



Study Protocol P3-C1-009

02/07/2024

Version 3.1

	D2.2.3 - Study Protocol for P3-C1-009	
	Authors: J.Politi, K.Verhamme	Version: 3.1
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DOCUMENT HISTORY

VERSION	DATE	DESCRIPTION
V1.0	07/06/2024	Initial version for EMA review
V2.0	26/06/2024	Updated version following EMA's assessment
V3.0	02/07/2024	Archiving version submitted to EMA
V3.1	02/07/2024	Final version uploaded on HMA-EMA Catalogue

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Study Title	DARWIN EU® - CGRP antagonists - treatment patterns and users characteristics
Protocol version identifier	V3.1
Date of last version of protocol	02/07/2024
EU PAS register number	EUPAS1000000240
Active substance	• Erenumab • Eptinezumab • Fremanezumab • Galcanezumab Therapeutic Drug class: N02CD
Medicinal product	Aimovig; Vyepti; Ajovy; Emgality
Research question and objectives	The aim of this study is to characterise individuals treated with CGRP antagonists for migraine. The specific study objectives are: 1. Characterisation of patients newly treated with CGRP antagonists (i.e. new user cohort) in terms of demographics, risk factors for erectile dysfunction, insomnia and hypertension and concomitant medications taken at index date. This characterisation will be stratified by sex. 2. Characterisation of treatment with CGRP antagonists in a cohort of new users in terms of duration of treatment 3. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population (irrespective of treatment) stratified by age groups and sex 4. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population initiating treatment with CGRP antagonists or other prophylactic treatments (anti-epileptics, TCA antidepressants, Beta-blockers, tricyclic antidepressants, calcium channel blockers), stratified by age groups and sex. 5. Incidence rate of erectile dysfunction, insomnia, and hypertension in the general population (as reference) stratified by age groups and sex
Country(ies) of study	This study will include 4 databases, representing 4 countries in Europe: • Spain: VID • Finland: FinOMOP - HILMO • Germany: IQVIA DA Germany • Croatia: NAJS
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LIST OF ABBREVIATIONS

Abbreviation	Name
CGRP	Calcitonin gene related peptide
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DOI	Declaration Of Interests
DQD	Data Quality Dashboard
ED	Erectile dysfunction
FINOMOP-HILMO	Finnish Care Register for Health Care
GP	General Practitioner
EHR	Electronic Health Record
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
NAJS	Croatian National Public Health Information System
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
PDE5	Phosphodiesterase-5
PRAC	Pharmacovigilance Risk Assessment Committee
PTSD	Post-traumatic stress disorder
SNOMED	Systematized Nomenclature of Medicine
SNRI	Serotonin and norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
VID	Valencia Health System Integrated Dataset

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1. TITLE

DARWIN EU® - CGRP antagonists - treatment patterns and user characteristics

2. RESPONSIBLE PARTIES – STUDY TEAM

STUDY TEAM ROLE	NAMES	ORGANISATION
Study Project Manager/Principal Investigator	Julieta Politi	Erasmus MC
	Katia Verhamme	Erasmus MC
Data Scientist	Ross Williams	Erasmus MC
	Maarten van Kessel	Erasmus MC
	Cesar Barbosa	Erasmus MC
	Ger Inberg	Erasmus MC
Epidemiologist/ Clinical Domain Expert	Julieta Politi	Erasmus MC
	Katia Verhamme	Erasmus MC
Data Partner*	Names	Organization
FINOMOP - HILMO	Tuomo Nieminen Tiina Wahlfors	THL
IQVIA DA Germany	James Brash	IQVIA
	Isabella Kaczmarczyk	
	Dina Vojinovic	
NAJS	Jakov Vukovic	Croatian Institute of Public Health
VID	Gabriel Sanf��lix Gimeno	FISABIO
	Francisco S��nchez S��ez	

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

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3. ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY PROTOCOL)

Title

DARWIN EU® - CGRP antagonists - treatment patterns and users characteristics

Rationale and Background

Galcanezumab, erenumab, and eptinezumab are monoclonal antibodies that interfere with the signalling pathway of the Calcitonin-Gene-Related Peptide (CGRP), which is involved in the pathophysiology of migraine. These novel therapies are indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month. The PRAC recently discussed signals on a potential association between the use of these drugs and insomnia, erectile dysfunction, and increased blood pressure.

Through this study, we aim to characterise patients with migraine newly treated with one of these drugs, in order to contextualise the signal assessment. In addition, we aim to investigate the incidence rate of erectile dysfunction, insomnia and increased blood pressure in a population of newly diagnosed migraine patients, and in the general population.

Research Question and Objectives

The aim of this study is to characterise individuals treated with CGRP antagonists for migraine.

The specific study objectives are:

1. Characterisation of patients newly treated with CGRP antagonists (i.e. new user cohort) in terms of demographics, risk factors for erectile dysfunction, insomnia, hypertension, and concomitant medications taken at index date. The characterisation will be stratified by sex.
2. Characterisation of treatment with CGRP antagonists in a cohort of new users in terms of duration of treatment.
3. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population (irrespective of treatment) stratified by age groups and sex.
4. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population initiating treatment with CGRP antagonists or other prophylactic treatments (anti-epileptics, TCA antidepressants, Beta-blockers, tricyclic antidepressants, calcium channel blockers), stratified by age groups and sex.
5. Incidence rate of erectile dysfunction, insomnia, and hypertension in the general population (as reference) stratified by age groups and sex

Research Methods

Study design

Patient-level drug utilisation study.

Study Period

From January 1st, 2018 (first EU approval) to 31st December 2023 (when the study end date is not reached in a data source, the study end for that data source will be the last date of available data)

Population

For this study, we will have different cohorts, namely:

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- Population of individuals newly initiating first treatment with any of the CGRP antagonists of interest (objectives 1 and 2).
- Population of individuals with newly diagnosed migraine (objectives 3 and 4).
- General population, consisting of all individuals in the database with at least 365 days of database history (objective 5).

