Observational Database Study Protocol

Long-term cardiovascular safety and real-world use of eptinezumab

An observational, historical cohort study of patients initiating eptinezumab in routine clinical practice.

Eptinezumab (Vyepti™)

Study No.:	19756N
Sponsor:	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Main author:	[redacted]
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PASS Information – Study 19756N – Long-term cardiovascular safety and real-world use of eptinezumab

Title	Long-term cardiovascular safety and real-world use of eptinezumab - An observational, historical cohort study of patients initiating eptinezumab in routine clinical practice
Protocol edition No.	7.0 (the version No. in the footer is the system version No.)
Date of protocol edition	09-NOV-2024
EU PAS register No.	Study to be registered later
Active substance	Eptinezumab *ATC group* N02CD "Calcitonin gene-related peptide (CGRP) antagonists" *ATC code* N02CD05
Medicinal product	Vyepti® Concentrate for solution for infusion.
Product reference	H0005287
Procedure No.	EMEA/H/C/5287
Marketing Authorisation Holder(s)	H. Lundbeck A/S (Lundbeck) 2500 Valby (Copenhagen), Denmark
Joint PASS	No
Research question and objectives	Eptinezumab has been granted a marketing authorisation approval by the EU Commission on January 24, 2022. In the Risk Management Plan (RMP), a post-authorisation safety study (PASS) using longitudinal administrative healthcare and/or claims databases has been proposed as an additional pharmacovigilance activity in the pharmacovigilance plan. This study has been regarded by the PRAC as an additional pharmacovigilance activity category 3. Primary objectives: • To assess the long-term cardiovascular risk in migraine patients treated with eptinezumab, in comparison to appropriate control cohorts of patients with migraine who were not treated with eptinezumab

	• To evaluate the long-term cardiovascular risk in migraine patients with a known history of cardiovascular disease using eptinezumab in comparison to migraine patients with a known history of cardiovascular disease not using eptinezumab Secondary objective: • To characterize the utilization of eptinezumab in routine clinical practice
Countries of study	Denmark, Germany, Italy, USA
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Marketing Authorisation Holder

Marketing Authorisation Holder (MAH)	H. Lundbeck A/S (Lundbeck) 2500 Valby, Denmark
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1 Table of Contents

1 Table of Contents 6

2 List of Abbreviations 9

3 Responsible Parties 10

4 Abstract 11

5 Amendments and updates 17

6 Milestones 18

7 Rationale and background 19

8 Research question and objectives 19

9 Research methods 19

9.1 Study design 19

9.2 Setting 20

9.2.1 Inclusion Criteria 22

9.2.2 Exclusion Criteria 22

9.2.3 Censoring Criteria 23

9.3 Variables 24

9.3.1 Outcomes 24

9.3.1.1 Primary outcome 24

9.3.1.2 Secondary outcomes 24

9.3.2 Exposures of special interest 25

9.3.3 Other variables 25

9.3.3.1 Demographics 26

9.3.3.2 Drug exposure 26

9.3.3.3 Medical conditions 27

9.3.3.4 Health care resource utilization (HCRU) 28

9.3.3.5 Other 29

9.4 Data source(s) 29

9.4.1 Denmark: Danish National Registers 29

9.4.2 Germany: German Pharmacoepidemiological Research Database (GePaRD) 30

9.4.3 Italy: Agenzia Regionale di Sanità della Toscana (ARS) 30

9.4.4 USA: Merative MarketScan Database 30

9.5 Study size 31

9.6 Data management 31

9.7 Data analysis 32

9.7.1 Descriptive Statistics 33

9.7.2 Analyses 33

9.7.3 Cohort balancing 33

9.7.4 Cohort analyses 36

9.7.5 Sensitivity Analyses 36

9.7.6 Subgroup Analyses 37

9.7.7 Meta-Analyses 37

9.7.8 Missing data 38

9.8 Quality control 38

9.9 Limitations of the research methods 38

9.10 Other aspects 40
10 Protection of human subjects 40
11 Management and reporting of adverse events/adverse reactions 42
12 Plans for disseminating and communicating study results 42
12.1 Study progress report 42
12.2 Final study report 42
12.3 Publications 42
13 References 42

Annexes

Annex I List of Stand-alone Documents 45
Annex II ENCePP Checklist for Study Protocols 46
Annex III Code lists 53

2 List of Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
ACS	Acute coronary syndrome
ASD	Absolute standardized difference
AT II	Angiotensin II receptor
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
CRO	Clinical research organisation
CV	Cardiovascular
DDD	Defined daily doses
EE	EE exposure cohort
GPV	Global Pharmacovigilance
HCRU	Health care resource utilization
ICD-10	International Classification of Diseases, 10th revision
IRR	Incidence rate ratio
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular event
MEC	Migraine medication exposure cohort
MNEC	Migraine medication non-exposure control cohort
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	non-ST elevation myocardial infarction
PCI	Percutaneous coronary intervention
PRAC	Pharmacovigilance risk assessment committee
PS	Propensity score
PSUR	Periodic safety update report
SAP	Statistical analysis plan
SoC	Migraine standard-of-care control cohort
STEMI	ST elevation myocardial infarction
TIA	Transitory ischemic attack

3 Responsible Parties

Sponsor Personnel	
RWE Lead:	[redacted] H. Lundbeck A/S, Value Evidence & Patient Insights 9 Ottiliavej 2500 Valby Denmark
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Healthcare databases
Denmark / National Health Registers
Germany / GePaRD
Italy / ARS
USA / Merative MarketScan

4 Abstract

Sponsor H. Lundbeck A/S	**Study protocol version** 7.0	**Date of protocol version** 09 Nov 2024
Main author [redacted] H. Lundbeck A/S, Value Evidence & Patient Insights		
Title of Study Long-term cardiovascular safety and real-world use of eptinezumab. An observational, historical cohort study of patients initiating eptinezumab in routine clinical practice.		
Rationale and background Migraine is a chronic condition; therefore, long-term eptinezumab use is expected in routine clinical practice. Adverse events such as cardiovascular (CV) diseases might be infrequent and might appear only after long-term patient exposure. However, the long-term safety of eptinezumab beyond 2 years has not been investigated in the clinical trial program. Additionally, patients with (a history of) cardiovascular disease and/or serious cardiovascular risk were excluded from the clinical trial population, while use in this group of patients may occur in routine clinical practice. Therefore, long-term cardiovascular safety, including the safe use of eptinezumab in patients with a known history of cardiovascular disease, requires further characterisation in real-world clinical practice.		
Research question and objectives Primary objectives: – To assess the long-term cardiovascular risk in migraine patients treated with eptinezumab, in comparison to appropriate control cohorts of patients with migraine who were not treated with eptinezumab – To evaluate the long-term cardiovascular risk in migraine patients with a known history of cardiovascular disease using eptinezumab in comparison to migraine patients with a known history of cardiovascular disease not using eptinezumab Secondary objective: – To characterize the utilization of eptinezumab in routine clinical practice		

Study Design
This will be a 6-year observational, multi-national historical cohort study using longitudinal administrative healthcare and/or claims databases from at least three countries covering different geographic regions in the EU, and one database from the US. The study will include migraine patients treated with eptinezumab in routine clinical practice and followed-up for a maximum of six years from exposure start. The following control cohorts will be identified: 1. A cohort of migraine patients treated with non-CGRP targeting preventive migraine medications; 2. a cohort of migraine patients not treated with any preventive migraine medication; and 3. a cohort of migraine patients representing standard-of-care (i.e. without making any restrictions on the use or non-use of preventive migraine therapy). A major adverse cardiovascular event (MACE), defined as nonfatal stroke, nonfatal acute coronary syndrome, or cardiovascular death, will be the primary study outcome. The risk of MACE in patients treated with eptinezumab will be compared with the risk in control cohorts of patients with migraine who were not treated with eptinezumab. All analyses will be performed separately in each included healthcare databases. The risk estimates from the individual healthcare databases will then be pooled in meta-analyses to increase statistical power of the final combined analysis. Measures of heterogeneity will be displayed and discussed. One of the analyses will evaluate if risk estimates from the US database differ from pooled risk estimates of European databases.
The study inclusion period will be from eptinezumab launch date in the respective country until 31 December 2026. Patients fulfilling the criteria for study inclusion during this time period will be included. Each patient will be assigned an index date that defines their start of follow-up. One year prior to and up to the index date will form the pre-index assessment period, during which patient characteristics and migraine treatment history will be identified. All variables measured during the pre-index assessment period will be considered as baseline characteristics of the patient. The study follow-up period will be from eptinezumab launch date in the respective country until 31 December 2028. This ensures that all patients included in the study could in principle be followed up for a minimum of two years.

Population

Patients will be included into the following three study cohorts:

- **Eptinezumab exposure (EE) cohort**: Migraine patients with at least on eptinezumab infusion during the study inclusion period will be included in the EE cohort. The date of their first eptinezumab exposure (=first infusion) will be defined as their index date and eptinezumab will be defined as their index treatment. All patients in the EE cohort will thus be incident (new) users of eptinezumab but may have used other preventive therapies in the past. In case of treatment with another CGRP-targeting migraine medication (acute or preventive) during follow-up, patient time will be censored.
- **Migraine preventive medication exposure control (MEC) cohort (primary control cohort)**: Migraine patients initiating treatment with a non-CGRP targeting preventive migraine medication during the study inclusion period will be included in the MEC cohort. Only incident (new) users of the respective preventive migraine medication will be included. The date of their first new exposure to a non-CGRP targeting preventive migraine medication will be defined as their index date, and the respective preventive drug will be the index treatment. Patients with exposure to eptinezumab prior to the index date will not be eligible for inclusion. In case of treatment with any CGRP-targeting migraine medication (acute or preventive) during follow-up, patient time will be censored.
- **Migraine preventive medication non-exposure control (MNEC) cohort (secondary control cohort)**: Migraine patients not exposed to any preventive migraine medication will be included in the MNEC cohort. With first exposure to a preventive migraine medication during follow-up, patient time will be censored. As there is no 'exposure event' (e.g. a pharmacy dispensing) defining the start of follow-up in these patients, a random index date during the study inclusion period will be assigned for each patient before assessing study eligibility. In case of treatment with any CGRP-targeting migraine medication (acute or preventive) during follow-up, patient time will be censored.
- **Migraine standard-of-care control (SoC) cohort (secondary control cohort)**: Migraine patients not exposed to eptinezumab will be included in the MNEC cohort. No further eligibility criteria will be applied with respect to use or non-use of preventive migraine medications or the use of CGRP-targeting migraine medications. After first exposure to eptinezumab, patients will no longer be eligible for inclusion into this cohort. As there is no 'exposure event' (e.g. a pharmacy dispensing) defining the start of follow-up in these patients, a random index date during the study inclusion period will be assigned for each patient before assessing study eligibility.

Patients may be included in one or more of the control cohorts first and then switch to the EE cohort in case of eptinezumab initiation. Patients in the EE cohort are not allowed to switch to any of the control cohorts to avoid any potential carry-over effects of eptinezumab exposure. Patients may be included in more than one of the control cohorts (e.g. in the MNEC cohort first, and then in the MEC cohort). The rationale for having three control cohorts is to create a set of comparisons that allow a detailed assessment of the cardiovascular risk and of a potential impact of (residual) confounding. All control cohorts will control for the background risk associated with the biologic and behavioral factors associated with migraine. The MEC cohort (but not the MNEC or SoC cohorts) will by definition control for factors associated with the use of preventive migraine medications (e.g. migraine disease severity). Therefore, the MEC cohort will be primary control cohort in this study. The secondary comparisons (vs. MNEC and SoC cohorts) are expected to contribute to interpretation of study findings in the context of preventive migraine treatment channeling (e.g. selective prescribing to those with higher migraine disease severity; comparability of patient populations) and potential residual confounding. The SoC cohort represents the most inclusive patient cohort and also includes patients with exposure to CGRP-targeting migraine medications.

