abovementioned pens. The cumulative dose and the cumulative duration were summarized using mean and standard deviation, median and IQR, and maxima/minima (maxima/minima were reported to the extent allowed by data protection regulations).

9.9.2.3.6 Cumulative incidences, rates and prevalences

Cumulative incidences were calculated using the Aalen-Johansen estimator, while taking into account competing events (as defined in Table 9-3) (Marubini et al 1995). Rates of the endpoints were computed as the number of first events during the follow-up divided by the total person-time at risk in a given treatment cohort (Dobson et al 1991). In each treatment cohort, the follow-up began on the day following the index date and ended on the date of a given endpoint, treatment discontinuation or switch, dispensing of erenumab or other CGRPs (for BOT and OPM only), a dispensing of botulinum toxin (for OPM only), emigration, death or 31-Dec-2022, whichever came first. Only the first event occurrence in each treatment cohort was considered. The endpoints were not considered as competing with each other. Rates were reported with 95% Poisson confidence intervals (CIs). Prevalence of the exploratory endpoints in the pregnancy analysis population were summarized using numbers and proportions (expressed in %). Table 9-3 summarizes analytic approaches for the different analysis types.

Table 9-3 Overview of analysis methods, follow-up, competing events and censoring

Source output file (Appendix 2)	Analysis	Endpoint	Analysis method	Analysis time point	Competing events	Censoring
Table 2	Proportion of erenumab persistence	Time to discontinuation of erenumab (including switch to other CGRP)	Kaplan-Meier	6 months, 1, 2, 3, 4 years	NA	Death/Emigration/End of study
Table 2	Cumulative incidence of erenumab discontinuation	Time to discontinuation of erenumab (including switch to other CGRP)	Aalen-Johansen	6 months, 1, 2, 3, 4 years	Death	Emigration/End of study
Table 2	Cumulative incidence of erenumab switch to another CGRP	Time to switch to other CGRP	Aalen-Johansen	6 months, 1, 2, 3, 4 years	Death/ Discontinuation (without switch)	Emigration/End of study
Table 2	Proportion of erenumab initiators who fill 80% of annual dispensings	Time to 10 dispensings	Aalen-Johansen	1 year	Death	Emigration/End of study

Table 2	Proportion of erenumab initiators who fill 80% of annual dispensings	Time to 20 dispensings	Aalen-Johansen	2 years	Death	Emigration/End of study
Table 2	Proportion of erenumab initiators who fill 80% of annual dispensings	Time to 30 dispensings	Aalen-Johansen	3 years	Death	Emigration/End of study
Table 2	Proportion of erenumab initiators who fill 80% of annual dispensings	Time to 40 dispensings	Aalen-Johansen	4 years	Death	Emigration/End of study
Table 3	Cumulative incidence of restarting erenumab	Time from erenumab discontinuation to restart	Aalen-Johansen	6, months, 1 year	Death	Emigration/End of study
Figure 2	Cumulative incidence of erenumab discontinuation	Time to discontinuation of erenumab (including switch to other CGRP)	Kaplan-Meier	Continuous	NA	Death/Emigration/End of study
Table 16-23	Cumulative incidence of CV endpoints	Time to <CV endpoint>	Aalen-Johansen	1, 2, 3, 4 years, max follow-up	Death	Treatment discontinuation or switch, dispensing of erenumab or other CGRPs (for BOT and OPM only), dispensing of BOT (OPM only)/Emigration/End of study

9.9.2.4 Pregnancy periods

The following pregnancy periods were defined: preconception was defined from 90 days before the last menstrual period (LMP), included until the first day before the LMP; the first trimester was defined from the LMP to LMP+97 days (both dates inclusive); second trimester, from LMP+98 days to LMP+202 days (both dates included); third trimester, from LMP+203 days (included) until date of delivery (excluded).

9.9.2.5 Meta-analyses

Country-specific patients' characteristics were combined by summing the aggregate country-specific cell counts. Country-specific rates, and cumulative incidences were combined using random-effects meta-analyses techniques appropriate for descriptive statistics. Rates were

analyzed on log scale, and cumulative incidences were analyzed on log-log scale. The between-study variance was estimated using a restricted maximum likelihood estimator. Meta-analyses were not performed in the pregnancy population. Heterogeneity was quantified using the I-squared statistic with associated 95% CI using the ***meta*** package in R (Borenstein et al 2010).

9.9.2.6 Missing values

Whenever applicable, the number of observations with missing data were summarized as a separate category in descriptive analysis. In general, in studies based on secondary data, absence of a record is assumed to indicate absence of the event of interest. In Finland, whenever dispensing records of cohort-defining medications had insufficient info to determine the duration of dispensing, those were imputed as the median durations per ATC code.

9.9.3 Sensitivity analyses

The following sensitivity analyses were conducted:

- Re-computing erenumab persistence extending the grace periods to 60 days
- Re-computing rates of the CV endpoints (exploratory objectives) extending the grace periods to 60 days
- Re-computing rates of the CV endpoints (exploratory objectives) over total follow-up (censoring by death or emigration but not at discontinuation or switch of the prophylactic migraine medication initiated at index date)
- Assessing selected baseline characteristics and rates of the CV endpoints in the treatment cohorts in the Main Analysis Population, restricting the population in the other prophylactic migraine medication cohort to patients with either a dispensing of a CGRP antagonist before the index date or with at least one hospital diagnosis of migraine before or at the index date, to capture most erenumab eligible population

The following strata were defined for the analyses of the first exploratory objective:

- Re-computing the overall rates of the CV endpoints stratified by calendar periods within the patient identification period, defined important landmarks of the COVID-19 pandemic that were assumed to affect patterns of healthcare utilization. For countries without lockdown (Sweden, Finland), a proxy date was used for start and end of the measures affecting healthcare utilization (pre-COVID-19 period: 08-Aug-2018 (included) – start date of the first lockdown (excluded), COVID-19 period start date of the first lockdown (excluded) –end date of the last lockdown (included); post-COVID-19 period end date of the last lockdown (excluded) – 30-Sep-2022 (included). Country-specific lockdown dates are provided in the SAP, Appendix 1 – List of stand-alone documents, Section 15.1.6.

9.9.4 Amendments to the Statistical Analysis Plan

The following refinements and clarifications of the SAP, none of which changed the basic design, objectives, or endpoints, were applied:

1. Migraine criteria: to fulfill criteria for established migraine, two, instead of one, outpatient hospital and primary care were required for definition of migraine to increase specificity of migraine identification. Additionally, in Finland, only primary diagnoses of migraine were considered for the definition of migraine.

2. Treatment cohorts: as other CGRP antagonists became available for treatment of chronic migraine and given that different prophylactic migraine agents represent different migraine severity and may not have the same indication as erenumab, the initially planned treatment cohort of other prophylactic migraine agents was subclassified into three separate treatment cohorts.
3. Unexpectedly, we observed co-use of ERE and OCG with BOT and therefore, we considered BOT dispensings occurring during continuous use of erenumab or other CGRP antagonists as add-on rather than a switch. Thus, switch could only occur between the ERE and OCG cohort.
4. Switches from orals and injectables were treated in the same way, whereby the date of dispensing of a new agent is considered to be the date of the switch. This was based on observed dispensing patterns, which would make injected treatment times unrealistically long. Furthermore, clarified that for the members of the erenumab or other CGRP cohorts, switching counted only to other CGRP agents and not to botulinum toxin or other prophylactic migraine medication.
5. Inclusion criteria for the BOT treatment cohort were refined to reduce misclassification by non-indicated population. In Denmark, BOT dispensing must occur at a neurology department. In Norway and Sweden, hospital administrations of BOT required a primary diagnosis of migraine at the same encounter.
6. Previously certain opioids were reported as acute migraine medications. However, current European guidelines recommend abstaining from using opioids as acute migraine treatment. To reflect such guidelines, all opioids were reported as comedications (Eigenbrodt et al 2021).
7. In Finland, eligibility for the migraine population identified by hospital diagnosis was based on primary migraine diagnoses only, instead of any hospital diagnoses (primary or secondary). This was done to improve specificity of identification of the indicated population.
8. Assumed duration of all botulinum toxin dispensings was updated to 12 weeks for all countries.
9. Based on data flow and prescribing practices, a maximum stock of 9 months' worth of medication in Denmark and Norway and 3 months' worth of medication in Sweden and Finland was added.
10. There were slight variations in the interpretation of the protocol and the SAP by the data holders across countries. Specifically, in the Finnish data holders identified all users of the study medications in Finland between 2018 and 2022, for whom data from 2008 to 2022 were extracted on all other study variables. This could exclude migraine patients diagnosed and treated before 2018 who completely discontinued migraine treatment before 2018. In Sweden, the data extraction potentially resulted in missing from the source population of patients with who either had early pre-2018 diagnosis migraine or were treated only with non-CRPG prophylactic agents outside the N02C ATC codes. In Finland, this could exclude migraine patients diagnosed and treated before 2018 who discontinued migraine treatment

during 2018-2022. These minor variations in data extraction do not affect inclusion of erenumab users or the other study results.

9.10 Quality control

Data in the Nordic registries are generally of high quality (Wettermark et al 2013, Schmidt et al 2015, Laugesen et al 2021). 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, Lund et al 2024). Linkage of data from different data sources was exact via a unique personal identifier that remains unchanged throughout life. Dispensing records, although not perfect measures of medication intake, were considered superior to any other method. Furthermore, dispensings (used in this study) were superior to prescriptions, as they represent primary compliance, i.e., indicate a medication sale to a patient.

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

10 Results

All source output tables, figures and listings are provided as standalone documents, Appendix 2. This report provides results from Denmark, Finland, Norway, and Sweden.

10.1 Participants

Table 10-1 shows the inclusion of patients to the population according to the eligibility criteria (Appendix 2, Denmark Listing 1, Finland Listing 1, Norway Listing 1 and Sweden Listing 1). After applying the eligibility criteria, the study population included 33,218 unique patients in Denmark, 91,415 unique patients in Finland, 74,047 unique patients in Norway, and 47,173 unique patients in Sweden. After being included in the study, patients could contribute to more than one treatment cohort, as described above. Appendix 2, Denmark Listing 1, Finland Listing 1, Norway Listing 1 and Sweden Listing 1.

Table 10-1 Attrition table for the Main Population

Criterion/characteristic	Denmark	Finland	Norway	Sweden
Satisfying migraine criterion	212142	149375	336999	86208
Dispensing of ERE in inclusion period	1845	5011	8447	5199
Exclusion: Dispensing of ERE before study start	-	-	23	-
Exclusion: age<18 years at index date	N<5	47	10	21
Exclusion: lack of 1 year residence prior to index date	Masked	15	138	20
Dispensing of OCG in inclusion period	723	4424	7533	4033
Exclusion: age<18 years at index date	-	27	78	2
Exclusion: lack of 1 year residence prior to index date	N<5	15	4	2
Exclusion: Dispensing of ERE on index date	Masked	12	9	-
Exclusion: lack of 1 year washout period	N<5	6	15	17
Dispensing of BOT* in inclusion period	267	3029	12163	10257
Exclusion: age<18 years at index date	-	32	140	7
Exclusion: lack of 1 year residence prior to index date	-	8	6	6
Exclusion: within period of use of ERE or OCG	N<5	225	1006	31
Exclusion: lack of 1 year washout period	Masked	803	3506	3178
Dispensing of OPM in inclusion period	49015	128401	105352	81607
Exclusion: age<18 years at index date	473	4650	1440	178
Exclusion: lack of 1 year residence prior to index date	135	260	111	42
Exclusion: within period of use of ERE, OCG or BOT	56	453	2204	99
Exclusion: several different OPMs on index date	45	443	1928	234
Exclusion: lack of 1 year washout period	15921	34446	33668	40200
ERE, OCG, BOT or OPM cohort	33218	91415	74047	47173
Contributing to two or more treatment cohorts	1585	6226	11087	7695
ERE cohort	1835	4949	8276	5158
OCG cohort	712	4364	7427	4012
BOT cohort	147	1961	7505	7035
OPM cohort	32385	88149	66001	40854

ERE: erenumab; OCG: other CGRPs; BOT: botolinum toxin; OPM: other prophylactic migraine medication. Numbers in exclusion categories are mutually exclusive. *Satisfying country-specific criteria described in cohort inclusion criteria.

There were 23 individuals in Norway who were, per protocol, excluded from the ERE cohort due to dispensings of erenumab prior to the study start date.

10.2 Descriptive data

Between 08-Aug-2018 and 30-Sep-2022, there were 1,835 (Denmark) / 4,949 (Finland) /8,276 (Norway) / 5,158 (Sweden) patients initiating erenumab, including 561 (Denmark) / 1,816 (Finland) / 2,442 (Norway) / 1,455 (Sweden) patients with a history of a CV disorder. Table 10-2 and Appendix 2, Table 1 show demographic characteristics of the 20,218 erenumab initiators, combined across all countries, overall and by CV history. Norway accounted for the largest (40.9%) and Denmark the smallest (9.1%) proportion of erenumab initiators across the four Nordic countries. Overall, 84.7% of the initiators were female. The median (IQR) age (SD) was 43.7 (12.6) years, and 67.4% started erenumab as monotherapy.