Data sources

1. Finnish Care Register for Health Care (FINOMOP-HILMO), Finland
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Croatian National Public Health Information System (NAJS), Croatia
4. Valencia Health System Integrated Dataset (VID), Spain

Exposure of interest

CGRP antagonist use. Specifically, erenumab, eptinezumab, fremanezumab, and galcanezumab

Outcomes of interest:

- Erectile dysfunction: Incident events during the study period
- Insomnia: Incident events during the study period
- Hypertension: incident events during the study period (only clinical diagnosis will be considered and no measurements)

The index dates will be different for the different cohorts of interest and will consist of:

- For the population being exposed to the CGRP antagonists of interest: Date of first treatment of CGRP during the study period
- For the newly diagnosed migraine population: date of new diagnosis of migraine (being diagnosed during study period)
- For the cohort of newly diagnosed migraine initiating treatment with prophylactic treatment, the index date is the date of the first prescription of the prophylactic treatment class (CGRP antagonist, beta-blockers, anti-epileptics, tricyclic antidepressants, calcium channel blocker)
- For the general population: date on which the patient fulfils inclusion criteria to be included in the study (i.e. one year of database history and present in the database within 2018-2023)

Data analyses

Characterisation of individuals newly initiating treatment with CGRP antagonists will be done using the *CohortCharacteristics* and *CohortDiagnostics* R packages. For the second objective, we will use the *DrugUtilisation* analytical pipeline to characterise CGRP antagonist use, including counts (%) for each substance, duration of treatment, and concomitant medications taken at index date. For the calculation of the incidence rates of the outcomes of interest, the *IncidencePrevalence* R package will be used, stratified by age and sex. A minimum cell counts of 5 will be used when reporting results, with any smaller count reported as "<5". All analyses will be reported by country/database, overall and stratified by sex, when possible (minimum cell count reached).

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4. AMENDMENTS AND UPDATES

NUMBER	DATE	SECTION OF STUDY PROTOCOL	AMENDMENT OR UPDATE	REASON

5. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	7/06/2024
Final Study Protocol	1/07/2024
Creation of Analytical code	June 2024
Execution of Analytical Code on the data	July/August 2024
Draft Study Report	19/08/2024
Final Study Report	15/09/2024

6. RATIONALE AND BACKGROUND

Migraine is a chronic and often debilitating disease affecting around 15% of adult subjects¹⁻³, and one of the top 20 causes of disability worldwide¹. It is typically characterised by recurrent disabling attacks of headache, accompanied by photo- and phonophobia and/or severe nausea and/or vomiting and other accompanying symptoms, including aura⁴.

The aetiology of migraine is considered multifactorial. Some monogenic variants have been described, although rare. Spreading depolarisation probably causes aura and possibly also triggers trigeminal sensory activation, the underlying mechanism for the headache. The pathophysiology is not completely understood, although calcitonin gene-related peptide (CGRP) has been identified to play a major role⁵:

Management of migraine attacks usually requires drugs to relieve pain. Still, in some patients, because of frequency, severity and impact on quality of life, preventive treatment is required to reduce the occurrence of acute attacks and the need for pain relief medication. Preventive treatments include calcium-channel antagonists, antidepressants, antiepileptics, and anti-hypertensives developed for indications other than migraine and subsequently repurposed for migraine based on clinical studies⁶⁻⁹. However, efficacy is often insufficient, and there is a delay between the start of therapy and its effect. Poor tolerability and side effects are important limitations of available preventive treatments and may hinder treatment adherence. In this sense, treatment adherence is low, dropping to 20% after one year¹⁰. Additionally, comorbidities, such as depression, epilepsy, stroke and myocardial infarction, limit the use of some prophylactic drugs.

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Monoclonal antibodies acting on the CGRP or on its receptor are new drugs used to prevent migraine by interfering in the signalling pathway of the CGRP, which is involved in the pathophysiology of migraine. These drugs, approved for their use in migraine prophylaxis in adults who have at least 4 migraine days per month, target either the calcitonin gene-related peptide receptor (erenumab) or the calcitonin gene-related peptide (eptinezumab, fremanezumab, and galcanezumab)¹¹⁻¹³. Galcanezumab and erenumab and fremanezumab are available in pre-filled pens for subcutaneous use once a month (every 4 weeks), while eptinezumab is formulated as a concentrate for intravenous infusion solution and administered once every three months in an outpatient setting (every 12 weeks).

CGRP is known to be a potent vasodilator⁵. In addition to its role in migraine, CGRP is involved in other physiological processes, such as regulating blood pressure^{14 15}, having chronotropic and inotropic effects on the heart, and maintaining cerebral and cardiovascular homeostasis¹⁶.

Erectile dysfunction (ED) is the inability to get and keep a penis erection; it is a complex event involving the psychological, neurological, endocrine, vascular, and anatomical systems aspects. Neither ED nor any sexual dysfunctions are listed in the Summaries of Product Characteristics of any CGRP antagonists. There is some biological plausibility about the relation of these molecules with ED in the scientific literature, with a small number of case reports in males, while in females, there are some reports of sexual dysfunction^{17 18}.

Insomnia most often represents an individual's report of difficulty with sleep, which could entail difficulties falling asleep, staying asleep, or experiencing nonrestorative sleep despite adequate sleep circumstances, which can impact daily activities. Sleep disorders such as insomnia can affect migraine attack frequency. Insomnia is not listed in the Summaries of Product Characteristics of any CGRP antagonists. Erenumab does not cross the blood-brain barrier, so a directly mediated effect would be unlikely¹⁹. Some literature suggests an improvement in sleep quality among CGRP antagonist users^{19 20}.

Elevated blood pressure, also referred to as hypertension, occurs when the force of blood flowing through the blood vessels is consistently too high. The normal range is usually less than 120mmHg for systolic blood pressure and less than 80mmHg for diastolic blood pressure. Elevated blood pressure can lead to serious health problems, including heart attack or stroke. Elevated blood pressure is not listed in the Summaries of Product Characteristics of any CGRP antagonists. However, some literature suggests increased systolic blood pressure (compared to baseline) in individuals treated with erenumab²¹.