Variables

The variables in this study will be defined based on prescriptions / dispensations, diagnoses, procedures and other medical events (e.g. hospitalizations) recorded in the respective healthcare database. A database specific study protocol will be developed for each database that include the most appropriate definitions for the respective data source. To increase study homogeneity, the definitions will be aligned to this master study protocol as far as possible. Information will be collected on the following information:

- **Outcomes**: A major adverse CV event (MACE), defined as nonfatal stroke, nonfatal acute coronary syndrome (ACS) or CV death will be the primary study outcome. The following outcomes will be defined as secondary study outcomes: Non-fatal stroke; Stroke; Ischemic stroke; Non-fatal ACS; ACS; CV death; Transitory ischemic attack (TIA); Angina pectoris (all subtypes, i.e. independently from coding of stable/instable); Percutaneous coronary intervention (PCI); Heart failure.
- **Exposures of special interest**: These are exposure information on eptinezumab and other CGRP-targeting preventive migraine medications, as well as non-CGRP targeting preventive migraine medications: amitriptyline, topiramate, valproate / divalproex, atenolol, bisoprolol, metoprolol, propranolol, candesartan, flunarizine and OnabotulinumtoxinA.
- **Other variables**: Other variables are collected to assess potential confounding factors, and to identify patients with a known history of cardiovascular disease (=subgroup of special interest). Variables include demographics; drug exposure information to drugs used in migraine, other neurological conditions, pain, an in CV diseases; relevant diagnoses (e.g. migraine, other neurological conditions, CV diseases and CV risk factors); proxies of migraine disease severity; and variables in relation to health care resource utilization (e.g. hospitalisations, physician visits).

Data sources

The database selection for this PASS was based on a systematic assessment of available healthcare databases in the EU and worldwide. Based on the collected information, the following healthcare databases are planned for this PASS:

- Denmark: Danish National Registers.
- Germany: Statutory health insurance data / German Pharmacoepidemiological Research Database (GePaRD)
- Italy: Local Healthcare Units / Agenzia Regionale di Sanità della Toscana (ARS)
- US: Merative MarketScan Database

All EU databases are listed as ENCePP data sources, and all databases including the US MarketScan database represent established databases for pharmacoepidemiological research.

Study size

The selection of healthcare databases was based on the goal to reach 80% statistical power for detecting a 2-fold increase in the risk of MACE risk in the EE cohort as compared to the MEC cohort (2-sided significance level of 0.05). A Monte Carlo based study power simulation was performed with the following assumptions: Study period 2022 to 2028; CV event rate: 6.9 per 1,000 PYs in patients with migraine; Incidence rate ratio (IRR) to be detected = 2; observed number of events follow Poisson distribution; propensity score (PS) matched cohorts. It was further assumed that effect estimates of individual databases are combined in fixed-effects meta-analysis to increase statistical power. Eptinezumab sales projections were used to estimate the expected exposure in different healthcare databases planned to be included in this PASS (i.e. GePaRD (Germany); ARS (Italy); Health registers (Denmark); and Merative MarketScan (US)). Assuming that an increase in CV risk may only occur after some time of cumulative exposure, power estimations were repeated for the estimated proportion of patients with an exposure duration of >=3 years (see panel below).

Panel. Power estimations

	Total N (EE cohort)	Matching ratio (EE:MEC)	Statistical power
Main analysis	28,394	1:1	>99.9%
		1:2	>99.9%
		1:3	>99.9%
		1:4	>99.9%
Subgroup: Patients with ≥3 years of exposure duration	1,484	1:1	94.0%
		1:2	98.6%
		1:3	99.4%
		1:4	99.6%

Data analysis

After identification of the study cohorts, cohort balancing (i.e. identification of appropriate control cohorts) will be performed within a PS based approach. Study analyses will be done in the sequence of 'cohort balancing' followed by the 'cohort analyses' in the unbalanced and balanced cohorts. A PS based approach will be used for cohort balancing. The following comparative analyses are planned:

1. EE vs. MEC (primary analysis)
2. EE vs. MNEC (secondary analysis)
3. EE vs. SoC (secondary analysis)

All comparative analyses will be performed independently from each other, i.e. with separate cohort balancing for each of the planned comparisons.

Overall summary statistics (n, mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables. Counts and percentages will be presented for categorical and binary variables. For each study outcome, descriptive analyses will include the numbers of patients at risk; numbers and proportions of patients with an event; and the corresponding event rates (number of patients with events divided by sum of person-time at risk) along with 95% confidence intervals.

Hazard ratios of the primary and secondary study outcomes, along with their 95% confidence intervals, will be estimated to assess the long-term cardiovascular risk in patients treated with eptinezumab, in comparison to each control cohort. For each of the three comparisons (EE vs. MEC; EE vs. MNEC; EE vs. SoC), hazard ratios will be estimated for the unbalanced and the balanced study cohorts using COX proportional hazard regression analysis. In addition, cumulative incidences will be estimated for the unbalanced and balanced cohorts. Subgroup analyses will be performed to evaluate the impact of a known history of cardiovascular diseases on the long-term cardiovascular risk in patients using eptinezumab in clinical practice, as well as the impact of migraine disease severity. Tabulation of covariate distribution in the unbalanced cohorts and cohort follow-up characteristics will characterize the utilization of eptinezumab in routine clinical practice.

Milestones

The study progress will be reported in the PSURs. Assuming a follow-up time of at least 2 years and up to 6 years per patient, a lag-time of data availability in the databases of 1 year, this would correspond to the following estimations:

Milestone	Date
Study protocol submitted for PRAC review/approval	Within 3 months from marketing authorization granting
Begin of study period (database specific)[1]	Launch date in the respective country
Launch date reached in all relevant countries	01-Jan-2023
Database specific study progress reports	30-Jun-2026[2]
PASS summary progress report	30-Jun-2026[3]
PASS patient count monitoring report	30-Jun-2028
End of study period	31-Dec-2028[4]
Full data availability in all healthcare databases	31-Dec-2029
Database analyses finalized	30-Jun-2030
Individual database study reports	30-Sep-2030
Final study report	31-Dec-2030

[1]Begin of the study period in the retrospective database analyses

[2]Study progress reports after 2 years of data since the first recorded use of eptinezumab have been accumulated in the respective health care databases, and assuming a lag-time of data availability in the databases of 1 year. In databases with longer lag-times, the milestone date would be delayed by the additional lag-time.

[3]The PASS summary progress report will be submitted together with the last completed database specific study progress report. In case of delay in finalisation of one or more database specific progress reports due data lag-times of more than 1 year, the PASS summary progress report will be delayed correspondingly and submitted together with the last completed database specific report.

[4]Assuming a lag-time of data availability in the databases of 1 year. In databases with a lag-time of up to 2 years, the study period would end up to one year earlier to ensure compliance with the milestone 'Database analyses finalized'.

All milestone and timeline estimates are conditional to potential market access issues.

5 Amendments and updates

None.

6 Milestones

The study progress will be reported in the PSURs. Assuming a follow-up time of at least 2 years and up to 6 years per patient, a lag-time of data availability in the databases of 1 year, this would correspond to the following estimations:

Milestone	Date
Study protocol submitted for PRAC review/approval	Within 3 months from marketing authorization granting
Registration in the EU PAS register	Within 3 months from acceptance of study protocol by EMA
Begin of study period (database specific)[1]	Launch date in the respective country
Launch date reached in all relevant countries	01-Jan-2023
Database specific study progress reports	30-Jun-2026[2]
PASS summary progress report	30-Jun-2026[3]
PASS patient count monitoring report	30-Jun-2028
End of study period	31-Dec-2028[4]
Full data availability in all healthcare databases	31-Dec-2029
Database analyses finalized	30-Jun-2030
Individual database study reports	30-Sep-2030
Final study report	31-Dec-2030

[1]Begin of the study period in the retrospective database analyses

[2]Study progress reports after 2 years of data since the first recorded use of eptinezumab have been accumulated in the respective health care databases, and assuming a lag-time of data availability in the databases of 1 year. In databases with longer lag-times, the milestone date would be delayed by the additional lag-time.

[3]The PASS summary progress report will be submitted together with the last completed database specific study progress report. In case of delay in finalisation of one or more database specific progress reports due data lag-times of more than 1 year, the PASS summary progress report will be delayed correspondingly and submitted together with the last completed database specific report.

[4]Assuming a lag-time of data availability in the databases of 1 year. In databases with a lag-time of up to 2 years, the study period would end up to one year earlier to ensure compliance with the milestone 'Database analyses finalized'.

All milestone and timeline estimates are conditional to potential market access issues.

7 Rationale and background

Eptinezumab is a humanized monoclonal antibody (mAb) that was developed for the preventive treatment of migraine in adults. It binds to α- and β- forms of human Calcitonin gene-related peptide (CGRP). During migraine attacks, there is an increase in the plasma levels of α- Calcitonin gene-related peptide (CGRP) in the external jugular vein [Goadsby PJ 1988]. Intravenous infusion of α-CGRP has caused migraine and headache in patients with migraine, suggesting that the increase in α-CGRP observed during spontaneous migraine attacks plays a causative role [Lassen LH 2002]. CGRP also has an important role in migraine by facilitating the transmission of migraine pain, thereby contributing to the induction of the pronociceptive stage through modulation of the central nervous system (CNS) [Lassen LH 2002; Moskowitz MA 1990].
α-CGRP dilates intracranial and extracranial blood vessels, and can additionally activate adjacent mast cells, which leads to the secretion of vasoactive, proinflammatory, and neurosensitizing mediators, thereby contributing to migraine pathogenesis [Theoharides TC 2005]. Because CGRP can mediate vasodilation, CGRP inhibition could theoretically be associated with an increased cardiovascular risk, especially in patients with pre-existing cardiovascular diseases.
The long-term safety of eptinezumab beyond 2 years has not been investigated in the clinical trial program. Additionally, patients with (a history of) cardiovascular disease and/or serious cardiovascular risk were excluded from the clinical trial population, while use in this group of patients may occur in routine clinical practice. Therefore, long-term cardiovascular safety, including the safe use of eptinezumab in patients with a known history of cardiovascular disease, requires further characterisation in real-world clinical practice.

8 Research question and objectives

Primary objectives:
- To assess the long-term cardiovascular risk in migraine patients treated with eptinezumab, in comparison to appropriate control cohorts of patients with migraine who were not treated with eptinezumab
- To evaluate the long-term cardiovascular risk in migraine patients with a known history of cardiovascular disease using eptinezumab in comparison to migraine patients with a known history of cardiovascular disease not using eptinezumab

Secondary objective:
- To characterize the utilization of eptinezumab in routine clinical practice

9 Research methods

9.1 Study design

This will be a 6-year observational, multi-national historical cohort study using longitudinal administrative healthcare and/or claims databases from at least three countries covering

different geographic regions in the EU, and one database from the US. The study will include migraine patients treated with eptinezumab in routine clinical practice and followed for a minimum of two years and up to six years from exposure start. The following control cohorts will be identified: 1. A cohort of migraine patients treated with non-CGRP targeting preventive migraine medications; 2. a cohort of migraine patients not treated with any preventive migraine medication; and 3. a cohort of migraine patients representing standard-of-care (i.e. without making any restrictions on the use or non-use of preventive migraine therapy).

A major adverse cardiovascular event (MACE), defined as nonfatal stroke, nonfatal acute coronary syndrome, or cardiovascular death, will be the primary study outcome. The risk of MACE in patients treated with eptinezumab will be compared with the risk in control cohorts of patients with migraine who were not treated with eptinezumab.