Table 10-2 Characteristics of patients initiating erenumab, overall and by CV history in Denmark, Finland, Norway, and Sweden

	Erenumab initiators		
	Total N=20218	With CV history N=6769	Without CV history N=13449
Country, n (%)			
Denmark	1835 (9.1)	561 (8.3)	1274 (9.5)
Finland	4949 (24.5)	1816 (26.8)	3133 (23.3)
Norway	8276 (40.9)	2442 (36.1)	5834 (43.4)
Sweden	5158 (25.5)	1950 (28.8)	3208 (23.9)
Calendar year of erenumab initiation, n (%)			
2018-2019	7015 (34.7)	2735 (40.4)	4280 (31.8)
2020	6691 (33.1)	2168 (32.0)	4523 (33.6)
2021	3749 (18.5)	1110 (16.4)	2639 (19.6)
2022	2763 (13.7)	756 (11.2)	2007 (14.9)
Sex, n (%)			
Female	17129 (84.7)	5595 (82.7)	11534 (85.8)
Male	3089 (15.3)	1174 (17.3)	1915 (14.2)
Age, years, mean (SD)	43.7 (12.6)	48.2 (12.1)	41.5 (12.2)
Age group, years, n (%)			
18-<30	3091 (15.3)	480 (7.1)	2611 (19.4)

	Total N=20218	Erenumab initiators With CV history N=6769	Erenumab initiators Without CV history N=13449
30-<40	4411 (21.8)	1103 (16.3)	3308 (24.6)
40-<50	6153 (30.4)	2134 (31.5)	4019 (29.9)
50-<60	4485 (22.2)	1922 (28.4)	2563 (19.1)
>=60	2078 (10.3)	1130 (16.7)	948 (7.0)
Erenumab initiation type			
Add-on	6594 (32.6)	2205 (32.6)	4389 (32.6)
Monotherapy	13624 (67.4)	4564 (67.4)	9060 (67.4)

IQR: interquartile range; SD: standard deviation.
All variables in this table are measured relative to the first-ever dispensing of erenumab during the patient inclusion period.

Appendix 2, Table 5 shows the distributions of the migraine-related characteristics by treatment cohort and Appendix 2, Denmark Table 2, Finland Table 2, Norway Table 2 and Sweden Table 2 show country-specific distributions of the migraine-related characteristics by treatment cohort. Appendix 2, Table 7 shows the distributions of the demographic and clinical characteristics by treatment cohort and Appendix 2, Denmark Table 3, Finland Table 3, Norway Table 3, and Sweden Table 3 show country-specific distributions of the demographic and clinical characteristics by treatment cohort.

10.3 Outcome data and main results

10.3.1 Results addressing the primary objective: erenumab utilization

10.3.1.1 Patient characteristics

Among the erenumab initiators, 85.9% (Denmark) / 86.1% (Finland) / 85.1% (Norway) / 82.4% (Sweden) were female. The median (IQR) age was 45 (36; 53) years (Denmark) / 44 (35; 52) (Finland); 43 (33; 51) years (Norway) / 46 (37; 54) years (Sweden). Initiation of erenumab occurred via a neurologist in 99.7% (Denmark) / 54.7% (Sweden) of the patients. The majority of patients initiated erenumab in the secondary/hospital sector, 99.7% (Denmark) / 93.4% (Sweden) (Table 10-3, Appendix 2, Denmark Table 1, Sweden Table 1). Data on prescriber specialty and health sector were unavailable in Norway. In Finland, only outpatient dispensings were available, and prescriber specialty information was missing for more than 90% of erenumab initiators. Appendix 2, Tables 1.1-1.3 show characteristics by subgroups and Appendix 2, Denmark Table 1.1-1.3, Finland Table 1.1-1.3, Norway Table 1.1-1.3, and Sweden Table 1.1-1.3 show country-specific characteristics by subgroups.

Table 10-3 Characteristics of erenumab initiators by country

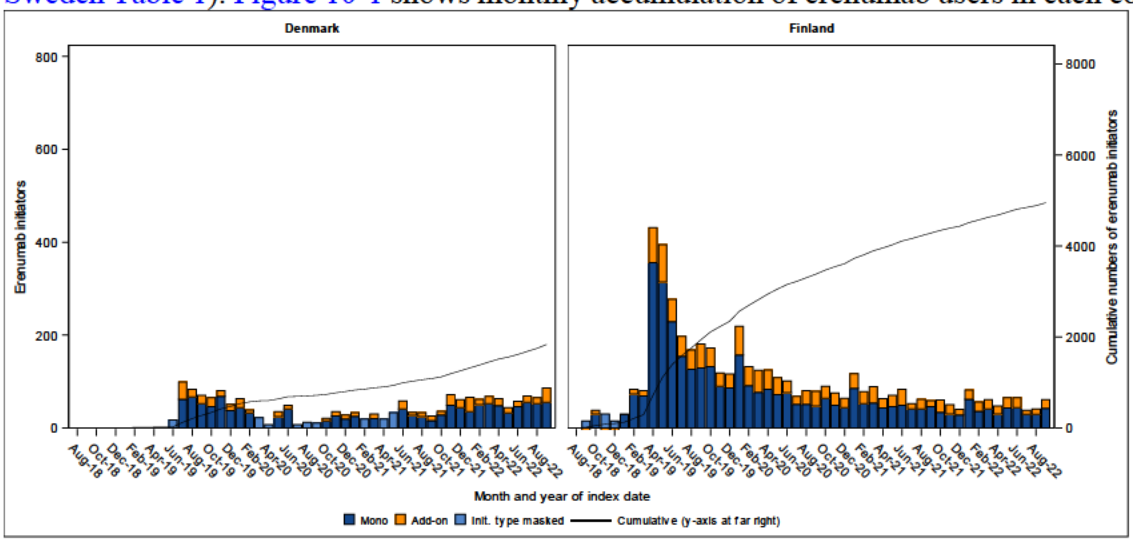
Characteristic	Denmark	Finland	Norway	Sweden
	N=1835	N=4949	N=8276	N=5158
Calendar year of erenumab initiation, n (%)				
2018-2019	472 (25.7)	2345 (47.4)	1448 (17.5)	2750 (53.3)
2020	329 (17.9)	1265 (25.6)	4062 (49.1)	1035 (20.1)
2021	454 (24.7)	823 (16.6)	1707 (20.6)	765 (14.8)
2022	580 (31.6)	516 (10.4)	1059 (12.8)	608 (11.8)
Sex, n (%)				
Female	1576 (85.9)	4261 (86.1)	7044 (85.1)	4248 (82.4)
Male	259 (14.1)	688 (13.9)	1232 (14.9)	910 (17.6)
Age, years, median (IQR)	45 (36;53)	44 (35;52)	43 (33;51)	46 (37;54)
Age, years, mean (SD)	45.1 (12.6)	43.7 (12.6)	42.3 (12.6)	45.7 (12.3)
Age group, years, n (%)				
18 - <30	260 (14.2)	781 (15.8)	1462 (17.7)	588 (11.4)
30 - <40	346 (18.9)	1114 (22.5)	1979 (23.9)	972 (18.8)
40 - <50	604 (32.9)	1521 (30.7)	2443 (29.5)	1585 (30.7)
50 - <60	410 (22.3)	1043 (21.1)	1678 (20.3)	1354 (26.3)
>=60	215 (11.7)	490 (9.9)	714 (8.6)	659 (12.8)
Prescriber specialty, n (%)				
Neurology (specialist)	1830 (99.7)	0	NA	2823 (54.7)
General practice	0	435 (8.8)	NA	348 (6.7)
Pain/anesthesia	0	0	NA	34 (0.7)
Internal medicine	0	0	NA	1097 (21.3)
Dentist	0	0	NA	0
Other specialist	0	0	NA	852 (16.5)
Missing	5 (0.3)	4514 (91.2)	NA	4 (0.1)
Prescriber health sector, n (%)				
Primary	5 (0.3)	NA	NA	341 (6.6)
Secondary/hospital	1830 (99.7)	NA	NA	4817 (93.4)
Erenumab initiation type				
Add-on	475 (25.9)	1314 (26.6)	4441 (53.7)	364 (7.1)
Monotherapy	1360 (74.1)	3635 (73.4)	3835 (46.3)	4794 (92.9)

Characteristic	Denmark	Finland	Norway	Sweden
Erenumab package strength at initial dispensing				
70 mg only (one or more)	NA	Masked	5588 (67.5)	4873 (94.5)
140 mg only (one or more)	NA	985 (19.9)	2675 (32.3)	282 (5.5)
Both 70 mg and 140 mg	NA	N<5	13 (0.2)	3 (0.1)

IQR: interquartile range; SD: standard deviation; NA not available.
All variables in this table are measured relative to the first-ever dispensing of erenumab during the patient inclusion period.

10.3.1.2 Erenumab initiation, persistence, switch to other CGRP antagonists, and restarting

The proportions of erenumab initiators starting the treatment as monotherapy, as defined in this study, were 1,360 (74.1%) (Denmark) / 3,635 (73.4%) (Finland) / 3,835 (46.3%) (Norway) and 4,794 (92.9%) (Sweden). (Appendix 2, Denmark Table 1, Finland Table 1, Norway Table 1, Sweden Table 1). Figure 10-1 shows monthly accumulation of erenumab users in each country.



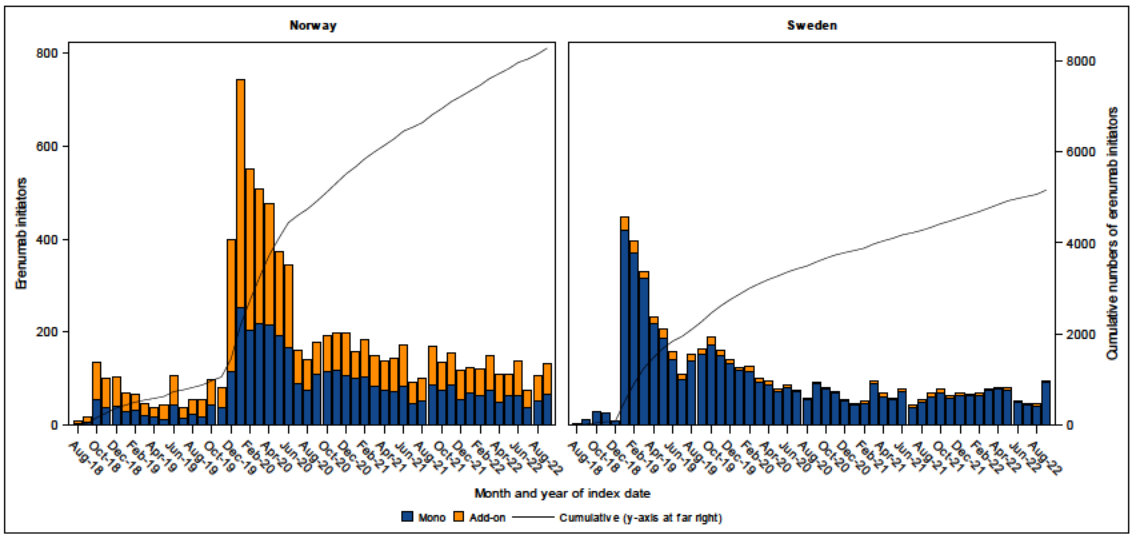


Figure 10-1 Monthly, annual, and cumulative erenumab initiation by country

Source: Appendix 2, Figure 1.

In the first year following the initiation, 43.2% (Denmark) / 53.6% (Finland) / 47.3% (Norway) / 48.8% (Sweden) of the initiators were persistent to the erenumab treatment. At three years of follow-up (timepoint available for all countries), persistence with erenumab was 17.8% (Denmark) / 20.7% (Finland) / 23.0% (Norway) / 10.4% (Sweden). At three years of follow-up, the proportion of patients switching to another CGRP antagonist was 23.3% (Denmark) / 37.5% (Finland) / 33.9% (Norway) / 37.0% (Sweden). (Appendix 2, Table 2, Figure 2 and 3). Appendix 2, Tables 2.1-2.3 show erenumab persistence, discontinuation and switch to other CGRP antagonists by subgroups. Among those classified as discontinuers of erenumab, restarting in 1 year post-discontinuation was recorded in 40.2% (Denmark) / 26.3% (Finland) / 27.9% (Norway) / 56.0% (Sweden) of patients (Appendix 2, Table 3). Appendix 2, Tables 3.1-3.3 show erenumab restarting post-discontinuation by subgroups. Switching from erenumab to another CGRP antagonist counted as discontinuation of erenumab. Switches from erenumab also include patients regardless of whether or not they restarted erenumab later. The median (IQR) cumulative duration of erenumab use, in days, was 511 (224; 952) (Finland) / 364 (168; 756) (Norway) / 448 (196; 924) (Sweden). The median (IQR) cumulative dose, in mg, was 1,820 (840; 3,500) (Finland) / 1050 (420; 2,100) (Norway) / 1,470 (630; 3,080) (Sweden) (Appendix 2, Table 4). The cumulative dose could not be computed in Denmark because hospital records of erenumab administration do not contain information on the amount dispensed. Appendix 2, Tables 4.1-4.3 show erenumab cumulative dispensed dose by subgroups. Figure 10-2 shows country-specific patterns of switching among erenumab and other CGRP antagonists following initiation of erenumab.