The PRAC is evaluating signals on a potential association between the use of these drugs and insomnia, erectile dysfunction, and increased blood pressure, all based on spontaneous case reports.

Through this study, we aim to characterise patients with migraine newly treated with this drug class, including the prevalence of risk factors for these events. In addition, we aim to investigate the incidence rate of erectile dysfunction, insomnia and increased blood pressure in a population of newly diagnosed migraine patients, and in the general population in order to contextualize the signal assessment.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of this study is to characterise individuals treated with CGRP antagonists for migraine.

The specific study objectives are:

1. Characterisation of patients newly treated with CGRP antagonists (i.e. new user cohort) in terms of demographics, risk factors for erectile dysfunction, insomnia and hypertension and concomitant medications taken at index date. This characterisation will be stratified by sex.

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2. Characterisation of treatment with CGRP antagonists in a cohort of new users in terms of duration of treatment.
3. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population (irrespective of treatment) stratified by age groups and sex.
4. Incidence rate of erectile dysfunction, insomnia, and hypertension in a newly diagnosed migraine population initiating treatment with CGRP antagonists or other prophylactic treatments (anti-epileptics, TCA antidepressants, Beta-blockers, tricyclic antidepressants, calcium channel blockers), stratified by age groups and sex.
5. Incidence rate of erectile dysfunction, insomnia, and hypertension in the general population (as reference) stratified by age groups and sex

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective 1 and 2:	To characterise individuals newly treated with CGRP antagonists stratified by sex and database. Characterisation will be done in terms of demographics, risk factors of the outcomes, concomitant medication, large scale characterisation and duration of use of CGRP antagonists.
Hypothesis:	N/A
Population (<i>mention key inclusion-exclusion criteria</i>):	Individuals starting first treatment with CGRP antagonist between 2018 and 2023 (new user's cohort)
Exposure:	Exposure to CGRP antagonists of interest
Comparator:	N/A
Outcome:	N/A
Time (<i>when follow up begins and ends</i>):	2018-2023. Date of first exposure to CGRP antagonists of interest until date of: 1) censoring or loss to follow-up, 2) end of data availability, or 3) the end date of exposure (whichever occurs first).
Setting:	Outpatient setting from 4 databases currently in DARWIN EU® covering 4 European countries
Main measure of effect:	Counts, proportions

B. Secondary research question and objective.

Objective 3, 4, and 5:	To estimate the incidence rate of erectile dysfunction, insomnia, and hypertension among individuals newly diagnosed with migraine, stratified by prophylactic treatment class, and in the overall population
Hypothesis:	N/A
Population (<i>mention key inclusion-exclusion criteria</i>):	Incident migraine cohort: Individuals with an incident migraine diagnosis during the study period. The population for objective 4 will be nested in this cohort (incident migraine), stratified by

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	prophylactic treatment class. General population cohort: All individuals within the study period
Exposure:	N/A
Comparator:	N/A
Outcome:	Erectile dysfunction, insomnia, and hypertension
Time (<i>when follow up begins and ends</i>):	Follow-up: (Objective 3) Incident migraine cohort: Follow-up will start from the date of the first entry (incident migraine diagnosis during the study period); until the earliest of the following: 1) censoring or loss to follow-up, 2) end of data availability, or 3) the first occurrence of the outcome of interest. (Objective 4) Incident migraine stratified by treatment class: Follow-up will start from the date of the first entry (first start of first prophylactic treatment class of interest following incident migraine diagnosis), and will continue up until the first of the following: 1) one-year from index date (as maximum), 2) censoring or loss to follow-up, 3) end of data availability, or 4) the first occurrence of the outcome of interest. As patients might be treated with different prophylactic treatment for the first-time following diagnosis, patient can contribute follow-up time to different exposure cohorts but the index date (date of first prescription of the prophylactic drug of interest) will differ by treatment class. (Objective 5) General population: Follow-up will start from the date of the first entry, until the earliest of the following: 1) censoring or loss to follow-up, 2) end of data availability, or 3) the first occurrence of the outcome of interest.
Setting:	Outpatient setting from 4 databases currently in DARWIN EU covering 4 European countries.
Main measure of effect:	Incidence-rates: (Objective 3 and 5) Rates will be obtained for each cohort for incident cases of ED, insomnia, and hypertension, and will be expressed as number of individuals with newly diagnosed cases per person-years and stratified by age groups and sex. (Objective 4) Additionally, rates the incident migraine will also be stratified by prophylactic treatment class.

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8. RESEARCH METHODS

8.1 Study Type and Study Design

The proposed design for this study is a patient-level DUS study, classified as “off-the-shelf” (C1), as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses. We will also perform a patient-level characterisation. Additionally, the incidence of the events of interest described in objectives 34, and 5 will be assessed using a population-level descriptive epidemiology design.

Table 2. Description of Potential Study Types and Related Study Designs.

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)
Patient-level characterisation	Cohort analysis	Off the shelf (C1)
Population-level descriptive epidemiology	Population-level cohort	Off the shelf (C1)

8.2 Study Setting and Data Sources

This study will use routinely collected health data from 4 databases in the DARWIN EU® network of data partners from 4 European countries. All databases were previously mapped to the OMOP CDM.

Data sources

1. Finnish Care Register for Health Care (FINOMOP-HILMO), Finland
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Croatian National Public Health Information System (NAJS), Croatia
4. Valencia Health System Integrated Dataset (VID), Spain

These databases fulfil the criteria required for patient-level drug utilisation, characterisation, and population-level study, allowing for large-scale characterisation while covering different regions of Europe. The selection of databases was based on the availability of data on the selected drugs of interest, the conditions of interest, and other variables needed to perform the described analyses. Furthermore, 3 out of 4 are nationwide data sources that can provide reliable denominator for the incidence rate calculation. Detailed information on the selected data sources is described in **Table 3**.