All analyses will be performed separately in each included healthcare databases. The risk estimates from the individual healthcare databases will then be pooled in meta-analyses to increase statistical power of the final combined analysis.

9.2 Setting

The *study inclusion period* will be from eptinezumab launch date in the respective country until 31 December 2026. Patients fulfilling the criteria for study inclusion during this time period will be included. Each patient will be assigned an *index date* that defines their start of follow-up. One year prior to and up to the index date will form the *pre-index assessment period*, during which patient characteristics and migraine treatment history will be identified. All variables measured during the pre-index assessment period will be considered as *baseline characteristics* of the patient. The *study follow-up period* will be from eptinezumab launch date in the respective country until 31 December 2028. This ensures that all patients included in the study could in principle be followed up for a minimum of two years.

Study cohorts

- **Eptinezumab exposure (EE) cohort**: Migraine patients with at least one eptinezumab infusion during the study inclusion period will be included in the EE cohort. The date of their first eptinezumab exposure (=first infusion) will be defined as their index date and eptinezumab will be defined as their index treatment. All patients in the EE cohort will thus be incident (new) users of eptinezumab but may have used other preventive therapies in the past. In case of treatment with another CGRP-targeting migraine medication (acute or preventive) during follow-up, patient time will be censored. In case no infusion dates are available in the respective database, proxy information for the index date will be used (e.g. pharmacy dispensing information).
- **Migraine preventive medication exposure control (MEC) cohort (primary control cohort)**: Migraine patients initiating treatment with a non-CGRP targeting preventive migraine medication during the study inclusion period will be included in the MEC cohort. Only incident (new) users of the respective preventive migraine medication will be included. The date of their first new exposure to a non-CGRP targeting preventive

migraine medication will be defined as their index date, and the respective preventive drug will be the index treatment. Patients with exposure to eptinezumab prior to the index date will not be eligible for inclusion. Information on the drugs defined as being non-CGRP preventive migraine medications (including ATC codes) are included in Appendix I / Panel 4.

- **Migraine preventive medication non-exposure control (MNEC) cohort (secondary control cohort)**: Migraine patients not exposed to any preventive migraine medication will be included in the MNEC cohort. With first exposure to a preventive migraine medication during follow-up, patient time will be censored. As there is no 'exposure event' (e.g. a pharmacy dispensing) defining the start of follow-up in these patients, a random index date during the study inclusion period will be assigned for each patient before assessing study eligibility. In case of treatment with any CGRP-targeting migraine medication (acute or preventive) during follow-up, patient time will be censored.
- **Migraine standard-of-care control (SoC) cohort (secondary control cohort)**: Migraine patients not exposed to eptinezumab will be included in the MNEC cohort. No further eligibility criteria will be applied with respect to use or non-use of preventive migraine medications or the use of CGRP-targeting migraine medications. With first exposure to eptinezumab, patients will no longer be eligible for inclusion into this cohort. As there is no 'exposure event' (e.g. a pharmacy dispensing) defining the start of follow-up in these patients, a random index date during the study inclusion period will be assigned for each patient before assessing study eligibility. The SoC cohort represents the most inclusive patient cohort and also includes patients with exposure to CGRP-targeting migraine medications.

Membership in different study cohorts:

- Each patient will be *included only once in each of the study cohort* (i.e. at the first day fulfilling the eligibility criteria of the respective cohort). For instance, a patient initiating two different non-CGRP targeting preventive migraine medication during the study inclusion period will only be included once in the MEC cohort (with the first preventive therapy initiation).

- Patients can *become members of different study cohorts* in case they fulfil the respective eligibility criteria. For instance, a patient may first be included in the MEC cohort and then in the EE cohort subsequently. When switching to the EE cohort, person-time at the previous cohort will be censored by definition (see section 9.2.3). To avoid any carry-over effects from eptinezumab exposure on subsequent CV risks, switching from the EE cohort to any of the control cohorts is prevented by the eligibility criteria (see sections 9.2.1 and 9.2.2). Patients may also be included in more than one of the control cohorts (e.g. in the MNEC cohort first, and then in the MEC cohort).

The rationale for having three control cohorts is to create a set of comparisons that allow a detailed assessment of the cardiovascular risk and of a potential impact of (residual) confounding. All control cohorts will control for the background risk associated with the biologic and behavioral factors associated with migraine. The MEC cohort (but not the MNEC or SoC cohorts) will by definition control for factors associated with the use of

preventive migraine medications (e.g. migraine disease severity). Therefore, the MEC cohort will be primary control cohort in this study. The secondary comparisons (vs. MNEC and SoC cohorts) are expected to contribute to interpretation of study findings in the context of preventive migraine treatment channeling (e.g. selective prescribing to those with higher migraine disease severity; comparability of patient populations) and potential residual confounding.

9.2.1 Inclusion Criteria

The inclusion criteria for the 4 study cohorts are displayed in Panel 1.

Panel 1. Inclusion criteria for the 4 study cohorts[1]

Inclusion criteria[1]	**EE cohort**	**MEC cohort**	**MNEC cohort**	**SoC cohort**
Medical information available for at least 1 year prior to the index date	**X**	**X**	**X**	**X**
Patient fulfils the criteria of having migraine[2]	**X**	**X**	**X**	**X**
Initiation of eptinezumab therapy during the study inclusion period	**X**			
Initiation of therapy with non-CGRP targeting preventive migraine medications during the study inclusion period		**X**		

EE = Eptinezumab exposure. MEC = Migraine medication exposure control (MEC). MNEC = Migraine medication non-exposure control (MNEC). SoC = Migraine standard-of-care control (SoC).
[1]To become eligible for one of the 4 study cohorts, all inclusion criteria indicated with 'X' for the respective study cohort have to be fulfilled.
[2]Modified migraine criteria based on Yusuf 2018 (see Annex III / Panel 10).

9.2.2 Exclusion Criteria

The exclusion criteria for the 4 study cohorts are displayed in Panel 2.

Panel 2. Exclusion criteria for the 4 study cohorts[1]

Exclusion criteria	EE cohort	MEC cohort	MNEC cohort	SoC cohort
Exposure to eptinezumab before the index date		X	X	X
Concomitant initiation (=new use) of two or more preventive migraine medications at the index date	X	X	X	
Use of preventive migraine medications within 3 months before or at the index date			X	
Treatment with CGRP-targeting migraine medications other than eptinezumab (acute or preventive) at the index date	X	X	X	
No longer under observation at the index date[2]			X	X

EE = Eptinezumab exposure. MEC = Migraine medication exposure control (MEC). MNEC = Migraine medication non-exposure control (MNEC). SoC = Migraine standard-of-care control (SoC).

[1]To become eligible for one of the 4 study cohorts, none of the exclusion criteria indicated with 'X' for the respective study should be fulfilled.

[2]This might occur in case of a randomly assigned index date (MNEC and SoC cohorts).

9.2.3 Censoring Criteria

EE cohort: Patients will be followed-up until end of continuous exposure to eptinezumab, treatment with another CGRP-targeting migraine medication (acute or preventive), end of database registration, end of study follow-up period, death, or occurrence of the respective outcome of interest, whichever will occur first. A sensitivity analysis will use an intention-to-treat-like approach in which the end of continuous exposure to eptinezumab will not trigger censoring.

MEC cohort: Patients will be followed-up until end of continuous exposure to the index drug, treatment with any CGRP-targeting migraine medication (acute or preventive), end of database registration, end of study follow-up period, death, or occurrence of the respective outcome of interest, whichever will occur first. A sensitivity analysis will use an intention-to-treat-like approach in which the end of continuous exposure to the index drug will not trigger censoring.

MNEC cohort: Patients will be followed-up until initiation of a preventive migraine medication, treatment with any CGRP-targeting migraine medication (acute or preventive), end of database registration, end of study follow-up period, death, or occurrence of the respective outcome of interest, whichever will occur first.

SoC cohort: Patients will be followed-up until end of database registration, treatment with eptinezumab, end of study follow-up period, death, or occurrence of the respective outcome of interest, whichever will occur first. The SoC cohort could include patient time exposed to CGRP-targeting migraine medications other than eptinezumab.

9.3 Variables

The variables in this study will be defined based on prescriptions / dispensations, diagnoses, procedures and other medical events (e.g. hospitalizations) recorded in the respective healthcare database. A database specific study protocol will be developed for each database that include the most appropriate definitions for the respective data source. This includes adaption of the code lists included in Annex III of this study protocol. To increase study homogeneity, the definitions will be aligned to this master study protocol as far as possible. As the primary focus will be to provide the best-available adjusted risk estimates, some differences in variable definitions and statistical models between the database studies may be considered necessary. For instance, if a certain type of proxy variable for migraine disease severity (such as health care resource utilization) is available in one database but not in the other, these variables would not be excluded with the goal to ensure alignment between databases. Instead, the aim would be to make most efficient use of each individual healthcare database and thus accept some methodological heterogeneity.

9.3.1 Outcomes

9.3.1.1 Primary outcome

A major adverse CV event (MACE), defined as nonfatal stroke, nonfatal acute coronary syndrome (ACS) or CV death will be the primary study outcome. ACS includes ST elevation myocardial infarction (STEMI); non-ST elevation myocardial infarction (NSTEMI) and unstable angina pectoris. In case CV death is not included as a separate outcome in the healthcare database, it is planned to use 'hospitalization for a CV cause with fatal outcome within 30 days' as a proxy for CV death.

9.3.1.2 Secondary outcomes

The following outcomes will be defined as secondary study outcomes:

- Non-fatal stroke
- Stroke
- Ischemic stroke
- Non-fatal ACS
- ACS
- CV death
- Transitory ischemic attack (TIA)
- Angina pectoris (all subtypes, i.e. independently from coding of stable/instable)
- Percutaneous coronary intervention (PCI)
- Heart failure

Non-fatal events will be defined as events without recorded death (any cause) within 30 days. ICD-10 codes for the primary and secondary outcomes are included in Appendix I / Panel 8. To distinguish new events during the follow-up period from repeated diagnoses of events that occurred before the index date, only acute events will be included (e.g. those leading to

hospitalization or an emergency room visit). As the way of identifying these events may differ between health care databases, details will be included in the database specific study protocols.

The baseline characteristics of patients in the four cohorts are also considered as outcomes of interest in this study, to address the study objective of characterizing the utilization of eptinezumab in routine clinical practice.

9.3.2 Exposures of special interest

Exposures of special interest are drugs used for the prevention of migraine attacks. Only those preventives included in the definition of the EE and MEC cohorts are considered as exposures of special interest. This includes:

- EE cohort: eptinezumab
- MEC cohort: Non-CGRP targeting preventive migraine medications, i.e. amitriptyline, topiramate, valproate / divalproex, atenolol, bisoprolol, metoprolol, propranolol, candesartan, flunarizine and OnabotulinumtoxinA

Drugs used in the treatment of acute migraine attacks, with a low level of evidence or with a CGRP targeting mechanism are included in the following section (to be considered as potentially confounding factors).

For all exposures of special interest, variables will be created to measure the extent of use (person days exposed) during the pre-index time period. The estimation of person days exposed will consider defined daily doses (DDDs) (see Appendix I / Panel 4); the first and the last prescription or dispensation date in the pre-index period; and other characteristics of the respective treatment (e.g. recommended time between two doses in case of CGRP-targeting preventive migraine medications). Details on the estimation will be included in the SAP.

For the index drug in the EE and the MEC cohorts, the duration of the initial treatment episode (i.e. from index date until stop or interruption of index drug treatment) will be calculated. An interruption or stop of the index drug will be defined as the first observed gap of more than 60 days between the estimated end of the available drug supply and the next prescription/dispensation. For drugs with oral administration, stockpiling will be considered. A grace period of 60 days is considered sufficient to address uncertainties on the daily dose that is actually used by the patient (i.e. deviating from the DDD) and on the adherence to treatment. The grace period of 60 days will be modified in a sensitivity analysis (to 0 days, 30 days and to 90 days) to evaluate the impact of this methodological aspect. Details on the estimation of the interruption or stop of the index drug will be included in the SAP.