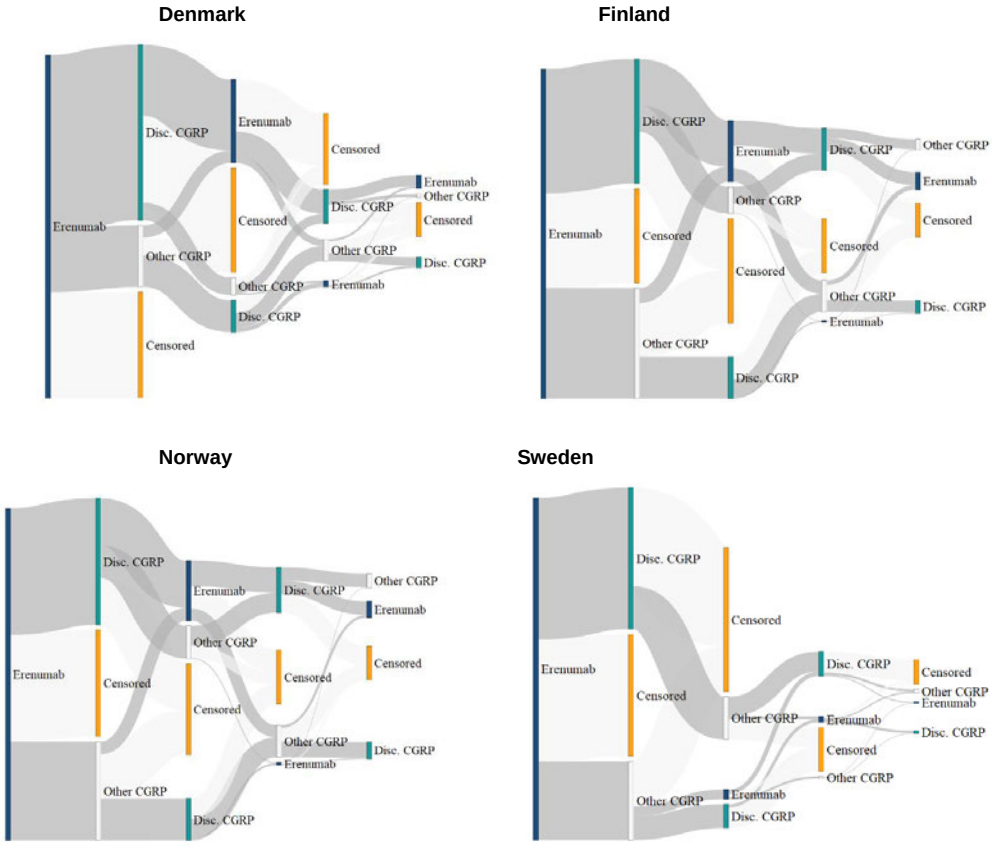


Figure 10-2 Sankey plots showing patterns of CGRP antagonist use following erenumab initiation in Denmark, Finland, Norway and Sweden

Disc. CGRP: Discontinued erenumab or other CGRP.

The figure shows patterns/sequence of use, regardless of time.

Source: Appendix 2, Figure 4

10.3.2 Results addressing secondary objectives: patients characteristics and history across cohort

Patient characteristics by treatment cohort, combined for the four countries are shown in Table 10-4, Appendix 2 Table 5 and Table 7. The ERE, OCG and BOT cohorts had similar characteristics and were all different from the OPM cohort. The OPM cohort was, on average, slightly older and had higher than the other three cohorts prevalences of moderate or severe hypertension, several comorbidities associated with CV risks, including diagnoses and treatment markers of diabetes, hypercholesterolemia, and obesity, and high comorbidity burden as measured by the Charlson Comorbidity Index score.

The OPM cohort had lower than the other three cohorts prevalences of previous use of any or multiple prophylactic or acute migraine medications, headache disorders, and chronic pain (Table 10-).

Table 10-4 Patient characteristics by treatment cohort

	Treatment cohort			
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**
	N=20218	**N=16515**	**N=16648**	**N=227389**
Country, n (%)				
Denmark	1835 (9.1)	712 (4.3)	147 (0.9)	32385 (14.2)
Finland	4949 (24.5)	4364 (26.4)	1961 (11.8)	88149 (38.8)
Norway	8276 (40.9)	7427 (45.0)	7505 (45.1)	66001 (29.0)
Sweden	5158 (25.5)	4012 (24.3)	7035 (42.3)	40854 (18.0)
Calendar year of index date, n (%)				
2018-2019	7015 (34.7)	259 (1.6)	5916 (35.5)	84286 (37.1)
2020	6691 (33.1)	5766 (34.9)	3512 (21.1)	52744 (23.2)
2021	3749 (18.5)	6275 (38.0)	4140 (24.9)	53391 (23.5)
2022	2763 (13.7)	4215 (25.5)	3080 (18.5)	36968 (16.3)
History of use of prophylactic migraine medication in the 12 months before index date, n (%)*				
Antiepileptics	4357 (21.6)	2892 (17.5)	2615 (15.7)	3602 (1.6)
Antihypertensives, beta-blockers	4905 (24.3)	3877 (23.5)	4220 (25.3)	18848 (8.3)
Antihypertensives, calcium channel blockers	59-62	11-17	5-8	70-73
Antihypertensives, other	3280 (16.2)	2415 (14.6)	1208 (7.3)	8765 (3.9)
Antidepressants, tricyclics	5635 (27.9)	4859 (29.4)	4121 (24.8)	9763 (4.3)
Antidepressants, serotonin norepinephrine reuptake inhibitors	612 (3.0)	631 (3.8)	396 (2.4)	2350 (1.0)

	Treatment cohort			
	Erenumab N=20218	**Other CGRP antagonists** N=16515	**Botulinum toxin** N=16648	**Other prophylactic migraine medications** N=227389
Other prophylactic migraine medications	4520 (22.4)	3878 (23.5)	24-27	727 (0.3)
CGRP antagonists	1069 (5.3)	6661 (40.3)	734 (4.4)	1174 (0.5)
History of use of acute migraine medication in the 12 months before index date, n (%)*				
Ergotamines	22-25	11-17	5-8	297 (0.1)
Triptans	16827 (83.2)	13551 (82.1)	10070 (60.5)	122481 (53.9)
Analgesics, NSAIDs	9463 (46.8)	8165 (49.4)	6329 (38.0)	101009 (44.4)
Analgesics, non-NSAID	6426 (31.8)	5480 (33.2)	4752 (28.5)	80620 (35.5)
Gepants	0	2 (0.0)	1 (0.0)	1 (0.0)
Number of previous different acute antimigraine agents 12 months before index date, n (%)				
0	996 (4.9)	779 (4.7)	2539 (15.3)	40613 (17.9)
1	4894 (24.2)	3521 (21.3)	4317 (25.9)	70256 (30.9)
2 or more	14328 (70.9)	12215 (74.0)	9792 (58.8)	116520 (51.2)
Number of previous different prophylactic antimigraine agents 12 months before index date, n (%)				
0	4595 (22.7)	2004 (12.1)	5716 (34.3)	185118 (81.4)
1	6636 (32.8)	5352 (32.4)	5811 (34.9)	35839 (15.8)
2 or more	8987 (44.5)	9159 (55.5)	5121 (30.8)	6432 (2.8)
Sex, n (%)				
Female	17129 (84.7)	14174 (85.8)	14357 (86.2)	184632 (81.2)
Male	3089 (15.3)	2341 (14.2)	2291 (13.8)	42757 (18.8)
Age at index date, years, mean (SD)	43.7 (12.6)	43.6 (12.4)	42.4 (12.9)	45.5 (15.1)
Age group at index date, years, n (%)				
18 - <30	3091 (15.3)	2469 (15.0)	2987 (17.9)	39460 (17.4)
30 - <40	4411 (21.8)	3769 (22.8)	4256 (25.6)	46070 (20.3)
40 - <50	6153 (30.4)	5006 (30.3)	4659 (28.0)	55032 (24.2)
50 - <60	4485 (22.2)	3656 (22.1)	3133 (18.8)	46806 (20.6)
>=60	2078 (10.3)	1615 (9.8)	1613 (9.7)	40021 (17.6)
Cardiovascular comorbidity, any, n (%)				
Hypertension, any	6640 (32.8)	5502 (33.3)	5211 (31.3)	77128 (33.9)
Hypertension, mild	5522 (27.3)	4584 (27.8)	4027 (24.2)	52875 (23.3)
Hypertension, moderate or severe	1118 (5.5)	918 (5.6)	1184 (7.1)	24253 (10.7)
Unstable angina	47-50	42-45	54-57	1474 (0.6)
Myocardial infarction	43-46	46-49	95-101	2604 (1.1)
Coronary revascularization via CABG or PCI	13-19	11-14	28-31	942 (0.4)

	Treatment cohort			
	Erenumab **N=20218**	**Other CGRP antagonists** **N=16515**	**Botulinum toxin** **N=16648**	**Other prophylactic migraine medications** **N=227389**
Ischemic stroke	139 (0.7)	110 (0.7)	188-191	3602 (1.6)
Hemorrhagic stroke	61 (0.3)	40-46	59 (0.4)	955 (0.4)
Transient ischemic attack	100 (0.5)	84 (0.5)	108 (0.6)	3093 (1.4)
Comorbidity associated with CV risk, n (%)				
Diabetes	909 (4.5)	896 (5.4)	1088 (6.5)	16800 (7.4)
Hypercholesterolemia	1767 (8.7)	1519 (9.2)	1244 (7.5)	33539 (14.7)
Obesity	1409 (7.0)	1242 (7.5)	1218 (7.3)	20226 (8.9)
COPD and asthma	4251 (21.0)	3702 (22.4)	3483 (20.9)	50028 (22.0)
Kidney disease	645 (3.2)	594 (3.6)	595-598	9732 (4.3)
Alcohol-related diseases	411 (2.0)	381 (2.3)	582-585	9523 (4.2)
Inflammatory bowel disease	440 (2.2)	382 (2.3)	407-410	5174 (2.3)
Rheumatic diseases	1314 (6.5)	1164 (7.0)	1175 (7.1)	17002 (7.5)
Psoriasis	601 (3.0)	512 (3.1)	541 (3.2)	6384 (2.8)
Other somatic or psychiatric comorbidity, n (%)				
Headaches	7071 (35.0)	5646 (34.2)	4944 (29.7)	37258 (16.4)
Cluster headache	896 (4.4)	905 (5.5)	546 (3.3)	5206 (2.3)
Vascular headache, not elsewhere classified	201-204	175 (1.1)	123-126	731 (0.3)
Tension-type headache	5581 (27.6)	4407 (26.7)	4150 (24.9)	29888 (13.1)
Chronic post-traumatic headache	257 (1.3)	198 (1.2)	163-166	949 (0.4)
Drug-induced headache	1455 (7.2)	986 (6.0)	675 (4.1)	2848 (1.3)
Other specified headache syndromes	1044 (5.2)	1016 (6.2)	812 (4.9)	3704 (1.6)
Epilepsy	477 (2.4)	412 (2.5)	379-382	4851 (2.1)
Mood [affective] disorders	5409 (26.8)	5048 (30.6)	4981 (29.9)	58013 (25.5)
Anxiety/stress disorders	5642 (27.9)	5419 (32.8)	5528 (33.2)	64485 (28.4)
Substance abuse	756 (3.7)	673 (4.1)	1008-1011	14383 (6.3)
Chronic pain	1679 (8.3)	1537 (9.3)	1846 (11.1)	14225 (6.3)
Sleep disorders	3244 (16.0)	3043 (18.4)	2848 (17.1)	36107 (15.9)
COVID-19 related characteristics, n (%)				
COVID-19 related diagnoses	2008 (9.9)	3216 (19.5)	2012-2015	22798 (10.0)
Charlson Comorbidity Index score, n (%)				
No comorbidity	15914 (78.7)	12786 (77.4)	12842 (77.1)	162841 (71.6)
Low comorbidity	2663 (13.2)	2299 (13.9)	2223 (13.4)	35881 (15.8)
High comorbidity	1641 (8.1)	1430 (8.7)	1583 (9.5)	28667 (12.6)