To assess the reliability of data sources, data partners are asked to describe their internal data quality process on the source data as part of the DARWIN EU onboarding procedure. To further ensure data quality, we utilise the Achilles software tool (<https://ohdsi.github.io/TheBookOfOhdsi/DataQuality.html#data-quality-checks>), which systematically characterises the data and presents it in a dashboard format that is inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, and measurement value distribution can be compared against expectations for the data. Additionally, the data quality dashboard (DQD) consistently provides more objective checks on plausibility across data sources. Regarding relevance, a more general-purpose diagnostic software tool, CohortDiagnostics,

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was developed. This package evaluates phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture, including data generation. It provides additional insights into cohort characteristics, record counts and index event misclassification. Furthermore, timeliness is guarded by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to clearly understand the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contain a 'data density' plot that is checked. This plot displays the number of records per OMOP domain monthly. This allows us to get insights into when data collection started, when new data sources were added and until when data was included.

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Table 3. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update	Ability to answer study objectives
HR	NAJS	Adequate number of patients exposed to CGRP, availability of medical history for patient characterization, reliable denominator for estimation of rates. Covers inpatient and outpatient care	Primary care, outpatient specialist care, and inpatient care.	EHR and registries.	5.4 million	2023-11-17	1, 2, 3, 4, and 5
DE	IQVIA DA Germany	Adequate number of patients exposed to CGRP, availability of medical history for cohort characterization.	Primary care and outpatient specialist care	EHR	43.1 million	2023-09-30	1, 2, 3, 4, and 5
FI	FINOMOP-HILMO	Adequate number of patients exposed to CGRP, availability of medical history for patient characterization, reliable denominator for estimation of rates. Covers inpatient and	Primary care, outpatient specialist care, and inpatient care.	EHR and Registries	7.33 million	2024-04-16	1, 2, 3, 4, and 5

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Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update	Ability to answer study objectives
		outpatient care.					
ES	VID	Adequate number of patients exposed to CGRP, availability of medical history for patient characterization, reliable denominator for estimation of rates. Covers inpatient and outpatient care.	Primary care, outpatient specialist care, and inpatient care.	EHR, and registries.	1.96 million	2022-01-01	1, 2, 3, 4, and 5 This database will only include female participants aged 12-55 years.

DE = Germany, ES = Spain, HR = Croatia, FI = Finland.

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FINOMOP-HILMO, Finland

This database covers both public and private, primary and specialised inpatient and outpatient health care encounters in Finland starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. The main content of the THL CDM is The Finnish Care Register for Health Care, which is a continuation of the former Hospital Discharge Register, which that originally gathered data on patients discharged from hospitals. The Care Register has comprehensive data on the use of services and service users from Finnish public inpatient and outpatient primary and specialised care nationwide. Since 1998, the register has covered both public outpatient and inpatient specialised care and private inpatient care (TerveysHilmo). From 2011 the register has covered public primary care (AvoHilmo). From 2020 the register has covered private outpatient care and occupational care. In addition, the CDM also contains the vaccination data from the Finnish National Vaccination Register, the vaccination data from the Finnish National Vaccination Register, and COVID-19 test results from the Finnish National Infectious Diseases Register, which is maintained by THL. The CDM includes all the above-mentioned data sources and is limited to observation periods commencing after 1.1.2011. The National Population is used to form the base population. This ensures up-to-date location (municipality of residence) of patients and complete death occurrences (although not the cause of death). Using the complete population as a basis for the person table also facilitates calculations on a population level, e.g. incidence rates. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.

IQVIA Disease Analyser (DA) Germany, Germany

IQVIA Disease Analyzer (DA) Germany is a database of de-identified electronic medical records from specialised and general primary practices (GP) in Germany since 1992. This dataset encompasses approximately 3% of all outpatient practices within Germany, ensuring a substantial representation of the national healthcare landscape.^{22 23} The sampling methods used for practice selection, taking into account physician's demographics, specialty focus, community size category and federal state location, was instrumental in constructing a database that accurately mirrors the diverse spectrum of healthcare providers in the country.²² Consequently, data within IQVIA DA Germany database has been demonstrated to be representative of general and specialised practices throughout Germany.

The database contains demographics records, basic medical data, disease diagnosis according to International Classification of Diseases, 10th revision (ICD-10), and prescription records.²³ While the database partly records information on deaths and procedures, it currently does not support linkage with external data sources and therefore, information on mortality is incomplete. Routine updates are conducted at regular intervals. Data quality is assessed based on several criteria, including completeness of information and correctness (e.g. linkage between diagnosis and prescriptions).

No registration or approval is required for drug utilisation studies. As previously demonstrated, IQVIA DA Germany is suitable for pharmacoepidemiologic and pharmacoeconomic studies²³⁻²⁵.

NAJS, Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health (CIPH). This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures, drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in

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health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others. The CDM population comprises all publicly insured persons residing in Croatia starting in 2015.

VID, Valencia, Spain

The Valencia Health System Integrated Dataset (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with about 5 million inhabitants and an annual birth cohort of 48 000 newborns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information, including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensing) and healthcare utilisation data from hospital care, emergency departments, specialised care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology (including COVID-19 test results registry), and public health databases from the population screening programmes. All the information in the VID databases can be linked individually through a single personal identification code. The databases were initiated at different times, but overall, the VID provides comprehensive individual-level data fed by all the databases from 2008 to 2022. This database will only participate with data of women aged 12-55 years, which is the data they have currently mapped and is readily available for study purposes.

8.3 Study Period

The study period will be from 01/01/2018 (the first EU approval of a CGRP antagonist) to 31/12/2023 (when the study end date is not reached in a data source, the study end for that data source will be the last date of available data) (see [Table 3](#) for more details).

8.4 Follow-up

For objective 2 study participants will be followed up from the start of the first CGRP antagonist treatment to the end of the first exposure era (to estimate treatment duration).