9.3.3 Other variables

Other variables are collected to assess potential confounding factors, and to identify patients with a known history of cardiovascular disease (=subgroup of special interest). All these

variables will be assessed during the 1-year period until and including the index date and are considered as baseline characteristics. 'Including the index date' means that all information assessed at the index date (e.g. diagnoses) will still be considered as being baseline characteristics. Codes for the variables are included in Appendix I / Panel 5; Panel 6; Panel 7; and Panel 9.

9.3.3.1 Demographics

Demographic variables will include gender, age, and socioeconomic variables and/or proxies (if available in the respective database).

9.3.3.2 Drug exposure

Drug exposures other than those of special interest (as specified in section 9.3.2) that will be assessed include:

- Other non-CGRP targeting preventive migraine medications
- CGRP monoclonal antibodies for migraine prevention
- Acute migraine medications (triptans, gepants, ergots)
- Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and other peripheral analgesics
- Opioids
- Antiepileptics
- Antidepressants
- Antipsychotics
- Benzodiazepines
- Antiemetics
- Angiotensin converting enzyme inhibitors (ACEI)
- Angiotensin II receptor (AT II) antagonists
- Calcium channel blockers
- Beta-blocking agents (other than those specified in section 9.3.2)
- Diuretics
- Other antihypertensive drugs
- Oral antidiabetics
- Insulin
- Aspirin and other platelet aggregation inhibitors
- Anticoagulants
- Corticosteroids
- Statins
- Non-statin lipid lowering drugs
- Nitrates
- Oral contraceptives
- Postmenopausal hormone replacement therapy

For each drug exposure category, the following variables will be created: Binary exposure information (yes/no); number of prescriptions/dispensations.
In addition, the following summary variables of drug exposure will be created:

- Number of different preventive migraine medications used (based on generic drug name level)
- Number of different acute migraine medications used (based on generic drug name level)
- Number of different drugs used (based on generic drug name level)

Additional drug exposure variables may be added to the database specific study protocols if considered necessary. These would be specified in the database specific study documents (study protocols and statistical analysis plans).

9.3.3.3 Medical conditions

Information on the following medical conditions will be retrieved from the databases:

- Migraine with aura (incl. complicated migraine)
- Migraine without aura
- Status migrainosus
- Cluster headache
- Vascular headache
- Tension-type headache
- Chronic post-traumatic headache
- Drug-induced headache
- Other headache syndromes
- Raynaud syndrome
- Inflammatory diseases of the CNS
- Systemic atrophies primarily affecting the central nervous system
- Extrapyramidal and movement disorders
- Other degenerative diseases of the CNS
- Demyelinating diseases of the CNS
- Epilepsy
- Status epilepticus
- TIA
- Vascular syndromes of brain in cerebrovascular diseases
- Sleep disorders
- Nerve, nerve root and plexus disorders
- Polyneuropathies and other disorders of the peripheral nervous system
- Diseases of myoneural junction and muscle
- Cerebral palsy and other paralytic syndromes
- Other disorders of the nervous system
- Organic, including symptomatic, mental disorders
- Mental and behavioural disorders due to psychoactive substance use
- Schizophrenia, schizotypal and delusional disorders
- Mood [affective] disorders

- Neurotic, stress-related and somatoform disorders
- Behavioural syndromes associated with physiological disturbances and physical factors
- Disorders of adult personality and behaviour
- Mental retardation
- Disorders of psychological development
- Behavioural and emotional disorders with onset usually occurring in childhood and adolescence
- Unspecified mental disorder
- Malignant neoplasm
- Metastatic malignant neoplasm
- Arthrosis
- Other joint disorders
- Myocardial infarction
- Chronic ischemic heart disease
- Chronic obstructive pulmonary disease
- Heart failure
- Stroke (all types)
- Cerebrovascular disease and pre-cerebrovascular disease, not resulting in cerebral infarction
- Other cerebrovascular diseases
- Arterial hypertension and hypertensive disease
- Arterial fibrillation and flutter
- Peripheral arterial disease
- Pulmonary heart disease / diseases of pulmonary circulation
- Hyperlipidemia
- Diabetes Mellitus (Type 1; type 2; not specified as type 1 or 2; with organ damages)
- Chronic liver diseases
- Kidney failure
- Obesity

For each medical condition, the following variables will be created: Diagnosis received (yes/no; number of diagnoses); diagnoses by treatment setting - outpatient, in-hospital / emergency room, other/unspecified (yes/no; number of diagnoses). Additional diagnostic variables may be added to the database specific study protocols if considered necessary. These would be specified in the database specific study documents (study protocols and statistical analysis plans).

9.3.3.4 Health care resource utilization (HCRU)

If available in the respective database, the following variables will be created:
- Hospitalisations / ER visits for migraine
- GP visits for migraine
- Specialists visits for migraine
- Hospitalisations / ER visits for CV causes

- GP visits for CV causes
- Specialists visits for CV causes
- Hospitalisations total (days in hospital)
- ER visits total
- Physician visits overall

9.3.3.5 Other

The following additional variables will be retrieved:
- Calendar year of index date
- Body mass index (BMI) (if available)
- Smoking status (if available)

9.4 Data source(s)

The database selection for this PASS was based on a systematic assessment of available healthcare databases worldwide. For EU, the assessment included feedback from data sources in Denmark, France, Italy, Netherlands, Sweden, UK, Germany, Finland, Norway, and Spain. The assessment captured availability of information on five data groups, i.e. patient demographics and medical history; diagnoses; treatments; outcomes; and HCRU. At the time of assessment, eptinezumab was not yet available on the market. To investigate whether exposure information on eptinezumab will be available in the respective database, it was thus asked if exposure information on IV treatments given for multiple sclerosis are included in the database (as eptinezumab will also be administered IV). Based on the collected information and population exposure estimations, the following healthcare databases are planned for this PASS:

- Denmark: Danish National Registers
- Germany: Statutory health insurance data / German Pharmacoepidemiological Research Database (GePaRD)
- Italy: Local Healthcare Units / Agenzia Regionale di Sanità della Toscana (ARS)
- USA: Merative MarketScan Database

All EU databases are listed as ENCePP data sources, and all databases including the US MarketScan database represent established databased for pharmacoepidemiological research.

9.4.1 Denmark: Danish National Registers

Danish health registers contain information on many important health and social aspects (Thygesen et al. 2011). As Danish citizens have a unique personal identification number, linkage at the individual level between these nationwide registers and other data sources is feasible and has been extensively used for pharmacoepidemiological research. Examples of Danish registers on health-related issues include Register of Causes of Death; National Patient Register; National Health Service Register; National Prescription Registry; Danish Heart

Register; and other disease-specific registers (Thygesen et al. 2011). The registers cover the whole Danish population, i.e. a total of currently 5.8 Mio inhabitants.

9.4.2 Germany: German Pharmacoepidemiological Research Database (GePaRD)

The GePaRD database is an administrative database consisting of claims data from statutory health isurances in Germany (Haug et al. 2021). In Germany, about 90% of the general population are covered by the statutory health insurance system. GePaRD includes healthcare data since 2004 on a total of 25 Mio subjects. Per year, there is information on approximately 17% of the German population (i.e. 14 Mio subjects) and all geographical regions of the country are represented (Haug et al. 2021). Lag time of the database is approximately 2 years. Data elements include for instance demographic information; hospitalisation data; outpatient and primary care data; and pharmacy dispensing data. The GePaRD database has been used for a large number of pharmacoepidemiological studies, including PASS.

9.4.3 Italy: Agenzia Regionale di Sanità della Toscana (ARS)

Italy has a universal healthcare system financed through general taxation (Gini R 2021) and thus covers the whole Italian population structured into different regions. The Italian regions provide healthcare providers, i.e. Local Health Units (LHUs) (Trifirò et al. 2019). The collection of healthcare service claims data by regional governments / LHUs is mandatory in Italy. ARS is the LHU of the Tuscany region in Italy and covers approx. 3.6 Mio inhabitants. Data elements include demographic information; hospital discharge records; co-payment exemptions information; drug dispensing in community pharmacies; drug dispensing in hospital pharmacies on discharge; outpatients specialist care, diagnostic tests and outpatient procedures; and the emergency department database (Trifirò et al. 2019). Data from Italian LHUs, including ARS has been used for multiple pharmacoepidemiological studies and represents an established data source.

9.4.4 USA: Merative MarketScan Database

The Merative MarketScan® Commercial Database contains de-identified, patient-level medical and drug data of reimbursed healthcare claims for employees, their spouses and dependents across the United States who are covered by employer-provided commercial insurance. The expected time lag for data to become available in the MarketScan database is approximately one year. MarketScan is selected because of meeting the following criteria: Sufficiently large population coverage (>10,000,000 people); longitudinal follow-up; detailed information about drug prescription claims (including information on drug compound, formulation, strength) for patients in outpatient settings; diagnostic information per ICD-10 codes for patients in out- and inpatient settings; healthcare visit information in out- and inpatient settings; and a maximum 1-year lag time in data availability. The MarketScan database has been used for several pharmacoepidemiological studies in migraine (e.g. Varnado et al. 2022; Pero et al. 2022) including studies focusing on vascular event rates (Gill et al. 2020).

9.5 Study size

The selection of healthcare databases was based on the goal to reach at least 80% statistical power for detecting a 2-fold increase in the risk of MACE risk in the EE cohort as compared to the MEC cohort (2-sided significance level of 0.05). A Monte Carlo based study power simulation was performed with the following assumptions: Study period 2022 to 2028; CV event rate: 6.9 per 1,000 PYs in patients with migraine (Gill et al. 2020); Incidence rate ratio (IRR) to be detected (IRR) = 2; observed number of events follow Poisson distribution; propensity score matched cohorts. It was further assumed that effect estimates of individual databases are combined in fixed-effects meta-analysis to increase statistical power. Eptinezumab sales projections were used to estimate the expected exposure in the different healthcare databases planned to be included in this PASS (i.e. GePaRD (Germany); ARS (Italy); Health registers (Denmark); MarketScan (USA)). Assuming that an increase in CV risk may only occur after some time of cumulative exposure, the number of patients with an exposure duration of >=3 years was estimated. These estimations considered estimated drug discontinuation rates (40% per year) and losses-to-follow-up in the databases (5% per year). Power estimations were repeated for the estimated proportion of patients with an exposure duration of >=3 years. The resulting statistical power for both analyses are included in Panel 3.

Panel 3. Power estimations[1]

	Total N (EE cohort)	Matching ratio (EE:MEC)	Statistical power
Main analysis	28,394	1:1	>99.9%
		1:2	>99.9%
		1:3	>99.9%
		1:4	>99.9%
Subgroup: Patients with ≥3 years of exposure duration	1,484	1:1	94.0%
		1:2	98.6%
		1:3	99.4%
		1:4	99.6%

[1]For: GePaRD (Germany); ARS (Italy); Health registers (Denmark); MarketScan (USA)

9.6 Data management

Data management will be performed individually by each research partner involved in this PASS, i.e. data will remain on local level and will not be transferred to Lundbeck. This includes the respective local procedures to ensure data protection, security and confidentiality. Results will be reported to Lundbeck only on an aggregated level, i.e. without any information that would allow patient identification. The statistical software program(s) used in each of the database specific analyses will be included in the respective study protocol and report. SAS Version 9.4 (SAS Institute, Cary NC) will be used for the meta-analyses.