	Treatment cohort			
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**
	N=20218	**N=16515**	**N=16648**	**N=227389**
Use of prescription medication that may affect CV risk, other than migraine medication 90 days before index date, n (%)				
Oral contraceptives	2234 (11.0)	1921 (11.6)	1976 (11.9)	22746 (10.0)
Lipid modifying agents	887 (4.4)	759 (4.6)	873 (5.2)	20709 (9.1)
Antiemetics	274 (1.4)	284 (1.7)	218-221	1703 (0.7)
Antithrombotics	590 (2.9)	458 (2.8)	720 (4.3)	16292 (7.2)
Antihypertensives (except used for migraine)	1492 (7.4)	1277 (7.7)	1592 (9.6)	35669 (15.7)
Antidiabetics	428 (2.1)	433 (2.6)	535 (3.2)	9278 (4.1)
Antirheumatics	2274-2277	2070-2073	1914 (11.5)	18080 (8.0)
Antidepressants (except used for migraine)	3183 (15.7)	2725 (16.5)	3004 (18.0)	37034 (16.3)
Antiepileptics (except used for migraine)	1492 (7.4)	1260 (7.6)	1061 (6.4)	15407 (6.8)
Antipsychotics	959 (4.7)	870 (5.3)	734 (4.4)	12592 (5.5)
Hypnotics and sedatives	2873 (14.2)	2471 (15.0)	2704 (16.2)	31403 (13.8)
Anxiolytics	1560 (7.7)	1356 (8.2)	1553 (9.3)	20914 (9.2)
Medication used in substance abuse	105 (0.5)	82 (0.5)	120-123	1696 (0.7)
Pain medications (except used for migraine)	5715 (28.3)	4861 (29.4)	3992 (24.0)	71257 (31.3)
NSAIDs	2574 (12.7)	2373 (14.4)	1206-1209	38357 (16.9)
Opioids	3308 (16.4)	2628 (15.9)	2991 (18.0)	35153 (15.5)
Markers of health care resource utilization				
Number of different medication classes dispensed (from among the above-listed classes) in 12 months before index date, n (%)				
0	3812 (18.9)	2656 (16.1)	3046 (18.3)	40841 (18.0)
1	5444 (26.9)	4498 (27.2)	4099 (24.6)	64679 (28.4)
2 or more	10962 (54.2)	9361 (56.7)	9503 (57.1)	121869 (53.6)
Number of hospitalizations in 12 months before index date, n (%)**				
0	18656 (92.3)	15317 (92.7)	15082 (90.6)	198557 (87.3)
1	1166 (5.8)	867 (5.2)	1129 (6.8)	19285 (8.5)
2 or more	396 (2.0)	331 (2.0)	437 (2.6)	9547 (4.2)
Number of planned outpatient hospital visits in 12 months before index date, n (%)				
0	4608-4611	3747 (22.7)	4544 (27.3)	126585 (55.7)
1	3126-3129	2646 (16.0)	3006 (18.1)	29763 (13.1)
2 or more	12481 (61.7)	10122 (61.3)	9098 (54.6)	71041 (31.2)
Number of emergency/unplanned/acute visits in 12 months before index date, n (%)*				

	Treatment cohort			
	Erenumab N=20218	**Other CGRP antagonists N=16515**	**Botulinum toxin N=16648**	**Other prophylactic migraine medications N=227389**
0	17369 (85.9)	14339 (86.8)	13924 (83.6)	192363 (84.6)
1	1802 (8.9)	1290 (7.8)	1661 (10.0)	22023 (9.7)
2 or more	1047 (5.2)	886 (5.4)	1063 (6.4)	13003 (5.7)
Number of general practitioner outpatient visits in 12 months before index date, n (%)				
0	10575 (52.3)	8181 (49.5)	9885 (59.4)	131183 (57.7)
1	1607 (7.9)	1697 (10.3)	1153 (6.9)	22156 (9.7)
2 or more	8036 (39.7)	6637 (40.2)	5610 (33.7)	74050 (32.6)
Socioeconomic characteristics				
Standardized household annual income, quartile***				
First quartile	3876 (19.2)	3050 (18.5)	3386 (20.3)	53518-53521
Second quartile	4134 (20.4)	3194 (19.3)	3538 (21.3)	53511 (23.5)
Third quartile	5251 (26.0)	4296 (26.0)	4317 (25.9)	53995 (23.7)
Fourth quartile	6270 (31.0)	5387 (32.6)	5236 (31.5)	51035 (22.4)
Missing	687 (3.4)	588 (3.6)	171 (1.0)	15327-15330
Highest education achieved at index date, n (%)				
Secondary compulsory	3418 (16.9)	2686-2689	2753-2756	58321 (25.6)
Vocational/high school	5637 (27.9)	4316 (26.1)	5213 (31.3)	62467 (27.5)
Higher education	9434 (46.7)	7963 (48.2)	7911 (47.5)	71255 (31.3)
Missing	1729 (8.6)	1547-1550	768-771	35346 (15.5)

CGRP: calcitonin-gene related peptide; COVID-19: coronavirus disease 2019; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; IQR: interquartile range; NSAID: nonsteroidal antiinflammatory drug; SD: standard deviation.
*Not mutually exclusive; agents listed in this category are restricted to those that may be used for migraine. Use varies by country.
**Emergency/acute/unplanned visits that result into a hospitalization with an overnight stay (without patient leaving the hospital) are counted in hospitalization category only.
***In Denmark, Finland and Sweden, individual income is used instead of household income.
Ranges reported for the purposes of masking to avoid re-computation of counts below 5 from complementary data.
Other prophylactic treatment are listed in Table 10-5.
Source: Appendix 2 Table 5 and Table 7

Country-specific migraine-related characteristics by treatment cohort are shown in Appendix 2, Denmark Table 2, Finland Table 2, Norway Table 2, Sweden Table 2. Country-specific characteristics by treatment cohort are shown in Appendix 2, Denmark Table 3, Finland Table 3, Norway Table 3, Sweden Table 3.

Appendix 2, Table 6 and Table 10-5 show the distribution of the prophylactic migraine medications dispensed on the index date in the OPM cohort. In Denmark, the most common

agents were metoprolol (30.5%), candesartan (26.4%), amitriptyline (18.5%) and propranolol (14.2%). In Finland, the most common agents were amitriptyline (23.3%), candesartan (22.3%), and propranolol (22.5%). In Norway, the most common agents were amitriptyline (29.4%), candesartan (26.5%), and metoprolol (26.0%). In Sweden, the most common agents were amitriptyline (34.5 %), metoprolol (24.1%), candesartan (18.7%) and propranolol (16.2%).

Table 10-5 Prophylactic migraine medication dispensed on index date in the Other prophylactic migraine medications treatment cohort in Denmark, Finland, Norway, and Sweden

	Combined	Denmark	Finland	Norway	Sweden
N (size of the country-specific and overall Other prophylactic migraine medication treatment cohort)	227389	32385	88149	66001	40854
Prophylactic migraine medication dispensed on index date, n (%)					
Amitriptyline	59973 (26.4)	6000 (18.5)	20511 (23.3)	19378 (29.4)	14084 (34.5)
Atenolol	144 (0.1)	Not applicable	144 (0.2)	Not applicable	Not applicable
Bisoprolol	12060 (5.3)	Not applicable	12060 (13.7)	Not applicable	Not applicable
Candesartan	53379 (23.5)	8558 (26.4)	19697 (22.3)	17495 (26.5)	7629 (18.7)
Clonidine	1167 (0.5)	Not applicable	Not applicable	1167 (1.8)	Not applicable
Flunarizine	175-178	142 (0.4)	N<5	2 (0.0)	30 (0.1)
Lisinopril	1195 (0.5)	540 (1.7)	99 (0.1)	556 (0.8)	Not applicable
Metoprolol	39870 (17.5)	9872 (30.5)	2996 (3.4)	17152 (26.0)	9850 (24.1)
Nortriptyline	5159 (2.3)	Not applicable	5159 (5.9)	Not applicable	Not applicable
Pizotifen	121-124	37 (0.1)	N<5	8 (0.0)	75 (0.2)
Propranolol	34962 (15.4)	4602 (14.2)	19795 (22.5)	3957 (6.0)	6608 (16.2)
Riboflavin	25 (0.0)	Not applicable	6 (0.0)	19 (0.0)	Not applicable
Topiramate	8059 (3.5)	2092 (6.5)	1323 (1.5)	2514 (3.8)	2130 (5.2)
Valproate	2464 (1.1)	542 (1.7)	866 (1.0)	608 (0.9)	448 (1.1)
Venlafaxine	8634 (3.8)	Not applicable	5489 (6.2)	3145 (4.8)	Not applicable

Ranges reported for the purposes of masking to avoid re-computation of counts below 5 from complementary data

10.3.3 Results addressing exploratory objective 1: event rates

This report provides crude rates of the pre-specified endpoints descriptively. This DUS was not designed for a formal comparative analysis.

10.3.3.1 Hypertension

Table 10-6 shows rates of hypertension by treatment cohort in Denmark, Finland, Norway, and Sweden. Planned stratifications, whenever possible to perform are listed in the source output, Appendix 2, Table 8). The rates differed by sex, age, and CV history. In the pooled analyses overall the rate per 1000 person-years for ERE was 130 (95% CI 112-151), for OCG 161 (95% CI 131-197), for BOT 259 (95% CI 134-498) and for OPM 454 (95% CI 422-487).

Table 10-6 Rates of hypertension by treatment cohort, age and sex, combined across Denmark, Finland, Norway, and Sweden

	ERE	OCG	BOT	OPM
N of patients	20218	16515	16648	227388
Events	2621	2145	1703	42089
Person-years	20815	14281	8031	94334
Rate per 1000 PY (95% CI)	130 (112 - 151)	161 (131 - 197)	259 (134 - 498)	454 (422 - 487)
I^2 (95% CI)	94 (87 - 97)	96 (92 - 98)	100 (100 - 100)	99 (98 - 99)
		Men		
N of patients	3089	2341	2291	42757
Events	518	426	372	10550
Person-years	2982	1871	836	16834
Rate per 1000 PY (95% CI)	179 (151 - 211)	233 (173 - 315)	508 (232 - 1115)	632 (602 - 664)
I^2 (95% CI)	73 (25 - 90)	91 (79 - 96)	98 (97 - 99)	87 (67 - 94)
		Women		
N of patients	17129	14174	14357	184631
Events	2103	1719	1331	31539
Person-years	17834	12409	7194	77500
Rate per 1000 PY (95% CI)	122 (106 - 140)	149 (123 - 180)	223 (116 - 427)	414 (385 - 445)
I^2 (95% CI)	91 (79 - 96)	93 (86 - 97)	100 (99 - 100)	98 (97 - 99)
		Age 18-<30 years		
N of patients	##	##	2987	39459
Events	##	##	68	1250
Person-years	##	##	1663	17795
Rate per 1000 PY (95% CI)	##	##	55 (27 - 114)	69 (52 - 91)
I^2 (95% CI)	##	##	87 (70 - 95)	93 (84 - 97)
		Age 30-<40 years		
N of patients	##	##	##	46070
Events	##	##	##	3403
Person-years	##	##	##	20912

Rate per 1000 PY (95% CI)	##	##	##	154 (133 - 179)
I^2 (95% CI)	##	##	##	91 (79 - 96)
		Age 40-<50 years		
N of patients	6153	5006	##	55032
Events	771	616	##	8324
Person-years	6584	4515	##	24307
Rate per 1000 PY (95% CI)	118 (105 - 132)	140 (117 - 168)	##	330 (280 - 389)
I^2 (95% CI)	59 (0 - 86)	80 (48 - 92)	##	98 (96 - 99)
		Age 50-<60 years		
N of patients	4485	3656	3133	46806
Events	860	719	502	12063
Person-years	4912	3206	1304	18543
Rate per 1000 PY (95% CI)	182 (158 - 211)	232 (195 - 276)	433 (255 - 735)	640 (563 - 727)
I^2 (95% CI)	73 (25 - 90)	82 (53 - 93)	98 (97 - 99)	98 (96 - 99)
		Age >=60 years		
N of patients	2078	1615	1613	40021
Events	613	465	514	17049
Person-years	1998	1244	495	12778
Rate per 1000 PY (95% CI)	309 (278 - 343)	374 (342 - 410)	1212 (551 - 2665)	1349 (1184 - 1536)
I^2 (95% CI)	40 (0 - 80)	0 (0 - 85)	98 (97 - 99)	99 (98 - 99)
		Without CV history		
N of patients	13449	10917	11311	147689
Events	491	367	147	5746
Person-years	15064	10272	6053	68691
Rate per 1000 PY (95% CI)	33 (29 - 37)	36 (29 - 45)	35 (20 - 61)	81 (70 - 93)
I^2 (95% CI)	40 (0 - 79)	75 (30 - 91)	90 (78 - 96)	94 (88 - 97)
		With CV history		
N of patients	6769	5598	5337	79699
Events	2130	1778	1556	36343
Person-years	5751	4008	1977	25643
Rate per 1000 PY (95% CI)	386 (326 - 458)	472 (393 - 567)	828 (476 - 1441)	1418 (1237 - 1627)
I^2 (95% CI)	91 (81 - 96)	91 (81 - 96)	99 (99 - 100)	99 (99 - 100)

CI confidence interval; CV cardiovascular: PY person-years.## Combined rates not displayed because of masking, See Source Appendix 2, Table 8 for country-specific rates

10.3.3.2 Cardiovascular events and conditions other than hypertension

Rates of cardiovascular events and conditions other than hypertension were low in all countries and all treatment cohorts. Rates were zero for most events in the ERE, OCG, BOT and OPM cohorts. Most events were observed in the largest – OPM – cohort. Combined rates were not estimated for events other than hypertension. Country-specific rates by treatment cohort are presented in Appendix 2, Table 9 for hospitalization for acute myocardial infarction; Table 10 for coronary artery revascularization by CABG or PCI; Table 11 for ischemic stroke; Table 12 for hemorrhagic stroke, Table 13 for TIA, Table 14 for CV death; Table 15 for MACE. Cumulative incidences of the respective endpoints are shown in Appendix 2, Table 16 through Table 23.