For objectives 3 and 4, participants will be followed up as follows:

Incident migraine population: from their date of first diagnosis (incident migraine cohort) until the earliest of the following: 1) censoring (loss to follow-up or death), 2) end of data availability, or 3) the first occurrence of outcomes of interest.

For stratification by prophylactic treatment class among incident migraine cohort: from the date of first prophylactic treatment initiation, until the earliest of the following: 1) censoring (loss to follow-up or death), 2) end of data availability, or 3) the first occurrence of outcomes of interest, 4) 1-year follow-up time. Individuals might contribute to different cohorts (different types of prophylactic treatment are used)

For objective 5, participants will be followed up:

Overall population: from the date of fulfilling inclusion criteria for the study (cohort of general population), until the earliest of the following: 1) censoring (loss to follow-up or death), 2) end of data availability, or 3) first occurrence of outcomes of interest.

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Table 4. Operational Definition of Time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting ¹	Code Type ²	Diagnosis position	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
Individuals initiating treatment with any CGRP antagonist of interest (objective 1 & 2)	Date of first treatment with CGRP antagonist during study period	Single entry	Incident	Anytime prior to study entry date	OP	Time	N/A	Prior CGRP antagonist use	N/A	N/A
Individuals with incident migraine diagnosis (objective 3, incident migraine cohort)	Date of diagnosis (incident diagnosis)	Single entry	Incident	Anytime prior to study entry date	OP	Clinical finding, time	N/A	Prior migraine diagnosis	N/A	N/A
Individuals with incident migraine diagnosis (objective 4, incident migraine cohort, prophylactic treatment stratification) initiation treatment	Date of first treatment with any of the selected prophylactic treatments classes (during study period, among	Single entry	Incident	Anytime prior to study entry date	OP	Clinical finding, time	N/A	Prior selected prophylactic treatment class, prior migraine	N/A	N/A

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Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting ¹	Code Type ²	Diagnosis position	Incident with respect to...	Measurement characteristic s/ validation	Source of algorithm
with any of the selected prophylactic drugs of interest	individuals with an incident migraine diagnosis)							diagnosis		

¹ IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

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An example of entry and exit into the denominator population is shown in [Figure 1](#). In this example, person ID 1 already has sufficient prior history before the study start date and the observation period ends after the study end date, so it will contribute during the complete study period. Person IDs 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the database (the end of the observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again once sufficient prior history is reached and exits at study end date.

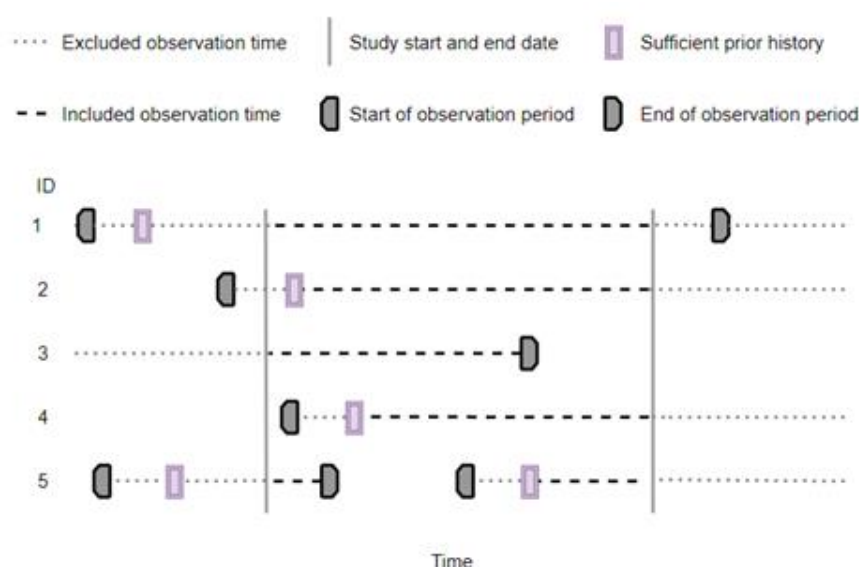


Figure 1. Included observation time for the denominator population

8.5 Study Population with inclusion and exclusion criteria

The study population will include all individuals present within the database during the study period (01/01/2018 and 31/12/2023; when the study end date is not reached in a data source, study end for that data source will be the last date of available data) and with at least one year of database history.

Two additional cohorts will be defined within this population: a cohort of individuals initiating treatment with any of the CGRP antagonists of interest (objectives 1 and 2) and a cohort of individuals with newly diagnosed migraine (objective 3). Within this cohort of individuals newly diagnosed with migraine, we will nest a cohort of individuals initiating prophylactic treatment class for the first time (objective 4) (CGRP antagonists, Beta Blockers, Anti-epileptics, Tricyclic Antidepressants or Calcium channel blockers).

The concept definition of migraine and CGRP antagonists are described in [Table S1](#), [Appendix I](#). The operational definitions of the inclusion and exclusion criteria are presented by means of [Table 5](#) and [Table 6](#), respectively.

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Table 5. Operational Definitions of Inclusion Criteria.

Criterion	Details	Order of application	Assessment window	Care Settings ¹	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2018-2023 (or the latest date available)	All individuals present in the period 2018-2023 (or the latest date available)	After	N/A	OP, OT	N/A	N/A	All individuals within selected databases	N/A	N/A
Prior database history	Study participants will be required to have 365 days of prior history observed before contributing observation time	Prior	[-365, -1]	OP, OT	N/A	N/A	All individuals within selected databases	N/A	N/A

¹ IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

Table 6. Operational Definitions of Exclusion Criteria.

Criterion	Details	Order of application	Assessment window	Care Settings ¹	Code Type	Diagnosis position ²	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

¹ IP = inpatient, OP = outpatient, , OT = other, n/a = not applicable

² Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

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8.6 Variables

8.6.1 Exposure/s

The operational definition of exposure is described in [Table 7](#).