Denmark: Danish National Registers

The data in the Danish National Registers are collected routinely on a national level and the registers are maintained by the government. Statistics Denmark offers remote access to all individual level data that is necessary to carry out research projects (Thygesen 2011). Individual level data from Statistics Denmark is not delivered to any external firm, institution, or person. Instead, datasets and linkages between datasets constructed at Statistics Denmark are stored at Statistics Denmark. Researchers employed at specific authorised environments can establish remote online access to these datasets stored at Statistics Denmark (Thygesen 2011).

Germany: German Pharmacoepidemiological Research Database (GePaRD)

The GePaRD database is consisting of administrative electronical health data provided by the respective statutory health insurances. Collection of patient-level data and linking of the different data elements occurs already on the insurance level (based on the individual health insurance number). The GePaRD database is maintained by Leipniz Institute for Prevention Research and Epidemiology – BIPS, and database access is only possible at BIPS in the context of approved research projects (Haug et al. 2021). Data from the health insurances is not transferred directly to BIPS, but via a third party trust center which ensures data plausibility checks and data pseudonymisation. The lag time of data being included in the database is approximately 2 years.

Italy: Agenzia Regionale di Sanità della Toscana (ARS)

Healthcare services provided to Italian inhabitants of Tuscany region which are reimbursed by the National Health System are included in different regional databases on regional (LHU) level. Patient-level linkage is done at LHU level, and pseudonymized patient identifiers for patient-level information in all data tables are provided to ARS. The lag time of data being included in the databases is approximately 3 to 6 months.

USA: Merative MarketScan datatbase

The Merative MarketScan database includes inpatient and outpatient medical, procedural, and outpatient pharmaceutical claims for millions of individuals who possess employer-sponsored health insurance, as well as their spouses and dependents (Kulaylat et al. 2019). As an administrative database, it is based on claims data that is linked on health insurance level. The database ensures HIPAA (US Health Insurance Portability and Accountability Act) compliance through rigorous measures to ensure protection of patient privacy, and all data are de-identified to users who obtain access to the database (Kulaylat et al. 2019). The lag time of data being included in the databases is approximately 12 months.

9.7 Data analysis

Database study analyses will be performed by a CRO or another contracted company or institute that has access to the respective health care database. Meta-analyses of the database specific effect estimates will be done by Lundbeck. Details on the statistical analyses will be given in a separate SAP.

9.7.1 Descriptive Statistics

All assessment data, including demographics, will be summarised by study cohort using descriptive techniques. Summary statistics (n, mean, standard deviation, median, minimum and maximum values) will be presented for continuous variables. Counts and percentages will be presented for categorical and binary variables. Differences between study cohorts, if relevant, will be reported based on (absolute) standardized differences.

Patient flow (i.e. selection into the 4 cohorts starting from the whole database population including overlap between the 4 cohorts) will be descriptively analysed and displayed e.g. in patient-flow diagrams. Cohort follow-up characteristics (e.g. person-time at risk, numbers and reasons for censoring) will also be analysed descriptively.

9.7.2 Analyses

Study analyses will be done the sequence 'cohort balancing' followed by the 'cohort analyses' in the balanced cohorts. A propensity score (PS) based approach will be used for cohort balancing. The following comparative analyses are planned:

1. EE vs. MEC (primary analysis)

2. EE vs. MNEC (secondary analysis)

3. EE vs. SoC (secondary analysis)

All comparative analyses will be performed independently from each other, i.e. with separate cohort balancing for each of the planned comparisons.

9.7.3 Cohort balancing

Goal of balancing is to ensure that the two cohorts (EE and the respective comparator cohort) are comparable with respect to the baseline risk of the cardiovascular outcomes of interest. Cohort balancing will be done for each of the planned three comparisons, and in these balanced cohorts the risks of all the study outcomes will be measured. The process of cohort balancing will include the following steps:

1. *Tabulation of covariate distribution in the unbalanced cohorts*: Cohort balancing will start with tabulating the (baseline) variables of both unbalanced cohorts along with the respective absolute standardized difference (ASD) for each variable (see section 9.3.3 for the variables that will be measured). Summary statistics of the ASDs on variable level along with histograms and/or box plots will also be provided (e.g. number of variables; ASD mean, median, min, max; ect).
2. *Variable selection for PS modelling*: Variable selection for PS modelling will be based on a set of predefined variables that are forced into the model (i.e. those that are considered as clinically relevant, see below). Additional variables may be selected for model inclusion based on an empirical evaluation of the respective ASDs. This also includes

variables on HCRU. Details on variable selection and on the maximum number of variables will be included in the SAP.

3. *PS modelling*: Statistical models will be utilized to model the probability of eptinezumab treatment (i.e. being member of the EE cohort rather than the respective comparator cohort) depending on the selected covariates. The resulting PS distributions in both cohorts will be provided and evaluated with respect to cohort overlap.
4. *PS-based cohort balancing*: Cohort balancing will then be done by applying established PS based methods (e.g. weighting, matching, stratification). Details on these methods will be included in the SAP.
5. *Tabulation of covariate distribution in the balanced cohorts*: Tabulation of (baseline) variables of both balanced cohorts including ASDs, and summary statistics of ASDs will be done in the same way as it was done for the unbalanced cohorts. In case cohort balancing is considered insufficient, potential reasons will be explored (e.g. problems with model convergence such as complete or quasi-complete separation of data points) and variable selection / coding may be refined.

The process of cohort balancing is finalized if the observed balance of baseline variables is considered sufficient (e.g. if ASDs are ≤0.1 for all variables selected for model inclusion). Details will be included in the SAP.

It is planned to force the following variables into the PS model (if available in the respective database):

Demographics etc
- Age
- Gender
- Calender year of index date

CV history
- Ischemic stroke
- Stroke, not classified as ischemic
- ACS
- Transitory ischemic attack (TIA)
- Angina pectoris or chronic ischemic heart disease
- Percutaneous coronary intervention (PCI)
- Heart failure
- Vascular syndromes of brain in cerebrovascular diseases
- Cerebrovascular disease and pre-cerebrovascular disease, not resulting in cerebral infarction
- Other cerebrovascular diseases
- Arterial fibrillation and flutter
- Peripheral arterial disease

CV risk factors
- Inflammatory polyarthropathies

- Chronic obstructive pulmonary disease
- Arterial hypertension and hypertensive disease
- Pulmonary heart disease / diseases of pulmonary circulation
- Hyperlipidemia
- Diabetes mellitus Type 1
- Diabetes mellitus Type 2
- Diabetes mellitus not specified as type 1 or 2
- Diabetes mellitus with organ damages
- Chronic liver diseases
- Kidney failure
- Obesity
- Body mass index (BMI) (if available)
- Smoking status (if available)

Proxies of migraine severity
- Number of hospitalisations / ER visits for migraine
- Number of GP visits for migraine
- Number of specialists visits for migraine
- Number of different acute and chronic migraine medications used in the year prior to cohort entry
- Sum of DDDs of acute migraine medications used in the year prior to cohort entry

Drug history
- Preventive migraine medications as used in the cohort definitions of the EE and MEC cohort
- Acute migraine treatments (triptans, rimegepant, ergotamins, others)
- Non-steroidal anti-inflammatory drugs
- Opioids
- Angiotensin converting enzyme inhibitors (ACEI)
- Angiotensin II receptor (AT II) antagonists
- Calcium channel blockers
- Beta-blocking agents
- Diuretics
- Other antihypertensive drugs
- Oral antidiabetics
- Insulin
- Aspirin and other platelet aggregation inhibitors
- Anticoagulants
- Corticosteroids
- Statins
- Non-statin lipid lowering drugs
- Nitrates
- Oral contraceptives
- Postmenopausal hormone replacement therapy

9.7.4 Cohort analyses

For each study outcome, descriptive analyses will include the numbers of patients at risk; numbers and proportions of patients with an event; and the corresponding event rates (number of patients with events divided by sum of person-time at risk) along with 95% confidence intervals.

Hazard ratios of the primary and secondary study outcomes, along with 95% confidence intervals, will be estimated to assess the long-term cardiovascular risk in patients treated with eptinezumab, in comparison to appropriate control cohorts of patients with migraine who were not treated with eptinezumab. For each of the three comparisons (EE vs. MEC; EE vs. MNEC; EE vs. SoC), hazard ratios will be estimated for the unbalanced and the balanced study cohorts using COX proportional hazard regression analyses. In addition, cumulative incidences will be estimated for the unbalanced and balanced cohorts. Analyses on the impact of cumulative exposure duration will be performed using Landmark analyses (with starting points after 1 year, 2 years, and 3 years of exposure). Landmark analyses will be performed in two ways: First, the patients in the analyses will not be re-balanced but analysed based on their baseline balancing. Second, patients in the Landmark analyses will be re-balanced based on the covariate status during the year prior to the Landmark cut-off date. The second analysis thus considers time-dependent changes in covariate status before the cut-off time point. To evaluate a potential impact of the mean daily dose, the mean DDD per day between cohort entry and end of follow-up (i.e. outcome event or censoring) will be calculated for all patients in the EE cohort and included in the time-to-event model. Details on the statistical models will be included in the SAP.

Subgroup analyses (section 9.7.6) will be performed to evaluate the impact of a known history of cardiovascular diseases on the long-term cardiovascular risk in patients using eptinezumab in clinical practice.

Tabulation of covariate distribution in the unbalanced cohorts (section 9.7.3) and cohort follow-up characteristics (section 9.7.1) will characterize the utilization of eptinezumab in routine clinical practice.

9.7.5 Sensitivity Analyses

The following sensitivity analyses are planned:

- The allowed gap of 60 days to identify continuous exposure to the index drug in the EE and the MEC cohort will be modified to 30 days and to 90 days to evaluate the impact of this methodological aspect on the study outcomes.

- A sensitivity analysis of the EE vs. MEC comparison will use an intention-to-treat-like approach in which the end of continuous exposure to the index drug (in EE or MEC cohorts) will not cause censoring, but observation will continue independently from subsequent exposures. In these analyses, switching from MEC to the EE cohort will not be allowed to avoid including the same person time at risk into both study cohorts.

- In patients who already had one of the study outcomes of interest in their medical history, it may sometimes be difficult to distinguish a new (incident) event from a repeated diagnosis of the previous event. One sensitivity analysis will thus be restricted to patients without the respective study outcome of interest in their medical history.

- The presence of residual unmeasured confounding is a risk to the causal interpretation of risk estimates from analyses based on observational data. In order to quantify how robust the observed association in the study is to unmeasured or uncontrolled confounding, the E-value will be calculated as a sensitivity analysis (VanderWeele TJ 2017).

9.7.6 Subgroup Analyses

One subgroup analysis will be performed according to baseline cardiovascular risk status. In this analysis, patients will be classified into the following subgroups: (1) Patients with a known history of CV disease; (2) patients without a known history of CV disease, but with at least one important CV risk factor (i.e. hyperlipidemia, hypertension, and/or diabetes mellitus); and (3) patients not classified into subgroups (1) or (2). Another analysis will combine patient groups (1) and (2). A history of cardiovascular diseases (ICD-10 I00-I99) will be defined as at least one CV diagnosis during the one-year pre-index period.

One subgroup analysis will be performed in patients with ≥3 years of available follow-up time (instead of the 2 years that are guaranteed by study design). It is expected that the relative proportion of long-term users (i.e. ≥2 years) will be increased in this subgroup.

In the EU, initiation of eptinezumab treatment is approved for patients who have at least 4 migraine days per month (i.e, ≥12 migraine days in the three-month period prior to the index date). One subgroup analysis will be based on acute migraine medication prescriptions/dispensations during the 3 months prior to the index date (≥12 DDDs vs. <12 DDDs of acute mig medications). Acute migraine medications (i.e., triptans, ergotamines) are listed in Annex III / Panel 5.