10.3.4 Results addressing exploratory objective 2: use of erenumab and other prophylactic migraine medication in pregnancy

10.3.4.1 Participants in Pregnancy Population

Table 10-7 shows the inclusion of patients to the Pregnancy Population according to the eligibility criteria (Appendix 2, Denmark Listing 2, Finland Listing 2, Norway Listing 2 and Sweden Listing 2). In Denmark, among 13,633 pregnancies among women with migraine, fewer than 5 pregnancies were exposed to erenumab, and the counts are therefore not reported in accordance with data protection rules. Pregnancy analyses in Denmark were not conducted due to a low observation count in the erenumab cohort. After applying the eligibility criteria, the Pregnancy Population included 16,469 pregnancies in Finland, 22,517 pregnancies in Norway, and 6,236 pregnancies in Sweden among women with migraine. Number of live born infants born of these women were 16,657 in Finland, 22,229 in Norway, and 6,359 in Sweden.

Table 10-7 Attrition table for the Pregnancy Population

Characteristic	Denmark	Finland	Norway	Sweden
Pregnancies ending in delivery of a liveborn or stillborn infant between 08 September 2018 and 30 September 2022 by women with migraine*	13633	16469	22517	6236
Exclusion: missing gestational age	11 (0.1%)	0 (0.0%)	24 (0.1%)	0 (0.0%)
Included pregnancies among women with migraine	13622 (99.9%)	16469 (100.0%)	22493 (99.9%)	6236 (100.0%)
Liveborn infants born of women with migraine	Not reported**	16657	22229	6359

*In Norway, the pregnancy population includes pregnancies ending in abortions from week 12 and onwards, livebirth or stillbirth

**Linkage to offspring not carried out <5 pregnancies were exposed to erenumab

Appendix 2, Figure 5 shows the distribution of trimester of dispensing of erenumab in the pregnancy population.

10.3.4.2 Descriptive data of Pregnancy Population

Appendix 2, Table 24 shows characteristics of the Pregnancy population according to migraine treatment category and Appendix 2, Finland Table 4, Norway Table 4 and Sweden Table 4 show country-specific distributions of the characteristics of the Pregnancy Population according to migraine treatment category.

Table 10-8 shows characteristics of the pregnancy population combined across the countries. Most of the pregnancies in all treatment categories were between age 20 and 35 years. Prevalences of most comorbidities were low and did not differ substantially across the treatment categories. Pregnancies with erenumab exposure had a slightly higher overall comorbidity burden as measured by the Charlson Comorbidity Index score than all treatment categories except OPM. Prevalence of use of different prophylactic or acute antimigraine agents in 12 months before LMP was generally higher in the prophylactic agents treatment groups.

Table 10-8 Characteristics of the Pregnancy Population: pregnancies ending in a live or a stillbirth by treatment category based on use 90 day preconception or any time during pregnancy in Finland, Norway, and Sweden

	Treatment category					
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**	**Acute migraine treatment only**	**Untreated migraine**
	N=208	**N=82**	**N=653**	**N=5372**	**N=13246**	**N=25637**
Country, n (%)						
Finland	44 (21.2)	14 (17.1)	36 (5.5)	2801 (52.1)	3485 (26.3)	10089 (39.4)
Norway	98 (47.1)	52 (63.4)	369 (56.5)	1340 (24.9)	7899 (59.6)	12735 (49.7)
Sweden	66 (31.7)	16 (19.5)	248 (38.0)	1231 (22.9)	1862 (14.1)	2813 (11.0)
Calendar year of delivery, n (%)						
2018	0	0	37-40	305 (5.7)	794 (6.0)	1564 (6.1)
2019	2 (1.0)	0	136 (20.8)	1061 (19.8)	3034 (22.9)	5605 (21.9)
2020	45 (21.6)	2 (2.4)	160 (24.5)	1315 (24.5)	3162 (23.9)	6065 (23.7)
2021	96 (46.2)	36 (43.9)	158 (24.2)	1470 (27.4)	3626 (27.4)	7016 (27.4)
2022	65 (31.3)	44 (53.7)	159-162	1221 (22.7)	2630 (19.9)	5387 (21.0)
Age at LMP, years, n (%)						
<20	0	0	2 (0.3)	118 (2.2)	175 (1.3)	485 (1.9)
20-35	160 (76.9)	69-72	496 (76.0)	4263 (79.4)	10637 (80.3)	21347 (83.3)
>35	48 (23.1)	10-13	155 (23.7)	991 (18.4)	2434 (18.4)	3805 (14.8)
Age at LMP, years, mean (SD)	31.6 (4.8)	30.1 (5.0)	31.5 (4.7)	30.4 (5.3)	30.4 (5.0)	29.8 (4.9)
Parity, n (%)						

	Treatment category					
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**	**Acute migraine treatment only**	**Untreated migraine**
	N=208	**N=82**	**N=653**	**N=5372**	**N=13246**	**N=25637**
0	109 (52.4)	54 (65.9)	334-337	2454 (45.7)	5783 (43.7)	10571 (41.2)
1	55 (26.4)	14-17	210 (32.2)	1572 (29.3)	4568 (34.5)	9618 (37.5)
>1	44 (21.2)	12-15	106-109	1346 (25.1)	2895 (21.9)	5448 (21.3)
Missing	0	0	0	0	0	0
Smoking during pregnancy, n (%)						
Yes	7-10	2-5	5 (0.8)	492 (9.2)	654 (4.9)	1369 (5.3)
No	187 (89.9)	71 (86.6)	597-600	4529 (84.3)	11504 (86.8)	22374 (87.3)
Missing	12-15	6-9	48-51	351 (6.5)	1088 (8.2)	1894 (7.4)
Body mass index, kg/m2, n (%)						
<18.5	8 (3.8)	5 (6.1)	16-19	87 (1.6)	309 (2.3)	653 (2.5)
18.5-<25.0	102 (49.0)	40 (48.8)	321 (49.2)	2236 (41.6)	6153 (46.5)	12597 (49.1)
25.0-<30.0	62 (29.8)	18-21	158 (24.2)	1417 (26.4)	3403 (25.7)	6423 (25.1)
>=30.0	33 (15.9)	10-13	96 (14.7)	1405 (26.2)	2675 (20.2)	4640 (18.1)
Missing	3 (1.4)	5 (6.1)	60-63	227 (4.2)	706 (5.3)	1324 (5.2)
Cardiovascular comorbidity any time before LMP, n (%)						
Hypertension, any	40 (19.2)	16-19	107 (16.4)	940 (17.5)	1272 (9.6)	2014 (7.9)
Hypertension, mild	40 (19.2)	16-19	98 (15.0)	771 (14.4)	1146 (8.7)	1790 (7.0)
Hypertension, moderate	0	0	8 (1.2)	152 (2.8)	112 (0.8)	188 (0.7)
Hypertension, severe	0	0	1 (0.2)	17 (0.3)	13-16	36 (0.1)
Unstable angina	0	0	0	1-4	1-4	1-4
Myocardial infarction	0	0	0	1 (0.0)	4-7	2 (0.0)
Coronary revascularization via CABG or PCI	0	0	0	0	1 (0.0)	0
Ischemic stroke	1-4	0	1 (0.2)	17 (0.3)	14-17	70 (0.3)

	Treatment category					
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**	**Acute migraine treatment only**	**Untreated migraine**
	N=208	**N=82**	**N=653**	**N=5372**	**N=13246**	**N=25637**
Hemorrhagic stroke	0	0	1 (0.2)	3-6	7-10	27 (0.1)
Transient ischemic attack	0	0	1 (0.2)	17 (0.3)	10-13	67 (0.3)
Comorbidity associated with CV risk any time before LMP, n (%)						
Diabetes	15 (7.2)	6 (7.3)	26-29	357 (6.6)	667 (5.0)	1161 (4.5)
Hypercholesterolemia	3 (1.4)	1 (1.2)	17 (2.6)	129 (2.4)	222 (1.7)	372 (1.5)
Obesity	9-12	5 (6.1)	44 (6.7)	473 (8.8)	1045 (7.9)	1564 (6.1)
COPD and asthma	45 (21.6)	22-25	137-140	959 (17.9)	2910 (22.0)	4744 (18.5)
Kidney disease	6-9	2-5	20 (3.1)	305 (5.7)	474 (3.6)	1025 (4.0)
Alcohol-related diseases	5 (2.4)	5-8	19-22	262 (4.9)	404 (3.0)	803 (3.1)
Inflammatory bowel disease	3 (1.4)	1 (1.2)	10 (1.5)	115 (2.1)	288 (2.2)	411 (1.6)
Rheumatic diseases	15 (7.2)	3-6	36 (5.5)	303 (5.6)	583 (4.4)	886 (3.5)
Psoriasis	1-4	2 (2.4)	14 (2.1)	100 (1.9)	258 (1.9)	459 (1.8)
Other somatic or psychiatric comorbidity any time before LMP, n (%)						
Headaches	73 (35.1)	26-29	239 (36.6)	1080 (20.1)	1433 (10.8)	2925 (11.4)
Cluster headache	5-8	4 (4.9)	13 (2.0)	73 (1.4)	154 (1.2)	226 (0.9)
Vascular headache, not elsewhere classified	5-8	2 (2.4)	9 (1.4)	20 (0.4)	34 (0.3)	60 (0.2)
Tension-type headache	64 (30.8)	16-19	211 (32.3)	966 (18.0)	1216 (9.2)	2600 (10.1)
Chronic pain	14-17	8 (9.8)	57-60	232 (4.3)	364 (2.7)	373 (1.5)
Sleep disorders	17 (8.2)	2-5	32-35	530 (9.9)	649 (4.9)	1315 (5.1)

	Treatment category					
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**	**Acute migraine treatment only**	**Untreated migraine**
	N=208	**N=82**	**N=653**	**N=5372**	**N=13246**	**N=25637**
Charlson Comorbidity Index score at LMP, n (%)						
No comorbidity	173 (83.2)	66-69	556 (85.1)	4240 (78.9)	11376 (85.9)	22038 (86.0)
Low comorbidity	23 (11.1)	9-12	70 (10.7)	805 (15.0)	1405 (10.6)	2680 (10.5)
High comorbidity	12 (5.8)	4 (4.9)	27 (4.1)	327 (6.1)	465 (3.5)	919 (3.6)
Use of prophylactic migraine medication from preconception to delivery, n (%)*						
Antiepileptics	12-15	5-8	16-19	178 (3.3)	0	0
Antihypertensives, beta-blockers	34 (16.3)	8 (9.8)	74 (11.3)	3151 (58.7)	0	0
Antihypertensives, calcium channel blockers	0	0	0	1 (0.0)	0	0
Antihypertensives, other	2-5	3-6	8-11	450 (8.4)	0	0
Antidepressants, tricyclics	28 (13.5)	7-10	76 (11.6)	1596 (29.7)	0	0
Antidepressants, serotonin norepinephrine reuptake inhibitors	1-4	2 (2.4)	5-8	379 (7.1)	0	0
Other prophylactic migraine medications	29 (13.9)	28 (34.1)	407 (62.3)	13 (0.2)	0	0
CGRP antagonists	207 (99.5)	82 (100.0)	0	0	0	0

	Treatment category					
	Erenumab N=208	**Other CGRP antagonists** N=82	**Botulinum toxin** N=653	**Other prophylactic migraine medications** N=5372	**Acute migraine treatment only** N=13246	**Untreated migraine** N=25637
Use of acute migraine medication from preconception to delivery, n (%)						
Ergotamines	0	0	0	0	1 (0.0)	0
Triptans	160 (76.9)	62 (75.6)	384 (58.8)	2647 (49.3)	10166 (76.7)	0
Analgesics, NSAIDs	73 (35.1)	24 (29.3)	150 (23.0)	1784 (33.2)	4292 (32.4)	2172 (8.5)
Analgesics, non-NSAID non-opioid	79 (38.0)	31 (37.8)	201 (30.8)	2093 (39.0)	4379 (33.1)	2974 (11.6)
Number of previous different acute antimigraine agents 12 months before LMP, n (%)						
0	17 (8.2)	5 (6.1)	114 (17.5)	1290 (24.0)	1472 (11.1)	16738 (65.3)
1	54 (26.0)	17 (20.7)	172-175	1600 (29.8)	5717 (43.2)	5873 (22.9)
2 or more	137 (65.9)	60 (73.2)	364-367	2482 (46.2)	6057 (45.7)	3026 (11.8)
Number of previous different prophylactic antimigraine agents 12 months before LMP, n (%)						
0	3 (1.4)	0	170 (26.0)	419 (7.8)	12274 (92.7)	24758 (96.6)
1	81 (38.9)	20-23	277 (42.4)	4079 (75.9)	851 (6.4)	783 (3.1)
2 or more	124 (59.6)	59-62	206 (31.5)	874 (16.3)	121 (0.9)	96 (0.4)