Drugs of interest are CGRP antagonists and other migraine prophylactic drugs²⁶⁻²⁹, along with the use of medicines that help contextualise exposure to CGRP antagonists (see also section 8.6.3. – Other covariates of interest). The drugs of interest will be defined based on the respective RxNorm codes (see also [Table S1](#), [Appendix I](#)).

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Table 7. Operational Definitions of Exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
Erenumab, Eptinezumab, Fremanezumab, Galcanezumab	Preliminary code lists provided in Appendix I	[-Inf, -1] for incident use only	Anytime post start of the study period	IP, OP, and OT	RxNorm	N/A	Individuals newly treated with CGRP antagonists (objective 1 & 2); Incident migraine population	Any of the specified drugs, within class of interest	N/A	N/A
Antiepileptics (Valproate, Topiramate)	Preliminary code lists provided in Appendix I	[-Inf, -1] for incident use only	Anytime post start of the study period	IP, OP, and OT	RxNorm	N/A	Incident migraine population	Any of the specified drugs, within class of interest	N/A	N/A

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Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
Beta-blockers (Metoprolol, Propranolol, timolol)	Preliminary code lists provided in Appendix I	[-Inf, -1] for incident use only	Anytime post start of the study period	IP, OP, and OT	RxNorm	N/A	Incident migraine population	Any of the specified drugs, within class of interest	N/A	N/A
Tricyclic antidepressants (Amitriptyline)	Preliminary code lists provided in Appendix I	[-Inf, -1] for incident use only	Anytime post start of the study period	IP, OP, and OT	RxNorm	N/A	Incident migraine population	Any of the specified drugs, within class of interest	N/A	N/A
Calcium antagonists (Flunarizine)	Preliminary code lists provided in	[-Inf, -1] for incident use only	Anytime post start of the study period	IP, OP, and OT	RxNorm	N/A	Incident migraine population	Any of the specified drugs, within	N/A	N/A

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	Julietta Politi	Version: 3.1
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Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Diagnosis position ²	Applied to study populations	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
	Appendix I							class of interest		
Other medications of interest	Preliminary code lists provided in Appendix I	N/A	365 days prior to the start of the study period	IP, OP, and OT	RxNorm	N/A	Individuals newly treated with CGRP antagonists	N/A	N/A	N/A

¹ IP = inpatient, OP = outpatient, , OT = other, n/a = not applicable

² Specify whether a diagnosis code is required to be in the primary position (the main reason for encounter)

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8.6.2 Outcome/s

The operational definition of the outcomes is presented in Table 8. All preliminary lists of codes for identifying the outcomes of interest are available in [Appendix I. Table 1](#).

Table 8. Operational Definitions of Outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings ¹	Code Type	Diagnosis Position ²	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
Erectile dysfunction	Incident cases during the study period	Yes	Count	$[\infty, 0)$	IP, OP, and OT	SNOMED	N/A	All eligible individuals within the database considered for objectives 3 4, and 5 (cohorts: newly diagnosed migraine, and general population)	N/A	N/A
Insomnia	Incident cases during the study period	Yes	Count	$[\infty, 0)$	IP, OP, and OT	SNOMED	N/A	All eligible individuals within the database considered for objectives 3, 4, and 5 (cohorts: newly diagnosed migraine, and	N/A	N/A

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Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings ¹	Code Type	Diagnosis Position ²	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
								general population)		
Hypertension	Incident cases during the study period	Yes	Count	$[\infty, 0)$	IP, OP, and OT	SNOMED	N/A	All eligible individuals within the database considered for objectives 3, 4, and 5 (cohorts: newly diagnosed migraine, and general population)	N/A	N/A

¹ IP = inpatient, OP = outpatient, , OT = other, n/a = not applicable

² Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

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8.6.3 Other covariates, including confounders, effect modifiers and other variables

This section describes the study covariates conceptually and provides the context or rationale for the choices. The operational definition of the covariates is described in [Table 9](#).

Covariates for the patient-level characterisation (Objective 1)

To characterise the new initiators of CGRP antagonist drugs, the covariates will include:

- age at the index date (first prescription of CGRP antagonist) (<18, 18-44, 45-64, 65-79, and ≥80)
- sex (male/ female).
- comorbidities considered risk factors for ED, insomnia and hypertension will be assessed within 365 days before the index date. These comorbidities will be identified based on the presence of disease codes. The preliminary code list for each condition of interest is available in [Appendix I](#).

Table 2:

Endocrine/metabolism:

- Diabetes
- Hyperthyroidism
- Hypopotassaemia
- Obesity and overweight

Cardiovascular:

- Heart disease

Urinary system:

- Chronic kidney disease
- Injuries of pudendal arteries, veins, or nerves

Oncological:

- Cancer
- Prostate surgery or radiation treatment for cancer

Respiratory:

- Asthma

Gastrointestinal

- Gastroesophageal reflux disease (GERD)

Neurological disorders:

- Parkinson's disease and dementia (including Alzheimer's disease)
- Migraine

Mental health disorders:

- anxiety, depression, PTSD

Sleep-related disorders:

- Sleep apnoea, restless legs syndrome

- Comedications: Prior use of these medications of interest will be assessed in different time windows before the index date (0-30 days, 31-90 days, 91-365 days). The preliminary list of codes for drugs of interest is available in [Appendix I](#). **Table 3**.