If feasible by sample size, other subgroup analyses will be performed based on prior exposure to preventive migraine medications (i.e. switchers vs. new users), and based on the eptinezumab dose most often used by the respective patient (100 mg vs. 300 mg).

Cohort balancing will be repeated in all subgroups before the respective analyses.

9.7.7 Meta-Analyses

Meta-analyses of the risk estimates (hazard ratios) from the database specific analyses will be performed based on established methods also used by the Cochrane collaboration [Deeks JJ 2010]. As the number of health care databases involved in this study will most probably be less than 5, it is planned to use fixed-effects models for pooling [Jackson D 2017]. Measures of heterogeneity (e.g. I^2) will be displayed and discussed. One of the analyses will evaluate if risk estimates from the US database differ from pooled risk estimates of European databases.

The results of the meta-analyses will be included in the final combined study report that summarizes the results of all individual database analyses.

9.7.8 Missing data

Given the difficulty to identify missing data in healthcare databases, missing data will not be imputed. The absence of a disease record, for instance, assumes the condition is absent. However, for some conditions this leads to misclassification if the presence or absence of a condition is not systematically captured with medical claims. This may particularly be an issue for life-style habits such as smoking. It is assumed that any misclassification arising from missing data will affect the study cohorts equally (i.e., non-differential misclassification), and any directional bias because of missing data is not expected.

9.8 Quality control

Database and/or institution specific standard operation procedures will be followed to ensure data quality and integrity of the underlying data source and the retrieved study data sets. This includes procedures to ensure correct data retrieval and data processing, quality checks of the program code, safe and confidential storage and archiving of study data and statistical programming, and documentation of study procedures and analyses (including writing of study protocols, analysis plans, and study reports). All study results will be independently reviewed by database owners / vendors and Lundbeck representatives.

9.9 Limitations of the research methods

A number of limitations are expected in this observational database study. In addition to the usual limitations of observational research (e.g. residual confounding), the following specific aspects need to be considered:

- Even though the database specific study protocols will be aligned to this master study protocol as far as possible, exact outcome definitions may differ between health care databases due to differences in coding schemes, coding habits, or the respective health system. However, it is expected that the impact on *relative* effect measures (e.g. hazard ratios) is rather low and meta-analyses for these measures are still valid. Measures of heterogeneity (e.g. I^2) will be displayed and discussed.

- The outcome of CV death will not be directly available in the ARS and GePaRD databases and thus proxy definitions will have to be used (i.e. cardiovascular event with timely related death from any cause). Details on these proxy definitions will be included in the database specific study protocols for ARS and GePaRD. Any differences between the outcome definitions in the databases will be summarized and discussed in the final combined study report along with the results of the meta-analyses.

- Eptinezumab is expected to be channelled to patients with severe migraine and high attack frequency. It may thus be challenging to identify a suitable comparator group of subjects not exposed to CGRP-targeting preventive migraine therapies. This will be evaluated in

the process of cohort balancing (section 9.7.3) and discussed in the database specific study reports, as well as the final combined study report.

- In all databases included, there is no direct link between a prescription / dispensation of a preventive migraine medication and the actual indication of use. This complicates defining the exposure of primary interest. For instance, it would be unknown if a patient with migraine and hypertension initiates a betablocker therapy for hypertension or for migraine attack prevention (or both). The analyses will thus consider only drugs as migraine preventive therapies that are classified as having evidence level A or B [Silberstein 2012; Simpson DM 2016], or that are recommended as first, second, or third line therapies [Eigenbrodt AB 2021].

- DDDs are used for the estimation of person times exposed to the exposures of special interest. There is uncertainty on this approximation, as it is influenced by the actually used daily dose and the treatment adherence (e.g. days on which the patient forgot to take the medication). To address this uncertainty, a rather broad grace period of 60 days between the estimated end of the available drug supply and the next prescription/dispensation is allowed in the definition of continued use. In addition, the grace period of 60 days will be modified in a sensitivity analysis (to 0 days, 30 days and to 90 days) to evaluate the impact of this methodological aspect.

- As one of the study objectives is to evaluate the impact of a known history of cardiovascular diseases on the long-term CV risk in patients using eptinezumab, concurrent treatment with drugs that are often used in CV patients may occur. This includes drugs that are also used as preventive migraine medications (e.g. betablocker). Patients in the eptinezumab cohort may thus be co-treated with such drugs that are also used as comparator drugs in the MEC cohort. As the analyses will be adjusted for baseline patient characteristics (including pre-treatment with CV drugs), it is not expected that this will bias the comparisons.

- The identification of patients with migraine in healthcare databases might be difficult. For patients with a migraine diagnosis who are treated with eptinezumab (EE cohort), it can be expected that nearly 100% will be migraine patients (due to the approved indication of eptinezumab). However, the preventive migraine therapies in the primary control cohort (MEC) are mainly used for other indications (e.g. depression, CV diseases, epilepsy). Requiring additional prescription history of migraine specific drugs (e.g. triptans) as an inclusion criterion is not adequate as this may lead to pre-selection of a certain subset of patients (e.g. because triptans are contraindicated in some important CV diseases). Instead it is expected that the cohort balancing approach will lead to an implicit selection (or higher weighting) of suitable control patients in the comparator cohorts.

- It cannot be excluded that certain drugs used as preventive migraine therapies in the MEC cohort may affect the risk of CV outcomes. Given that eptinezumab and the preventive migraine therapies in the MEC cohort represent treatment alternatives to be compared, this is considered acceptable.

- Potential market access issues and consideration of eptinezumab in clinical guidelines may affect the use of eptinezumab in clinical practice and potentially delay the inclusion of a sufficient number of patients into the EE cohort. Patient numbers will be monitored and reported in the Study Progress Report, along with any potential measures for this PASS.

- Diagnoses originating from general practice will be available in GePaRD (Germany), but not in the databases from Denmark or Italy. This represents a limitation in terms of completeness of data and potential residual confounding for the databases from Denmark or Italy. However, it is expected that considering prior CV drug usage will be sufficient to allow appropriate cohort balancing. In addition, information on CV diseases that are diagnosed during a hospitalisation will be available for all databases in this PASS.

- A proxy to define the severity of migraine was added to identify patients who had at least 4 migraine days per month. There is currently no information on the positive predictive value and negative predictive value of this proxy to identify such patients. Due to the lack of a gold standard in the healthcare databases, it will also not be possible to estimate the positive and negative predictive values of this proxy within the planned study. It is considered likely, however, that most patients with this characteristic have received acute migraine medication prescriptions/dispensations for at least 12 DDDs in the previous 3 months.

- In all databases, there is no information on lifestyle behaviour, smoking or alcohol exposure not leading to a diagnosis, and type or severity of migraine symptoms. It is, however, expected that the available information from diagnoses etc. will be sufficient to control for potential confounding from these patient characteristics.

9.10 Other aspects

None.

10 Protection of human subjects

Data protection for the data stored in the health care databases will be ensured according to the respective national and institutional regulations and requirements.

Data will be processed in accordance with the specifications outlined by the Danish Data Protection Agency to ensure that requirements regarding personal data protection are met. If an external organisation will process data on behalf of Lundbeck, a contractual procedure will be signed between Lundbeck and the external organisation to ensure compliance with the abovementioned legislation.

Denmark: Danish National Registers

The rules regulating the processing of personal data in electronic and manual registers are laid down in The Act on Processing of Personal Data (Act No. 429 of 31 May 2000 with amendments) (Thygesen et al. 2011). Individual level data from Statistics Denmark is not delivered to any external firm, institution, or person. Instead, datasets and linkages between datasets constructed at Statistics Denmark are stored at Statistics Denmark. Researchers employed at specific authorised environments can establish remote online access to these datasets stored at Statistics Denmark (Thygesen et al. 2011). Although researcher may get access to rather detailed individual level data, they are only allowed to publish statistical analyses and results at an aggregate level where no single person or enterprise may be identified. For security reasons, only researchers employed at authorised research institutions can get access to individual level data at Statistics Denmark.

Germany: German Pharmacoepidemiological Research Database (GePaRD)

Data contained in the GePaRD are legally still owned by the respective statutory health insurance (Haug et al. 2021). Access to the database is granted only at BIPS in the context of approved research projects. All patient-level data is pseudonymized before it is transferred from a third party trust center to BIPS. Only aggregate level analyses and results are allowed to be transferred and published. All involved health insurances, the Federal Office for Social Security, and the Senator for Science, Health, and Consumer Protection in Bremen have to approve the use of GePaRD for a specific research project. According to the Ethics committee of the University of Bremen, studies based on GePaRD are exempt from institutional review board approval (Haug et al. 2021).

Italy: Agenzia Regionale di Sanità della Toscana (ARS)

All data transferred to ARS are pseudonymized with a regional identifier (Gini R 2021). According to regional law, ARS can execute studies after approval of the control board of the Regional Council. Unless linkage with external data sources is planned, no approval from an Ethics Committee is necessary. Person level data are not transferred from ARS, but only aggregated level analyses and results.

USA: Merative MarketScan Database

The Merative MarketScan Database database contains de-identified individual-specific details for those covered by 1 of over 300 contributing employers that sponsor private health insurance, as well as data on both the spouses and the dependents of the employees (Kulaylat et al. 2019). Some patient characteristics such as race or income are not included in the database. The database ensures HIPAA (US Health Insurance Portability and Accountability Act) compliance through rigorous measures to ensure protection of patient privacy, and all data are de-identified to users who obtain access to the database (Kulaylat et al. 2019).

11 Management and reporting of adverse events/adverse reactions

This study does not include primary data collection from patients and therefore adverse event/reactions are not collected.

12 Plans for disseminating and communicating study results

12.1 Study progress report

Database specific study progress reports will be produced after 2 years of data since the first recorded use of eptinezumab have been accumulated in the respective health care databases. The reports will be prepared by the CRO or the respective vendor, will be sent to Value Evidence and Patient Insights and to Global Pharmacovigilance (GPV) at H. Lundbeck A/S and stored in accordance with Lundbeck standard operational procedure. Lundbeck A/S will summarize the findings of the database specific study progress reports in a PASS Summary Progress Report once the study progress reports of all databases were received. The study progress reports will include descriptive analyses of patients in all study cohorts identified so far (e.g. baseline characteristics including CV disease status and CV risk factors) and numbers of patients in the subgroups defined by their baseline cardiovascular risk status (section 9.7.6). For patients exposed to eptinezumab in the study inclusion period, the analyses will be stratified by inclusion into the EE cohort (yes/no), and details on the reasons for study exclusion will be provided for all patients not included into the EE cohort. The PASS Summary Progress Report will discuss the status of the project considering the study objectives and conclude if any measures are considered necessary (e.g. inclusion of additional healthcare databases to increase study power).

12.2 Final study report

Upon completion of the study, database specific study reports will be prepared by the CRO or the respective vendor. The report will be sent to Value Evidence and Patient Insights and to Global Pharmacovigilance (GPV) at H. Lundbeck A/S and stored in accordance with Lundbeck standard operational procedure. Lundbeck A/S will summarize the findings of the database specific study reports in a final PASS Summary Report. This report will also include the results of the meta-analyses (section 9.7.7).

12.3 Publications

Lundbeck intends to use data from this study to prepare peer-review publications and other scientific communications such as abstracts, posters, and podiums presentations.

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Annex I

List of Stand-alone Documents

No.	Document Reference No.	Date	Title
1	Not yet defined	Not yet defined	Protocol / analysis plan of Danish database
2	Not yet defined	Not yet defined	Protocol / analysis plan of German database
3	Not yet defined	Not yet defined	Protocol / analysis plan of Italian database
4	Not yet defined	Not yet defined	Protocol / analysis plan of US database

Annex II

ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols

Study title: Long-term cardiovascular safety and real-world use of eptinezumab. An observational, historical cohort study of patients initiating eptinezumab in routine clinical practice.