	Treatment category					
	Erenumab N=208	**Other CGRP antagonists** N=82	**Botulinum toxin** N=653	**Other prophylactic migraine medications** N=5372	**Acute migraine treatment only** N=13246	**Untreated migraine** N=25637
Use of prescription medication that may affect CV risk, other than migraine medication from preconception to delivery, n (%)						
Oral contraceptives	19-22	6-9	42 (6.4)	452 (8.4)	1113 (8.4)	1585 (6.2)
Lipid modifying agents	1-4	0	2 (0.3)	41 (0.8)	43 (0.3)	53 (0.2)
Antiemetics	12-15	5-8	42-45	194 (3.6)	438 (3.3)	457 (1.8)
Antithrombotics	25-28	9 (11.0)	79 (12.1)	586 (10.9)	1089 (8.2)	1767 (6.9)
Antihypertensives (except used for migraine)	8-11	6-9	33-36	581 (10.8)	552 (4.2)	829 (3.2)
Antidiabetics	12-15	6-9	29-32	548 (10.2)	827 (6.2)	1510 (5.9)
Antirheumatics	31 (14.9)	13 (15.9)	85 (13.0)	341 (6.3)	2550 (19.3)	52-55
Antidepressants (except used for migraine)	26 (12.5)	5-8	92-95	1015 (18.9)	1112 (8.4)	1559 (6.1)
Antiepileptics (except used for migraine)	6 (2.9)	1-4	15-18	257 (4.8)	220 (1.7)	355 (1.4)
Antipsychotics	12 (5.8)	4-7	38 (5.8)	384 (7.1)	464 (3.5)	613 (2.4)
Hypnotics and sedatives	16-19	12-15	96-99	620 (11.5)	881 (6.7)	826 (3.2)
Anxiolytics	19 (9.1)	6-9	57 (8.7)	674 (12.5)	699 (5.3)	885 (3.5)
Medication used in substance abuse	1 (0.5)	0	5 (0.8)	33 (0.6)	41 (0.3)	44 (0.2)
Pain medications (except used for migraine)	88 (42.3)	41 (50.0)	224 (34.3)	2577 (48.0)	4183 (31.6)	5119 (20.0)
NSAIDs	31 (14.9)	13 (15.9)	32 (4.9)	1311 (24.4)	1402 (10.6)	2382 (9.3)
Opioids	64 (30.8)	25-28	194 (29.7)	1173 (21.8)	2587 (19.5)	1895 (7.4)

	Treatment category					
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**	**Acute migraine treatment only**	**Untreated migraine**
	N=208	**N=82**	**N=653**	**N=5372**	**N=13246**	**N=25637**
Use of a known teratogen from 90 days preconception and in the first trimester	5-8	2-5	9-12	210 (3.9)	166 (1.3)	319 (1.2)
COVID-19 related characteristics any time before LMP, n (%)						
COVID-19 related diagnoses	26 (12.5)	21-24	70-73	451 (8.4)	1572 (11.9)	2639 (10.3)
Reproductive history						
Hypertensive disorders of pregnancy	2-5	2 (2.4)	9-12	400 (7.4)	369 (2.8)	910 (3.5)
Cesarean	10-13	4 (4.9)	33-36	523 (9.7)	809 (6.1)	1876 (7.3)
Stillbirth	0	0	3 (0.5)	35 (0.7)	65 (0.5)	127 (0.5)
Spontaneous abortion	38 (18.3)	6 (7.3)	144 (22.1)	1249 (23.3)	3175 (24.0)	6040 (23.6)
Induced abortion	12 (5.8)	4-7	25 (3.8)	549 (10.2)	656 (5.0)	1894 (7.4)

In Norway, the pregnancy population includes pregnancies ending in abortions from week 12 and onwards, livebirth or stillbirth.
CGRP: calcitonin-gene related peptide; COVID-19: coronavirus disease 2019; COPD: chronic obstructive pulmonary disease; NSAID: nonsteroidal antiinflammatory drug.
*Not mutually exclusive; agents listed in this category are restricted to those that may be used for migraine. Use varies by country
Ranges reported for the purposes of masking to avoid re-computation of counts below 5 from complementary data.
Prophylactic medications considered in this definition are listed in Table 9-1.

10.3.4.3 Pregnancy complications by migraine treatment category

Appendix 2, Table 25 and Table 10-9 show pregnancy complications by migraine treatment category. In the population combined across three countries, prevalences of pregnancy complications were similar across the treatment categories.

Table 10-9 Pregnancy complications by migraine treatment category based on use 90 day preconception or any time during pregnancy in Finland, Norway, and Sweden

	Erenumab N=208	Other CGRP antagonists N=82	Botulinum toxin N=653	Other prophylactic migraine medications N=5372	Acute migraine treatment only N=13246	Untreated migraine N=25637
Hypertensive disorders of pregnancy, n (%)						
Any	14 (6.7)	4-7	51-54	600 (11.2)	1001 (7.6)	1655 (6.5)
Gestational hypertension	4 (1.9)	1 (1.2)	21 (3.2)	345 (6.4)	535 (4.0)	876 (3.4)
Preeclampsia	9 (4.3)	3-6	22-25	244 (4.5)	427 (3.2)	753 (2.9)
Eclampsia	0	0	0	2-5	3-6	5-8
Preeclampsia with superimposed hypertension	1 (0.5)	0	8 (1.2)	46-49	60-63	89-92
Placenta previa, n (%)	1 (0.5)	1 (1.2)	3 (0.5)	40 (0.7)	73 (0.6)	140 (0.5)
Placental abruption, n (%)	1 (0.5)	1 (1.2)	2 (0.3)	27 (0.5)	45 (0.3)	80 (0.3)
Gestational diabetes, n (%)	13 (6.3)	2-5	21 (3.2)	728 (13.6)	767 (5.8)	2007 (7.8)
Cesarean delivery, n (%)	49 (23.6)	18-21	158 (24.2)	1427 (26.6)	2781 (21.0)	4859 (19.0)
Stillbirth, n (%)	0	0	3 (0.5)	18 (0.3)	65 (0.5)	87 (0.3)

Source: Appendix 2, Table 25

Appendix 2, Finland Table 5, Norway Table 5 and Sweden Table 5 show country-specific distributions of pregnancy complications by migraine treatment category.

10.3.4.4 Birth outcomes

Appendix 2, Table 26 and Table 10-10 show birth outcomes by maternal migraine treatment category in the pregnancy population combined across the three countries. Prevalences were similar across the treatment categories.

Table 10-10 Birth outcomes among liveborn newborns by maternal migraine treatment category based on use 90 day preconception or any time during pregnancy in Finland, Norway, and Sweden

	Treatment category					
	Erenumab	Other CGRP antagonists	Botulinum toxin	Other prophylactic migraine medications	Acute migraine treatment only	Untreated migraine
Liveborn newborns	N=209	N=82	N=655	N=5410	N=13226	N=25663
Multifetal gestation, n (%)	4 (1.9)	0	22-25	161 (3.0)	312 (2.4)	557 (2.2)

	Treatment category					
	Erenumab	**Other CGRP antagonists**	**Botulinum toxin**	**Other prophylactic migraine medications**	**Acute migraine treatment only**	**Untreated migraine**
Birth weight in grams, mean (SD)	3499.4 (564.6)	3401.0 (528.7)	3446.5 (600.7)	3406.7 (605.4)	3489.7 (575.8)	3515.6 (567.5)
Low birth weight (<2500 g), n (%)	16-19	8-11	50-53	390 (7.2)	920 (7.0)	1541 (6.0)
Gestational age in weeks, mean (SD)	39.2 (1.6)	39.0 (1.7)	38.9 (2.0)	39.0 (2.1)	39.2 (1.9)	39.3 (1.9)
Preterm birth (<37 weeks), n (%)	11 (5.3)	3 (3.7)	49-52	426 (7.9)	725 (5.5)	1346 (5.2)
Small for gestational age, n (%)	12 (5.7)	5-8	35 (5.3)	516 (9.5)	882 (6.7)	1729 (6.7)

CGRP: calcitonin-gene related peptide; SD: standard deviation.

Source: Appendix 2, Table 26

Appendix 2, Finland Table 6, Norway Table 6 and Sweden Table 6 show country-specific distributions of birth outcomes by maternal migraine treatment category

Despite similarity of settings across countries, the heterogeneity of the results was high, based on the values of the I-squared statistics.

10.4 Other analyses

The results of the sensitivity analyses were largely in line with the results concerning primary, secondary, and exploratory endpoints. The full list of other analyses is presented in Section 9.4.4 of this report and the available results are presented in Appendix 2:

- Re-computing erenumab persistence extending the grace periods to 60 days. This analysis showed overall similar results to the main analysis albeit persistence was slightly greater in the sensitivity analysis than in the main analysis, in particular in Sweden. (Appendix 2, Figure 6)
- Re-computing rates of the CV endpoints (exploratory objectives) extending the grace periods to 60 days (Appendix 2, Table 29). This analysis showed overall similar results to the main analysis except for rates of hypertension in the OPM cohorts which appeared somewhat lower in the sensitivity analysis than in the main analysis.
- Re-computing rates of the CV endpoints (exploratory objectives) over total follow-up (censoring by death or emigration but not at discontinuation or switch of the prophylactic migraine medication initiated at index date) (Appendix 2, Table 30). Overall rates of CV endpoints were similar to the main analysis, albeit rates of hypertension appeared slightly lower in the sensitivity analysis than in the main analysis.
- Assessing selected baseline characteristics and rates of the CV endpoints in the treatment cohorts in the Main Analysis Population, restricting the population to patients with either a dispensing of a CGRP antagonist or with a hospital diagnosis of migraine before or at the index date, to capture most erenumab eligible population (Appendix 2, Denmark Tables 7-

8, Finland Tables 7-8, Norway Tables 7-8, Sweden Tables 7-8, and Tables 27, 28 and 31). This sensitivity analysis reduced the size of the OPM cohorts in all four countries, but distributions of patient characteristics were similar to that of the main analysis. CV rates were also similar to the main analysis except rates of hypertension which were lower in Denmark and Norway in the sensitivity analysis than in the main analysis.

- Re-computing the overall rates of the CV endpoints stratified by calendar periods within the patient identification period, defined important landmarks of the COVID-19 pandemic that were assumed to affect patterns of healthcare utilization (Appendix 2, Tables 32-34). Rates of CV endpoints were generally similar in the three periods to those of the main analysis, except for rates of hypertension in Sweden which appeared greater in the three periods for the ERE, OCG, and OPM cohort. Per data protection rules, sensitivity analyses are only reported for Denmark when sufficient number of patients were observed.

10.5 Adverse events/adverse reactions

This postauthorization study, based on secondary data, is a population-based cohort study based on routinely and prospectively collected data and therefore it is not feasible to make a causality assessment at the individual case level. No safety data beyond the planned analyses in this study were collected.

11 Discussion

11.1 Key results

Between 08-Aug-2018 and 30-Sep-2022, there were 20,218 initiators of erenumab: 1,835 in Denmark, 4,949 in Finland, 8,276 in Norway, and 5,158 in Sweden. Erenumab was nearly exclusively prescribed in the secondary care (data on sector available in Denmark and Sweden), and primarily by neurologists. Overall, 17,129 (84.7%) of the erenumab initiators were women and median age at erenumab initiation was 43.7 years. Across all countries, 13,624 (67.4%) persons initiated erenumab as monotherapy, and type of initiation varied by country. Among the 20,218 erenumab initiators, 6,769 had a history of cardiovascular disease. Overall, 14,328 (70.9%) had a history of use of 2 or more acute antimigraine agents and 8,987 (44.5%) had a history of use of 2 or more prophylactic migraine agents in the 12 months before initiation. At three years post-initiation (timepoint available for all countries), persistence with erenumab varied from 10.4% in Sweden to 23.0% in Norway, and switching among the CGRP antagonist treatment was common in all countries.