Briefly, the comedications of interest can be classified into:

- Other anti-migraine treatments (focusing on prophylactic treatments):
 - Anti-epileptics (Valproate, topiramate)
 - Beta-blockers (e.g., propranolol, metoprolol, and timolol)
 - Tricyclic antidepressants (Amitriptyline)

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- Calcium antagonists (flunarizine)
- Triptans
- Drugs used as treatment for with erectile dysfunction:
 - PDE5 inhibitors and alprostadil
- Drugs used as treatment for insomnia:
 - Zolpidem and zopiclone
 - Benzodiazepines
 - Antidepressants:
 - SSRI
 - SNRI
 - Others
- Drugs used as treatment for hypertension:
 - Diuretics
 - Beta-blockers
 - ACE inhibitors
 - Angiotensin II receptor blockers
 - Calcium channel blockers
 - Alpha-blockers
 - Alpha-2 receptor agonists
 - Combined alpha and beta-blockers
 - Vasodilators

Large-scale characterisation: Drugs (by RxNorm code) and conditions (by standard SNOMED code) within predefined windows will be assessed. Conditions and drugs used before the index date will be assessed using different time windows. While all conditions and medications above 1% will be recorded, only the 10 most frequent conditions and drugs will be described within the report.

The following time windows will be used for the large-scale characterisation:

- 365 days to 1 day before the index date

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Table 9. Operational Definitions of Covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings ¹	Code Type	Diagnosis Position ²	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Demographics	Age at index date and sex	Numeric, continuous, binary	All history	IP, OP, and OT	N/A	N/A	All first users of the selected CGRP antagonists of interest	N/A	N/A
Risk factors (Health conditions of interest)	Prespecified conditions of interest prior to index date	Count, Binary	[-365, -1],	IP, OP, and OT	SNO MED	N/A	All first users of the selected CGRP antagonists of interest	N/A	N/A
Other medicines of interest	Prespecified Drug prescriptions prior to index date	Count, Binary	[-365, -91], [-90, -31], [-30, -1], [at index]	IP, OP, and OT	RxNorm	N/A	All first users of the selected CGRP antagonists of interest	N/A	N/A
Health Conditions, medication use	All history prior to the index date (for large-scale characterisation)	Count, Binary	[-365, -1],	IP, OP, and OT	SNO MED	N/A	All first users of the selected CGRP antagonists of interest	N/A	N/A

¹ IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

² Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

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8.7 Study size

No sample size has been calculated as this is a descriptive Drug Utilisation Study where we are interested in the characteristics of all incident cases of new users of CGRP antagonists in each database. The expected number of users of CGRP antagonists is expected to be roughly between 500-2000 in total (based on feasibility counts).

8.8 Analysis

The type of analysis in this study is described in **Table 10**.

Table 10. Description of Study Types and Type of Analysis.

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Patient Level DUS	Off-the-shelf (C1)	- Patient level characterisation and large-scale characterisation - Frequency and % of prespecified conditions and medicines
Population-level descriptive epidemiology	Off-the-shelf (C1)	- Incidence rates of the condition of interest

8.8.1 Federated Network analysis

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in RStudio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment (DRE) and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.8.2 Patient privacy protection

A minimum cell counts of 5 will be used when reporting results, with any smaller counts reported as “<5” to comply with privacy protection regulations.

8.8.1 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package “IncidencePrevalence” for the calculation of the outcomes of interest. We will use the “DrugUtilization” package to calculate the duration of interest and the *CohortCharacteristics* and *CohortDiagnostics* R packages to describe the characteristics of individuals initiating treatment with CGRP antagonists:

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Drug exposure calculation

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 90 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 2**, first row.

<i>Gap era joint mode</i>	Schematics	Dose in between	Cumulative dose	Cumulative time
“first”		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
“second”		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
“zero”		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
“join”	 first exposure time = x_1, dose = d_1 gap time = x_{12} second exposure time = x_2, dose = d_2	NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 2. Gap-era joint mode

As previously stated, for each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the start and end date of the exposure, and will be calculated as the duration of the first treatment era of the CGRP antagonist of interest during the study period. Treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration. For databases where duration cannot be calculated, treatment duration will not be provided.

8.8.2 Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year of the index prescription.

Age

Age at index date will be calculated using January 1st of the year of birth as a proxy for the actual birthday. The following age groups will be used for stratification: <18, 18-44, 45-64, 65-79, and ≥ 80

Sex

Results will be presented stratified by sex (men/women).

8.8.3 Population-level incidence calculations

Incidence rates of the outcomes of interest, for the incident migraine and the general population, will be calculated as the number of newly diagnosed individuals with the outcome of interest divided by the person-years as contributed by the population at risk of the outcome during the period for each calendar year. Follow-up is censored upon the end of the observation period, the outcome of interest or upon death whichever comes first. Incidence rates will be given together with 95% Poisson confidence intervals. **Figure 3** represents an example of incidence rate estimation.

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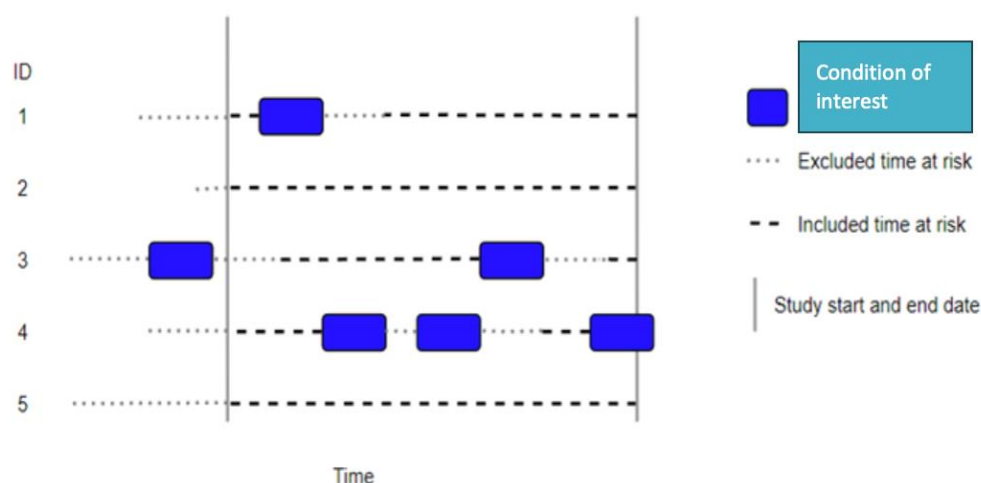


Figure 3. Example of incidence rate estimation.