EU PAS Register® number: N/A

Study reference number (if applicable): 19756N

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7, 8
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or sub-group to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.4
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.4
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☐	☐	☒	
4.2.3 Country of origin	☐	☐	☒	
4.2.4 Disease/indication	☒	☐	☐	
4.2.5 Duration of follow-up	☒	☐	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.7.4
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Limitations of outcome measurement are discussed in the limitations section (9.9)

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Limitations in relation to information bias are discussed in the limitations section (9.9)

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.6

Comments:

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

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.4

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.6
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8

Comments:

Study results will be independently reviewed by database owners and Lundbeck representatives

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.7.5, 9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5, 9.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: 10/August/2022

Signature: _____

Annex III

Code lists

The code lists in this annex are reference lists for the respective database specific study protocol, and may need to be adapted to the respective national coding schemes etc. Such adaptions would be specified in the database specific study protocols. It is planned to specify only drugs in the database specific study protocols that are approved and available in the respective country (during the study period).

Panel 4. ATC codes for preventive migraine medications, as used in the cohort definitions of the EE and MEC cohort

Drug name	ATC Code[1]	WHO DDD	Usual administration schedule
Eptinezumab	N02CD05	-	Every 12 weeks
Amitriptyline	N06AA09	75 mg	Daily
Topiramate	N03AX11	300 mg	Daily
Valproate/Divalproex	N03AG01	1500 mg	Daily
Atenolol	C07AB03	75 mg	Daily
Bisoprolol	C07AB07	10 mg	Daily
Metoprolol	C07AB02	150 mg	Daily
Propranolol	C07AA05	160 mg	Daily
Candesartan	C09CA06	8 mg	Daily
Flunarizine	N07CA03	10 mg	Daily
OnabotulinumtoxinA (Botulinum toxin)	M03AX01	-	Every 12 weeks

[1]ATC codes for combination products (e.g. metoprolol in combination with a diuretic) are *not* considered in this list, as these are not used for migraine prevention but other indications.

Panel 5. ATC codes for migraine medications, as used for exclusion criteria and pre-index exposure assessment[1]

Drug name	ATC Code(s)[2]
Preventive treatments	
Eptinezumab	N02CD05
Erenumab	N02CD01
Galcanezumab	N02CD02
Fremanezumab	N02CD03
Rimegepant	N02CD06
Amitriptyline	Mono: N06AA09; Combinations: N06CA01
Venlafaxine	N06AX16
Topiramate	N03AX11
Valproate/Divalproex	N03AG01
Atenolol	Mono: C07AB03; Combinations: C07FB03; C07CB03; C07CB53; C07BB03; C07DB01; C07AB11
Bisoprolol	Mono: C07AB07; Combinations: C07FX04; C07FB07; C07BB07; C09BX02; C09BX04; C09BX05
Metoprolol	Mono: C07AB02; Combinations: C07FX03; C07FB13; C07FB02; C07FX05; C07CB02; C07BB02; C07BB52
Propranolol	Mono: C07AA05; Combinations: C07AA05; C07BA05
Nadolol	C07AA12; Combinations: C07BA12

Drug name	ATC Code(s)[2]
Timolol	Mono: C07AA06; Combinations: C07BA06; C07DA06
OnabotulinumtoxinA (Botulinum toxin)	M03AX01
Lisinopril	Mono: C09AA03; Combinations: C09BB03; C09BA03; C10BX07
Candesartan	Mono: C09CA06; Combinations: C09DB07; C09DA06; C09DX06
Flunarizine	
Clonidine	Mono: C02AC01; N02CX02; Combinations: C02LC01; C02LC51
Guanfacine	C02AC02
Carbamazepine	N03AF01
Nebivolol	Mono: C07AB12; Combinations: C07FB12; C07BB12; C09DX05
Pindolol	Mono: C07AA03; Combinations: C07CA03
Cyproheptadine	R06AX02
Acetazolamide	-
Picotamide	B01AC03
Fluvoxamine	N06AB08
Fluoxetine	Mono: N06AB03; Combinations: N06CA03
Gabapentin	N03AX12
Protriptyline	N06AA11
Bisoprolol	Mono: C07AB07; Combinations: C07FX04; C07FB07; C07BB07; C09BX02; C09BX04; C09BX05
Nicardipine	Nicardipine
Nifedipine	Mono: C08CA05; Combinations: C07FB03; C08GA01; C08CA55
Nimodipine	C08CA06
Verapamil	Mono: C08DA01; Combinations: C09BB10; C08DA51
Cyclandelate	C04AX01
Acute treatments	
Sumatriptan	N02CC01
Naratriptan	N02CC02
Zolmitriptan	N02CC03
Rizatriptan	N02CC04
Almotriptan	N02CC05
Eletriptan	N02CC06
Frovatriptan	N02CC07
Rimegepant	N02CD06
Dihydroergotamine	Mono: N02CA01; Combinations: N02CA51
Ergotamine	Mono: N02CA02; Combinations: N02CA52; N02CA72
Methysergide	N02CA04
Lisuride	N02CA07

[1]This table will be adapted in the country-specific study protocol to consider only drug exposures that were available in the respective database.

[2]As this list is intended to identify e.g. exposure prior to the index date or to define exclusion criteria, codes for combination products (e.g. metoprolol in combination with a diuretic) *are* included in this list. For drugs without DDDs that are of relevance for the respective database (i.e. approved and marketed during the study period),

country specific usual daily doses will be specified as DDDs in the database specific study protocols (as derived from the respective EU and/or national Summary of Product Characteristics).

Panel 6. ATC codes for Non-steroidal anti-inflammatory drugs and other analgesics[1]

Drug name	ATC Code(s)	DDDs[2]
Mofebutazone	M01AA02	750 mg
Oxyphenbutazone	M01AA03	300 mg
Clofezone	M01AA05	300 mg
Kebuzone	M01AA06	
Indometacin	M01AB01	100 mg
Sulindac	M01AB02	400 mg
Tolmetin	M01AB03	700 mg
Zomepirac	M01AB04	300 mg
Diclofenac	M01AB05	100 mg
Alclofenac	M01AB06	1250 mg
Bumadizone	M01AB07	400 mg
Etodolac	M01AB08	400 mg
Lonazolac	M01AB09	600 mg
Fentiazac	M01AB10	
Acemetacin	M01AB11	120 mg
Difenpiramide	M01AB12	
Oxametacin	M01AB13	
Proglumetacin	M01AB14	
Ketorolac	M01AB15	30 mg
Aceclofenac	M01AB16	200 mg
Indometacin, combinations	M01AB51	100 mg
Diclofenac, combinations	M01AB55	100 mg
Piroxicam	M01AC01	20 mg
Tenoxicam	M01AC02	20 mg
Droxicam	M01AC04	
Lornoxicam	M01AC05	12 mg
Meloxicam	M01AC06	15 mg
Meloxicam, combinations	M01AC56	
Ibuprofen	M01AE01	1200 mg
Naproxen	M01AE02	500 mg
Ketoprofen	M01AE03	150 mg
Fenoprofen	M01AE04	1200 mg
Fenbufen	M01AE05	600 mg
Benoxaprofen	M01AE06	
Pirprofen	M01AE08	400 mg
Flurbiprofen	M01AE09	200 mg
Indoprofen	M01AE10	
Tiaprofenic acid	M01AE11	600 mg
Oxaprozin	M01AE12	900 mg
Ibuproxam	M01AE13	
Dexibuprofen	M01AE14	800 mg

Drug name	ATC Code(s)	DDDs[2]
Flunoxaprofen	M01AE15	
Alminoprofen	M01AE16	
Dexketoprofen	M01AE17	75 mg
Naproxcinod	M01AE18	
Ibuprofen, combinations	M01AE51	
Naproxen and esomeprazole	M01AE52	500 mg
Ketoprofen, combinations	M01AE53	
Naproxen and misoprostol	M01AE56	
Mefenamic acid	M01AG01	1000 mg
Tolfenamic acid	M01AG02	300 mg
Flufenamic acid	M01AG03	500 mg
Meclofenamic acid	M01AG04	
Nabumetone	M01AX01	1000 mg
Niflumic acid	M01AX02	750 mg
Azapropazone	M01AX04	750 mg
Proquazone	M01AX13	900 mg
Orgotein	M01AX14	
Nimesulide	M01AX17	200 mg
Feprazone	M01AX18	
Morniflumate	M01AX22	
Tenidap	M01AX23	
Oxaceprol	M01AX24	
Feprazone, combinations	M01AX68	
Morphine	N02AA01	100 mg (O); 30 mg (P; R)
Opium	N02AA02	
Hydromorphone	N02AA03	20 mg (O); 4 mg (P; R)
Nicomorphine	N02AA04	30 mg
Oxycodone	N02AA05	75 mg (O); 30 mg (P)
Dihydrocodeine	N02AA08	150 mg
Papaveretum	N02AA10	
Oxymorphone	N02AA11	
Morphine, combinations	N02AA51	
Hydromorphone and naloxone	N02AA53	
Oxycodone and naloxone	N02AA55	75 mg
Oxycodone and naltrexone	N02AA56	
Dihydrocodeine, combinations	N02AA58	
Codeine, combinations excl. Psycholeptics	N02AA59	
Codeine, combinations with psycholeptics	N02AA79	
Ketobemidone	N02AB01	50 mg
Pethidine	N02AB02	400 mg
Fentanyl	N02AB03	600 mg (N; SL); 1200 mg (TD)
Pethidine, combinations excl. Psycholeptics	N02AB52	
Pethidine, combinations with	N02AB72	

Drug name	ATC Code(s)	DDDs[2]
psycholeptics		
Dextromoramide	N02AC01	20 mg (O;P); 40 mg (R)
Piritramide	N02AC03	45 mg
Dextropropoxyphene	N02AC04	200 mg (chloride); 300 mg (napsylate)
Bezitramide	N02AC05	15 mg
Methadone, combinations excl. Psycholeptics	N02AC52	
Dextropropoxyphene, combinations excl. Psycholeptics	N02AC54	
Dextropropoxyphene, combinations with psycholeptics	N02AC74	
Pentazocine	N02AD01	200 mg
Phenazocine	N02AD02	3 mg
Buprenorphine	N02AE01	1.2 mg
Butorphanol	N02AF01	12 mg
Nalbuphine	N02AF02	80 mg
Morphine and antispasmodics	N02AG01	
Ketobemidone and antispasmodics	N02AG02	
Pethidine and antispasmodics	N02AG03	
Hydromorphone and antispasmodics	N02AG04	
Dihydrocodeine and paracetamol	N02AJ01	
Dihydrocodeine and acetylsalicylic acid	N02AJ02	
Dihydrocodeine and other non-opioid analgesics	N02AJ03	
Codeine and paracetamol	N02AJ06	
Codeine and acetylsalicylic acid	N02AJ07	
Codeine and ibuprofen	N02AJ08	
Codeine and other non-opioid analgesics	N02AJ09	
Tramadol and paracetamol	N02AJ13	
Tramadol and dexketoprofen	N02AJ14	
Tramadol and other non-opioid analgesics	N02AJ15	
Tramadol and celecoxib	N02AJ16	
Oxycodone and paracetamol	N02AJ17	
Oxycodone and acetylsalicylic acid	N02AJ18	
Oxycodone and ibuprofen	N02AJ19	
Tilidine	N02AX01	200 mg
Tramadol	N02AX02	300 mg
Dezocine	N02AX03	
Meptazinol	N02AX05	1200 mg
Tapentadol	N02AX06	400 mg