Across the four countries, 16,515 patients entered the CGRP antagonists treatment cohort, 16,648 botulinum toxin treatment cohort, and 227,389 other prophylactic migraine medications treatment cohort. The erenumab and other CGRP antagonist treatment cohort and the botulinum toxin treatment cohort had a greater prevalence of history of use of more than 2 different acute and prophylactic migraine agents in preceding 12 months than patients in the other prophylactic migraine medication cohort, which was as expected given the reimbursement and treatment guidelines requiring patients to have tried at least 2 prophylactic migraine agents before initiating a CGRP antagonist. These fundings suggest that clinicians are adhering to the guidelines. About one-third of patients in all treatment cohorts had a history of hypertension, but a history of severe hypertension was higher in the other prophylactic migraine medications

cohort than in the other treatment cohorts. Prevalence of other comorbidities was generally low. The measured demographic, clinical, socioeconomic and clinical characteristics were similar in the initiators of erenumab, other CGRP antagonists and of botulinum toxin, and collectively differed from initiators of other prophylactic migraine medications. Characteristics of the treatment cohorts indicated that other prophylactic migraine medications treatment cohort may not be an optimal comparator cohort for evaluating safety of erenumab. In addition to other CGRP antagonists, the botulinum toxin cohort should be considered, possibly with more specific identification criteria to ensure inclusion of the appropriate indicated population.

During the follow-up, the crude rates per 1000 person-years of hypertension regardless of previous history of hypertension in the treatment cohorts were 130 for erenumab cohort, 161 in the other CGRP antagonists cohort, 259 in botulinum toxin cohort, and 454 in the other prophylactic migraine medication treatment cohort. The rates varied by sex, age and CV history, however, by design, no comparative analysis of the rates was undertaken. The rates of the remaining CV endpoints (hospitalization for acute myocardial infarction, artery revascularization by CABG or PCI, hospitalization for ischemic stroke, hospitalization for hemorrhagic stroke, and hospitalization for transient ischemic attack, CV death and MACE) were zero or close to zero among erenumab initiators, with low number of events.

The number of erenumab-exposed pregnancies did not exceed the reportable minimum in Denmark. In the three remaining countries, there were a total 208 pregnancies with a record of erenumab between 90 days preconception and pregnancy end: 44 in Finland, 98 in Norway (including those ending in abortive outcomes from gestational week 12) and 66 in Sweden. Among erenumab-exposed pregnancies, prevalence of any hypertensive disorders of pregnancy was 6.7%, prevalence of gestational diabetes 6.3%, cesarean delivery 23.6%. There were no stillbirths. Among 209 infants with maternal exposure to erenumab between 90-day preconception and delivery, mean gestational age was 39.2 weeks and prevalence of preterm birth was 5.3%. These exploratory analyses were not designed to assess the safety of erenumab during pregnancy but rather to inform the feasibility of potential future studies of reproductive safety.

11.2 Limitations

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

First, indication for medication use was not explicitly recorded in the available data sources, except for Norway, where reimbursement codes were used to identify persons with migraine by requiring migraine as an indication for unspecific acute migraine medications. Therefore, for patients treated with unspecific prophylactic migraine medications, there is inherent uncertainty about whether a given prophylactic medication was given for migraine or another indication. This uncertainty was alleviated by requiring evidence of migraine in the form of a diagnosis or specific treatment to be eligible for inclusion in the study as well as post-hoc further restriction of hospital BOT administrations to departments of neurology (in Denmark), or to those with concurrent primary diagnosis of migraine (Norway and Sweden). Still, 14 out of 147 persons in the Danish BOT cohort had previous diagnoses of other conditions, in addition to migraine,

such as dystonia which are also indications of botulinum toxin. Thus, for these patients, botulinum toxin may have been administered for migraine or other conditions. Even more uncertainty exists in assembling the OPM cohort, whereby while defined among the population with a history of migraine, the indication remains uncertain. Based on this and the OPM cohort characteristics, the OPM cohort may not represent the appropriate erenumab-indicated population comparison for a potential safety study.

Second, in Sweden triptans may be bought over-the-counter, and over the counter sales are not reported into the Swedish Prescribed Drug Register. This could lead to an underestimation of the number of persons with migraine and of use of acute migraine treatments when describing patient characteristics. However, as over-the-counter drugs are not reimbursable, we assume that persons missed are few and likely suffer from milder types of migraine.

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). For instance, persons picking up two pens of 70 mg erenumab on the same day may inject both on the same date or only one and keep the other pen for an injection on a later date. In Denmark, the data on the amount of the erenumab dispensed are not recorded in the Danish National Patient Registry. Duration of erenumab prescription is possibly underestimated in this report, since 35% (Denmark), 24% (Finland), 24% (Norway), and 54% (Sweden) of erenumab discontinuers appeared to have restarted erenumab within 6 months. Alternatively, these proportions of restarters reflect the requirement of breaks in treatment according to local guidelines (nNBV 2021, Käypä hoito 2024). For a period of time, such a requirement was also embedded in the reimbursement rules in Norway. There, erenumab was approved for reimbursement in December 2019 where a peak in erenumab initiation also was observed in our data. In April 2022, the reimbursement rules were updated requiring a break in treatment no later than 18 months after treatment initiation. As of January 2023, this rule was removed leaving the decision of timing of treatment breaks to the treating physician (Helfo 2024).

Fourth, the challenge of separating CV risk from migraine itself from that of the medication was another limitation. Some medications may be selectively prescribed or non-prescribed to migraine patients with CV risk factors, representing a channeling bias. Furthermore, the use of composite MACE outcomes may be suboptimal because of its potential to mask associations between treatment and MACE component endpoints (Ly et al 2023, Lund et al 2024).

Fifth, regarding CV risk factors, data on uncontrolled hypertension were not directly recorded in the respective registries because there were no measurements of blood pressure. Furthermore, diagnoses of hypertension may often be given in primary care and primary care diagnoses were not available in Sweden and Denmark, while use of a treatment proxy may overestimate the occurrence. In Finland, where diagnoses from primary care were available, the definition of hypertension was based on primary (=main) diagnoses to increase specificity and avoid contamination by prevalent events.

Sixth, use of primary diagnosis only to identify migraine patients in Finland (vs both primary and secondary diagnoses in the other countries) may limit comparability of the indicated population across the participating countries, which could be compensated to an extent by application of other criteria.

Finally, because of low event counts, the corresponding estimates of the rates of most CV events and conditions were imprecise, as measured by wide 95% confidence limits. The number of pregnancies exposed to CGRP antagonists were low.

11.3 Interpretation

This DUS based on routinely collected population-based secondary data in four Nordic countries, uptake of erenumab varied by country, with the largest number of users identified in Norway and the smallest in Denmark. A large majority of the erenumab initiators were women. Utilization of erenumab, including persistence, switching and discontinuation varied by country. The much lower percentage of initiations by neurologists in Sweden might reflect both that young doctors doing their rotations during their specialty training could prescribe erenumab under the supervision by neurologists and also, that many neurologists in smaller hospitals in Sweden belong to an internal medicine department with double specializations, listed in registries as internal medicine. The erenumab initiators cohort exhibited demographic, clinical, socioeconomic and other relevant characteristics similar to those of users of other CGRP antagonists and of botulinum toxin; however, there was less overlap in distributions of these factors with users of other prophylactic migraine medications. Owing to the reimbursement guidelines and on-label indications, users of the CGRP antagonists and botulinum toxin represent patients who fulfil the criteria of chronic migraine, while patients using non-specific migraine treatments have a larger proportion of patients with both episodic and chronic migraine. This should be considered when designing a future potential PASS for erenumab. Use of more than one active comparator from different drug classes is recommended, however, for non-specific migraine comparator treatments (such as botulinum toxin), steps should be taken to ensure inclusion of the correct indicated population. When planning a comparative analysis using routinely collected data, validity can be improved by applying the target trial emulation (Hernan et al 2016) and installing explicit safeguards such as the staging and clean room approach could be considered, as proposed in a recent publication by key opinion leaders in pharmacoepidemiology (Muntner et al 2024).

The most frequent CV condition was hypertension, and its rate varied by treatment cohort, age, sex and CV history. No comparative analysis by treatment was undertaken. Whenever information on indication is unavailable, the occurrence of hypertension as measured by treatment proxy alone may be overestimated. There were few events and rates of hospitalization for acute myocardial infarction, artery revascularization by CABG or PCI, hospitalization for ischemic stroke, hospitalization for hemorrhagic stroke, and of hospitalization for transient ischemic attack, CV death, and MACE among erenumab initiators were close to zero. The low rates are expected in a relatively young population of migraine patients.

Few pregnancies were exposed to erenumab or other CGRP antagonists. This is expected because of recent approval of these medications. Furthermore, some women may have stopped taking CGRP antagonists before getting pregnant.

11.4 Generalizability

The results of this study are expected to be generalizable to each participating Nordic country and other countries with similar tax-funded healthcare system and similar distribution of CV risk factors in the population. Utilization patterns differed across countries and may be most

informative to consider separately in each country given differences in guidelines, practices, and reimbursement policies.

12 Other information

None.

13 Conclusion

In nearly 4 years following approval of erenumab in the European Union, the uptake, persistence, and switching of erenumab varied in the four Nordic countries, despite generally similar setup of the underlying data sources and health care systems. Some of the variation may be explainable by country-specific differences in recording, prescribing, and reimbursement practices. As expected, majority of the erenumab initiators were young females, and erenumab was mainly prescribed by neurologists. The most common cardiovascular condition was hypertension. The rates of the other examined cardiovascular events and conditions were low, as expected in a younger population. By design, no formal comparative analysis by treatment was performed. In a potential comparative analysis, use of more than one active comparator, from different drug classes is recommended, and steps should be taken to ensure inclusion of the relevant indicated population. In the exploratory analysis in the pregnancy population, fewer than 5 pregnancies were exposed to erenumab in Denmark. In Finland, Norway and Sweden combined, 208 pregnancies had a record of erenumab dispensing. The results of this study may inform feasibility of potential future studies on overall and reproductive safety of novel migraine treatments. This descriptive study was not designed to assess the benefit-risk balance of erenumab.

14 References

[Adelborg K, Sundboll J, Munch T, et al. (2016)] Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: A population-based validation study. BMJ Open; 6(12):e012817.

[Ashina M (2020)] Migraine. N Engl J Med; 383(19):1866-1876.

[Ashina M, Goadsby PJ, Reuter U, et al. (2021)] Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial. Eur J Neurol; 28(5):1716-1725.

[Ashina M, Tepper S, Brandes J, et al. (2017)] Efficacy of erenumab (amg 334) in chronic migraine patients with prior prophylactic treatment failure: Subgroup analysis of the phase 2, randomised, double-blind, placebo-controlled study. European Journal of Neurology; 24:470-471.

[Bendtsen L, Sacco S, Ashina M, et al. (2018)] Guideline on the use of onabotulinumtoxina in chronic migraine: A consensus statement from the european headache federation. J Headache Pain; 19(1):91.

[Bigal ME, Walter S, Rapoport AM (2015)] Therapeutic antibodies against CGRP or its receptor. Br J Clin Pharmacol; 79(6):886-895.

[Blumenfeld AM, Kaur G, Mahajan A, et al. (2022)] Effectiveness and safety of chronic migraine preventive treatments: A systematic literature review. Pain Ther.

[Bomtempo FF, Rocha RB, Cenci GI, et al. (2023)] Long-term safety and effectiveness of erenumab in patients with migraine: A systematic review and single-arm meta-analysis. Clin Drug Investig; 43(1):45-59.

[Bonifacio GV, de Carvalho SC, Oliveira R, et al. (2022)] Gestational exposure to erenumab-the outcome of three pregnancies. Headache; 62(9):1218-1221.

[Borenstein M, Hedges LV, Higgins JP, et al. (2010)] A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods; 1(2):97-111.

[Campagna EJ, Muser E, Parks J, et al. (2014)] Methodological considerations in estimating adherence and persistence for a long-acting injectable medication. J Manag Care Spec Pharm; 20(7):756-766.

[Cantarelli L, Pestana Grafina D, Gonzalez Perez A, et al. (2023)] Efficacy and safety of erenumab, galcanezumab, and fremanezumab in the treatment of drug-resistant chronic migraine: Experience in real clinical practice. Ann Pharmacother; 57(4):416-424.

[de Hoon J, Van Hecken A, Vandermeulen C, et al. (2019)] Phase 1, randomized, parallel-group, double-blind, placebo-controlled trial to evaluate the effects of erenumab (amg 334) and concomitant sumatriptan on blood pressure in healthy volunteers. Cephalalgia; 39(1):100-110.

[de Hoon J, Van Hecken A, Vandermeulen C, et al. (2018)] Phase I, randomized, double-blind, placebo-controlled, single-dose, and multiple-dose studies of erenumab in healthy subjects and patients with migraine. Clin Pharmacol Ther; 103(5):815-825.

[Dobson AJ, Kuulasmaa K, Eberle E, et al. (1991)] Confidence intervals for weighted sums of poisson parameters. Stat Med; 10(3):457-462.

[Dodick DW, Ashina M, Brandes JL, et al. (2018)] ARISE: A phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia; 38(6):1026-1037.

[Dodick DW, Tepper SJ, Ailani J, et al. (2021)] Risk of hypertension in erenumab-treated patients with migraine: Analyses of clinical trial and postmarketing data. Headache; 61(9):1411-1420.

[Ehrlich M, Hentschke C, Sieder C, et al. (2022)] Erenumab versus topiramate: Post hoc efficacy analysis from the her-mes study. J Headache Pain; 23(1):141.

[Eigenbrodt AK, Ashina H, Khan S, et al. (2021)] Diagnosis and management of migraine in ten steps. Nat Rev Neurol; 17(8):501-514.

EMA (2018) Aimovig https://www.ema.europa.eu/en/medicines/human/EPAR/aimovig. Accessed on 20 January 2025.

EMA (2019a) Ajovy. https://www.ema.europa.eu/en/medicines/human/EPAR/ajovy. Accessed on 29 June 2020.

EMA (2019b) Emgality. https://www.ema.europa.eu/en/medicines/human/EPAR/emgality. Accessed on 29 June 2020.

EMA (2022) Vyepti. https://www.ema.europa.eu/en/medicines/human/EPAR/vyepti. Accessed on 19 March 2024.

[G. B. D. Disease Injury I, Prevalence C (2017)] Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the global burden of disease study 2016. Lancet; 390(10100):1211-1259.

[G. B. D. Neurological Disorders Collaborator Group (2017)] Global, regional, and national burden of neurological disorders during 1990-2015: A systematic analysis for the global burden of disease study 2015. Lancet Neurol; 16(11):877-897.

[Gagne JJ (2017)] New-user designs with conditional propensity scores: A unified complement to the traditional active comparator new-user approach. Pharmacoepidemiol Drug Saf; 26(4):469-471.

[Goadsby PJ, Reuter U, Hallstrom Y, et al. (2017)] A controlled trial of erenumab for episodic migraine. N Engl J Med; 377(22):2123-2132.

[Govatsmark RES, Janszky I, Slordahl SA, et al. (2018)] Completeness and correctness of acute myocardial infarction diagnoses in a medical quality register and an administrative health register. Scand J Public Health:1403494818803256.

[Hammar N, Alfredsson L, Rosen M, et al. (2001)] A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. Int J Epidemiol; 30 Suppl 1:S30-34.

Helfo (2024) Individuell stønad til Aimovig, ajovy, aquipta og emgality. https://www.helfo.no/lege/blaareseptordningen/individuell-stonad-til-aimovig-erenumab. Accessed on 29 November 2024.

[Hernan MA, Robins JM (2016)] Using big data to emulate a target trial when a randomized trial is not available. Am J Epidemiol; 183(8):758-764.

Huvudvarksforbundet (2023) Riktlinje för migrän. https://huvudvarksforbundet.se/riktlinje-for-migran/. Accessed on 20 March 2025.

Käypä hoito (2024) Migreeni. . https://www.kaypahoito.fi/hoi36050?tab=suositus. Accessed on 26 February 2025.

Käypä_hoito (2015) Migraine treatment guidelines (Finland). http://www.kaypahoito.fi/web/kh/suositukset/suositus?id=hoi36050#s12; https://www.terveysportti.fi/xmedia/hoi/hoi36050.pdf. Accessed on 11 January 2019.

[Langhoff-Roos J, Krebs L, Klungsoyr K, et al. (2014)] The Nordic medical birth registers--a potential goldmine for clinical research. Acta Obstet Gynecol Scand; 93(2):132-137.

[Laugesen K, Ludvigsson JF, Schmidt M, et al. (2021)] Nordic health registry-based research: A review of health care systems and key registries. Clin Epidemiol; 13:533-554.

Legemiddelverket (2019) Aimovig (erenumab) til profylaktisk behandling av migrene. https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/A/Aimovig_migrene_2019.pdf. Accessed on 1 September 2019.

[Liang D, Sessa M (2022)] Post-marketing safety surveillance of erenumab: New insight from eudravigilance. Expert Opin Drug Saf; 21(9):1205-1210.

[Lindblad U, Rastam L, Ranstam J, et al. (1993)] Validity of register data on acute myocardial infarction and acute stroke: The skaraborg hypertension project. Scand J Soc Med; 21(1):3-9.

[Linnersjo A, Hammar N, Gustavsson A, et al. (2000)] Recent time trends in acute myocardial infarction in Stockholm, Sweden. Int J Cardiol; 76(1):17-21.

[Lipton RB, Tepper SJ, Reuter U, et al. (2017)] Patient-reported outcomes in patients with chronic migraine receiving placebo or erenumab (amg 334) in a phase 2, randomized, double-blind study. Headache; 57:198-198.

[Luef BM, Andersen LB, Renault KM, et al. (2016)] Validation of hospital discharge diagnoses for hypertensive disorders of pregnancy. Acta Obstet Gynecol Scand; 95(11):1288-1294.

[Luhdorf P, Overvad K, Schmidt EB, et al. (2017)] Predictive value of stroke discharge diagnoses in the Danish National Patient Register. Scand J Public Health; 45(6):630-636.

[Lund KH, Fuglsang CH, Schmidt SAJ, et al. (2024)] Cardiovascular data quality in the Danish National Patient Registry (1977-2024): A systematic review. Clin Epidemiol; 16:865-900.

[Ly S, Manjaly P, Kamal K, et al. (2023)] Comorbid conditions associated with alopecia areata: A systematic review and meta-analysis. Am J Clin Dermatol; 24(6):875-893.

[Malmo V, Langhammer A, Bonaa KH, et al. (2016)] Validation of self-reported and hospital-diagnosed atrial fibrillation: The hunt study. Clin Epidemiol; 8:185-193.

[Marubini E, Valsecchi MG (1995)] Analysing survival data from clinical trials and observational studies. Chichester ; New York, J. Wiley.

Medicinrådet (2019) Medicinrådets anbefaling vedrørende erenumab som mulig standardbehandling til forebyggende behandling af migræne.

Https://medicinraadet.Dk/anbefalinger-og-vejledninger/anbefalinger-nye-laegemidler-og-indikationsudvidelser/a-g-anbefalinger/erenumab-aimovig. https://medicinraadet.dk/media/11149/medicinraadets-anbefaling-vedr-erenumab-til-migraene-vers-10.pdf. Accessed on 17 Nov

Medicinrådet (2021) Medicinrådets samling af vurderinger af anti-CGRP antistoffer til behandling af kronisk migræne, herunder kriterier for opstart, monitorering og seponering. https://medicinraadet.dk/media/au0bzf44/medicinr%C3%A5dets_samling_af_vurderinger_af_anti-cgrp-antistoffer_til_kronisk_migr%C3%A6ne-vers-1-0_-_m-_bilag_adlegacy.pdf. Accessed on 17 November 2022.

[Meid AD, Heider D, Adler JB, et al. (2016)] Comparative evaluation of methods approximating drug prescription durations in claims data: Modeling, simulation, and application to real data. Pharmacoepidemiol Drug Saf; 25(12):1434-1442.

[Muntner P, Hernandez RK, Kent ST, et al. (2024)] Staging and clean room: Constructs designed to facilitate transparency and reduce bias in comparative analyses of real-world data. Pharmacoepidemiol Drug Saf; 33(3):e5770.

Nevrologi.legehandboka.no (2022) Migrene. https://nevrologi.legehandboka.no/handboken/sykdomsgrupper/hodepine/migrene/migrene2. Accessed on 17 November 2022.

[Nielsen LH, Lokkegaard E, Andreasen AH, et al. (2008)] Using prescription registries to define continuous drug use: How to fill gaps between prescriptions. Pharmacoepidemiol Drug Saf; 17(4):384-388.

nNBV (2021) Migræne – behandling med CGRP antistoffer. https://nnbv.dk/cgrp-antagonist-behandling-af-migraene/. Accessed on 29 November 2024.

[Noseda R, Bedussi F, Gobbi C, et al. (2023)] Safety profile of monoclonal antibodies targeting the calcitonin gene-related peptide system in pregnancy: Updated analysis in vigibase®. Cephalalgia; 43(4):3331024231158083.

[Noseda R, Bedussi F, Gobbi C, et al. (2021)] Safety profile of erenumab, galcanezumab and fremanezumab in pregnancy and lactation: Analysis of the WHO pharmacovigilance database. Cephalalgia; 41(7):789-798.

[Oie LR, Madsbu MA, Giannadakis C, et al. (2018)] Validation of intracranial hemorrhage in the Norwegian patient registry. Brain Behav; 8(2):e00900.

[Rasmussen L, Pratt N, Hansen MR, et al. (2018)] Using the "proportion of patients covered" and the kaplan-meier survival analysis to describe treatment persistence. Pharmacoepidemiol Drug Saf; 27(8):867-871.

REFERENCEPROGRAM (2020) Diagnostik og behandling af hovedpinesygdomme og ansigtssmerter. https://dhos.dk/wp-content/uploads/2020/06/2932-Referenceprogram_2020_final_web-24.06.20.pdf. Accessed on 06 November 2024.

[Reuter U, Ehrlich M, Gendolla A, et al. (2022)] Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia; 42(2):108-118.

[Reuter U, Goadsby PJ, Ferrari MD, et al. (2024)] Efficacy and safety of erenumab in participants with episodic migraine in whom 2-4 prior preventive treatments had failed: Liberty 3-year study. Neurology; 102(10):e209349.

[Schenk H, Holle D, Nsaka M, et al. (2022)] Twelve-month safety, tolerability and susceptibility to adverse events of prophylactic migraine therapy with erenumab: A retrospective real-world study. J Headache Pain; 23(1):55.

[Schmidt M, Schmidt SA, Sandegaard JL, et al. (2015)] The Danish National Patient Registry: A review of content, data quality, and research potential. Clin Epidemiol; 7:449-490.

[Schneeweiss S, Rassen JA, Brown JS, et al. (2019)] Graphical depiction of longitudinal study designs in health care databases. Ann Intern Med; 170(6):398-406.

[Sessa M, Andersen M (2021)] New insight on the safety of erenumab: An analysis of spontaneous reports of adverse events recorded in the us Food and Drug Administration adverse event reporting system database. BioDrugs; 35(2):215-227.

[Soares I, Carneiro AV (2002)] Drug class effects: Definitions and practical applications. Rev Port Cardiol; 21(9):1031-1042.

[Stegmayr B, Asplund K (1992)] Measuring stroke in the population: Quality of routine statistics in comparison with a population-based stroke registry. Neuroepidemiology; 11(4-6):204-213.

[Steiner TJ, Stovner LJ, Jensen R, et al. (2020)] Migraine remains second among the world's causes of disability, and first among young women: Findings from gbd2019. J Headache Pain; 21(1):137.

[Steinmetz JD, Seeher KM, Schiess N, et al. (2024)] Global, regional, and national burden of disorders affecting the nervous system, 1990–2021: A systematic analysis for the global burden of disease study 2021. The Lancet Neurology; 23(4):344-381.

[Suissa S, Moodie EE, Dell'Aniello S (2017)] Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. Pharmacoepidemiol Drug Saf; 26(4):459-468.

[Sund R (2012)] Quality of the Finnish hospital discharge register: A systematic review. Scand J Public Health; 40(6):505-515.

[Sundboll J, Adelborg K, Munch T, et al. (2016)] Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: A validation study. BMJ Open; 6(11):e012832.

Sundhed.dk (2023) Kronisk migræne. https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/neurologi/tilstande-og-sygdomme/hovedpine/kronisk-migraene/ Accessed on 27 February 2024.

Sundhedsstyrelsen (2022) Behandling af migræne hos voksne i almen praksis. https://www.sst.dk/da/Udgivelser/2022/Rationel-farmakoterapi-4-2022/Behandling-af-migraene-hos-voksne-i-almen-praksis. Accessed on 17 November 2022.

[Tepper S, Ashina M, Reuter U, et al. (2017)] Safety and efficacy of erenumab for preventive treatment of chronic migraine: A randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol; 16(6):425-434.

[Thomsen LC, Klungsoyr K, Roten LT, et al. (2013)] Validity of the diagnosis of pre-eclampsia in the Medical Birth Registry of Norway. Acta Obstet Gynecol Scand; 92(8):943-950.

[Thomsen RW, Szepligeti SK, Xue F, et al. (2019)] Patterns of initial migraine treatment in Denmark: A population-based study. Pharmacoepidemiol Drug Saf; 28(3):322-329.

[Tolonen H, Salomaa V, Torppa J, et al. (2007)] The validation of the Finnish hospital discharge register and causes of death register data on stroke diagnoses. Eur J Cardiovasc Prev Rehabil; 14(3):380-385.

[Varmdal T, Bakken IJ, Janszky I, et al. (2016)] Comparison of the validity of stroke diagnoses in a medical quality register and an administrative health register. Scand J Public Health; 44(2):143-149.

[Vig SJ, Garza J, Tao Y (2022)] The use of erenumab for migraine prophylaxis during pregnancy: A case report and narrative review. Headache; 62(10):1256-1263.

[Viudez-Martinez A, Pascual-Carrasco A, Beltran-Blasco I, et al. (2022)] Effectiveness and safety of erenumab and galcanezumab in the prevention of chronic and episodic migraine: A retrospective cohort study. J Clin Pharm Ther; 47(6):814-823.

[Wettermark B, Zoega H, Furu K, et al. (2013)] The Nordic prescription databases as a resource for pharmacoepidemiological research--a literature review. Pharmacoepidemiol Drug Saf; 22(7):691-699.