Drug name	ATC Code(s)	DDDs[2]
Oliceridine	N02AX07	
Tilidine and naloxone	N02AX51	
Acetylsalicylic acid	N02BA01	3000 mg (O; R); 1000 mg (P)
Aloxiprin	N02BA02	3000 mg
Choline salicylate	N02BA03	3000 mg
Sodium salicylate	N02BA04	3000 mg
Salicylamide	N02BA05	3000 mg
Salsalate	N02BA06	3000 mg
Ethenzamide	N02BA07	3000 mg
Morpholine salicylate	N02BA08	
Dipyrocetyl	N02BA09	3000 mg
Benorilate	N02BA10	3000 mg
Diflunisal	N02BA11	750 mg
Potassium salicylate	N02BA12	7000 mg
Carbasalate calcium	N02BA15	3600 mg
Imidazole salicylate	N02BA16	
Acetylsalicylic acid, combinations excl. Psycholeptics	N02BA51	
Salicylamide, combinations excl. Psycholeptics	N02BA55	
Ethenzamide, combinations excl. Psycholeptics	N02BA57	
Dipyrocetyl, combinations excl. Psycholeptics	N02BA59	
Carbasalate calcium combinations excl. Psycholeptics	N02BA65	
Acetylsalicylic acid, combinations with psycholeptics	N02BA71	
Salicylamide, combinations with psycholeptics	N02BA75	
Ethenzamide, combinations with psycholeptics	N02BA77	
Dipyrocetyl, combinations with psycholeptics	N02BA79	
Phenazone	N02BB01	3000 mg
Metamizole sodium	N02BB02	3000 mg
Aminophenazone	N02BB03	500 mg
Propyphenazone	N02BB04	3000 mg
Nifenazone	N02BB05	
Phenazone, combinations excl. Psycholeptics	N02BB51	3000 mg
Metamizole sodium, combinations excl. Psycholeptics	N02BB52	
Aminophenazone, combinations excl. Psycholeptics	N02BB53	
Propyphenazone, combinations excl. Psycholeptics	N02BB54	3000 mg

Drug name	ATC Code(s)	DDDs[2]
Phenazone, combinations with psycholeptics	N02BB71	
Metamizole sodium, combinations with psycholeptics	N02BB72	
Aminophenazone, combinations with psycholeptics	N02BB73	
Propyphenazone, combinations with psycholeptics	N02BB74	
Paracetamol	N02BE01	3000 mg
Phenacetin	N02BE03	1800 mg
Bucetin	N02BE04	
Propacetamol	N02BE05	6000 mg
Paracetamol, combinations excl. Psycholeptics	N02BE51	
Phenacetin, combinations excl. Psycholeptics	N02BE53	
Bucetin, combinations excl. Psycholeptics	N02BE54	
Paracetamol, combinations with psycholeptics	N02BE71	
Phenacetin, combinations with psycholeptics	N02BE73	
Bucetin, combinations with psycholeptics	N02BE74	
Rimazolium	N02BG02	900 mg
Glafenine	N02BG03	800 mg
Floctafenine	N02BG04	1000 mg
Viminol	N02BG05	
Nefopam	N02BG06	
Flupirtine	N02BG07	400 mg
Ziconotide	N02BG08	12 µg
Methoxyflurane	N02BG09	
Cannabinoids	N02BG10	
Mirogabalin	N02BG11	25 mg
Tanezumab	N02BG12	

[1]This table will be adapted in the country-specific study protocol to consider only drug exposures that were available in the respective database.
[2]For drugs without DDDs that are of relevance for the respective database (i.e. approved and marketed during the study period), country specific usual daily doses will be specified as DDDs in the database specific study protocols (as derived from the respective EU and/or national Summary of Product Characteristics).

Panel 7. ATC codes for other drugs

Drug name / drug class name	ATC Code(s)
Antiepileptics	N03A
Antidepressants	N06A
Antipsychotics	N05A
Benzodiazepines	N05BA

Antiemetics (Metoclopramide, Domperidone, Trimethobenzamide, Prochlorperazine, Promethazine, Dimenhydrinate)[1]	A03FA01; A03FA03; R06AA10; N05AB04; R06AD02; R06AD52; R06AA11
Angiotensin converting enzyme inhibitors (ACEI)	C09A; C09B; C10BX07; C10BX15; C10BX12; C10BX11; C10BX14; C10BX13; C10BX06; C10BX18; C10BX17; C10BX04;
Angiotensin II receptor (AT II) antagonists	C09C; C09D; C10BX10; C10BX16
Calcium channel blockers	C08; C07FB02; C07FB03; C07FB07; C07FB12; C07FB13; C09BB02; C09BB03; C09BB04; C09BB05; C09BB06; C09BB07; C09BB10; C09BB12; C09BX01; C09BX03; C09BX04; C09DB01; C09DB02; C09DB04; C09DB05; C09DB06; C09DB07; C09DB08; C09DB09; C09DX01; C09DX03; C09DX06; C09DX07; C09XA53; C09XA54; C10BX03; C10BX07; C10BX09; C10BX11; C10BX14; C10BX18
Beta-blocking agents	C07
Diuretics	C03; C02L; C07B; C07C; C07D; C08G; C09BA; C09DA
Other antihypertensive drugs	C02
Oral antidiabetics	A10B
Insulin	A10A
Aspirin and other platelet aggregation inhibitors	B01AC
Anticoagulants	B01AA; B01AB
Corticosteroids	H02
Statins	C10AA; C10BX01; C10BA02; C10BA04; C10BX04; A10BH51; C10BA01; C10BX02; C10BA11; C10BA03; C10BA12; C10BX08; C10BX03; C10BA05; C10BA08; C10BX15; C10BX12; C10BX06; C10BX11; C10BX18; A10BH52; C10BX05; C10BX09; C10BA06; C10BA09; C10BX16; C10BA07; C10BX17; C10BX10; C10BX07; C10BX14; C10BX13
Non-statin lipid lowering drugs	C10AB; C10AC; C10AD; A10AX
Nitrates	C01DA
Oral contraceptives	G03A
Postmenopausal hormone replacement therapy	G03C; G03D; G03F

[1]Láinez MJ, García-Casado A, Gascón F. Optimal management of severe nausea and vomiting in migraine: improving patient outcomes. Patient Relat Outcome Meas. 2013;4:61-73.

Panel 8. ICD-10 codes for the primary and secondary outcomes

Outcome	Definition / ICD-10 codes
Non-fatal[1] stroke	I60; I61; I62; I63; I64
Non-fatal ACS	I20.0; I21; I22
CV death	Death with a primary or secondary outcome as the underlying

	cause (as listed in this table)
MACE	Non-fatal stroke; Non-fatal ACS; CV death
Stroke	I60; I61; I62; I63; I64
Ischemic stroke	I63
ACS	I20.0; I21; I22
Transitory ischemic attack (TIA)	G45
Angina pectoris (all subtypes, i.e. independently from coding of stable/instable)	I20; I25.1; I25.9
Percutaneous coronary intervention (PCI)	To be identified via procedure codes
Heart failure	I50; I11.0; I13.0; I13.2; I25.5; I42.0

[1]Non-fatal events are those without recorded death within 30 days of the event occurrence.

[2]If cause-of-death information is not available in the respective health care database, 'CV death' will be identified as one of the primary or secondary outcomes followed by death with 30 days of the event occurrence.

Panel 9. ICD-10 codes for migraine and concomitant diseases

Medical condition	**ICD-10 codes**
Migraine	G43
Migraine without aura	G43.0
Migraine with aura	G43.1; G43.3
Migraine with status migrainosus	G43.2
Cluster headache	G44.0
Vascular headache	G44.1
Tension-type headache	G44.2
Chronic post-traumatic headache	G44.3
Drug-induced headache	G44.4
Other headache syndromes	G44.8
Raynaud syndrome	I73.0
Inflammatory diseases of the CNS	G00-G09
Systemic atrophies primarily affecting the central nervous system	G10-G14
Extrapyramidal and movement disorders	G20-G26
Other degenerative diseases of the CNS	G30-G32
Demyelinating diseases of the CNS	G35-G37
Epilepsy	G40
Status epilepticus	G41
TIA	G45
Vascular syndromes of brain in cerebrovascular diseases	G46
Sleep disorders	G47
Nerve, nerve root and plexus disorders	G50-G59
Polyneuropathies and other disorders of the peripheral nervous system	G60-G64
Diseases of myoneural junction and muscle	G70-G73

Medical condition	ICD-10 codes
Cerebral palsy and other paralytic syndromes	G80-G83
Other disorders of the nervous system	G90-G99
Organic, including symptomatic, mental disorders	F00-F09
Mental and behavioural disorders due to psychoactive substance use	F10-F19
Schizophrenia, schizotypal and delusional disorders	F20-F29
Mood [affective] disorders	F30-F39
Neurotic, stress-related and somatoform disorders	F40-F48
Behavioural syndromes associated with physiological disturbances and physical factors	F50-F59
Disorders of adult personality and behaviour	F60-F69
Mental retardation	F70-F79
Disorders of psychological development	F80-F89
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	F90-F98
Unspecified mental disorder	F99-F99
Malignant neoplasm	C00-C97
Metastatic malignant neoplasm	C77; C78; C79
Hypothyroidism	E02
Hyperthyroidism	E05
Inflammatory polyarthropathies	M05-M14
Arthrosis	M15-M19
Other joint disorders	M20-M25
Myocardial infarction	I21; I22; I23; I25.2
Chronic ischemic heart disease	I20; I21; I22; I23; I24; I25
Chronic obstructive pulmonary disease	J44
Heart failure	I50; I11.0; I13.0; I13.2
Stroke	I60; I61; I62; I63; I64; I69.1; I69.2; I69.3; I69.4
Cerebrovascular disease and pre-cerebrovascular disease, not resulting in cerebral infarction	I65; I66; I69.8
Other cerebrovascular diseases	I67
Arterial hypertension and hypertensive disease	I10; I11; I12; I13; I14; I15
Arterial fibrillation and flutter	I48
Peripheral arterial disease	I70
Pulmonary heart disease / diseases of pulmonary circulation	I26; I27; I28
Hyperlipidemia	E78.0, E78.1, E78.2, E78.3, E78.4, E78.5
Diabetes mellitus Type 1	E10
Diabetes mellitus Type 2	E11
Diabetes mellitus not specified as type 1 or 2	E12; E13; E14; O24
Diabetes mellitus with organ damages	G59.0; G63.2; H28.0; H36.0; M14.2; N08.3
Chronic liver diseases	B18; E74.0; E76.1; K70; K71.3; K71.4; K71.5; K71.7; K72; K73; K74; K75.4; K75.8; T86.4
Kidney failure	K76.7; N17; N18; N19; O90.4

Medical condition	ICD-10 codes
Obesity	E66

Panel 10. Modified migraine criteria based on Yusuf 2018

Criteria[1]
Migraine diagnosis (ICD-10 G43) associated with an inpatient stay
Migraine diagnosis (ICD-10 G43) associated with a neurologist visit
Two migraine diagnoses (ICD-10 G43) associated with an outpatient physician or ED visit 7-180 days apart
One migraine diagnosis (ICD-10 G43) associated with an outpatient physician visit or ED visit AND one claim for a dispensing/administration of a migraine-specific treatment (see Panel 11 below) 7-180 days apart
Two claims for a dispensing/administration of a migraine-specific treatment (see Panel 11 below) 7-180 days apart

[1]At least one of these criteria has to be fulfilled

Panel 11. ATC codes for migraine-specific treatments

Drug name	ATC Code
Eptinezumab	N02CD05
Erenumab	N02CD01
Galcanezumab	N02CD02
Fremanezumab	N02CD03
Sumatriptan	N02CC01
Naratriptan	N02CC02
Zolmitriptan	N02CC03
Rizatriptan	N02CC04
Almotriptan	N02CC05
Eletriptan	N02CC06
Frovatriptan	N02CC07
Lasmiditan	N02CC08
Rimegepant	N02CD06