Patient ID 1 and 4 contribute time at risk between the study start until they have an incident outcome of interest. Patient ID 2 and 5 contribute time at risk between the study start and end date as no outcome of interest is observed between this period nor before the study start date. Patient ID 3 was excluded from the analysis and does not contribute time at risk since a previous diagnosis was observed before the study start date.

For the calculation of incidence rates in the cohort of individuals newly diagnosed with migraine and initiating treatment with prophylactic treatment, the numerator will consist of individuals with the outcome of interest occurring within one year following index date (i.e. date of first prescription of the prophylactic treatment of interest) and the denominator will consist of person time from index date until the end of observation period, outcome of interest, mortality or one year following the index date whichever comes first. Follow-up in individuals initiating treatment with prophylactic treatment is described in **Figure 4**. As can be observed, individuals might contribute to multiple exposure cohorts as individuals might be exposed to different classes of prophylactic drugs.

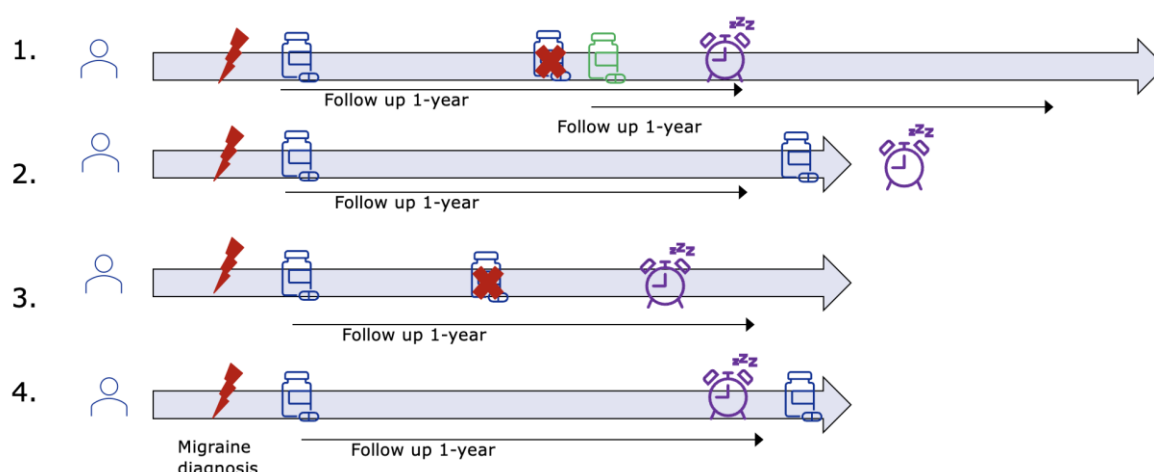


Figure 4. Example of follow-up time contribution for incidence rate estimation.

Patient 1 contributes to time at risk of drugs “blue” and “green” for a maximum of one year or until they have an incident outcome of interest (whichever occurs first). Index date is different for drug “blue” and drug “green” as the start date of the first prescription of the different drugs is different. The event (in this case, an alarm clock representing insomnia) would be counted in both cohorts (drugs blue and green). Patients 2, 3, and 4 only contribute time at risk for drug “blue”,

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from the start of the drug up to a year or until they have the event (if event occurs $\leq$ within one year following treatment initiation). Patients 3 and 4 have an incident outcome (an alarm clock representing insomnia) within one year, so they would be counted in the numerator for drug “blue”. Patient 2 has the event outside the one-year maximum follow-up, so the event is not counted.

8.8.4 Patient-level characteristics on/before index date

Characterisation of patients newly treated with CGRP antagonists: We will use the R package “PatientsProfiles” for the patient-level characterisation of demographics and predefined clinical characteristics, as well as large-scale characterisation. The co-variables to be presented in a summary baseline characteristics table have been described in section 8.6.3. Prior use of comedications of interest will be described for different time windows before the index date (0-30 days, 31-90 days, 91-365 days). The large-scale patient-level characterisation will be conducted to describe medical history and prior medication use (365 days to 1 day before the index date).

Objective 2. Characterisation of treatment with CGRP antagonists in a cohort of new users: The “DrugUtilisation” package will be used to characterise the use of CGRP antagonists. The number and % of patients receiving each of a pre-specified list of CGRP antagonist treatments including duration of treatment.

8.8.5 Output

New drug user, patient-level characterisation:

- Table 1. Number and proportion of participants treated with each CGRP antagonist type. Distribution (number and %) of prior comedications and comorbidities of interest. Overall and stratified by sex. Number of participants per pre-specified strata will be included where necessary/applicable.
- Table 2: Duration of treatment for each CGRP antagonist type.

Incidence rates for conditions of interest:

- Table 1. Number of participants, total number of incident cases and total time at risk in each data source during the study period. Number of participants per pre-specified strata will be included where necessary/applicable.
- Figure 1. Incidence rate/s of the outcome of interest over calendar time (year) overall in the incident migraine population and in the general population
- Figure 2. Incidence rate/s of the outcome of interest over calendar time (year) stratified by prophylactic treatment class.
- Figure 3. Incidence rate/s of the outcome of interest over calendar (year) stratified by sex and age
- Table 2. Numbers reported in **Figures 1, 2, and 3**.

8.9 Evidence synthesis

Results from analyses described in section 8.8 will be presented separately for each database, and no results meta-analysis will be conducted.

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9. DATA MANAGEMENT

9.1 Data management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM:

<https://ohdsi.github.io/CommonDataModel> and in The Book of OHDSI: <http://book.ohdsi.org>.

The analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2 Data storage and protection

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN Digital Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/2016 in the various member states.

10. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI <http://book.ohdsi.org/DataQuality.html>). In particular, data partners have run the OHDSI Data Quality Dashboard tool (<https://github.com/OHDSI/DataQualityDashboard>). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

	D2.2.3 - Study Protocol for P3-C1-009	
	Authors: J.Politi, K.Verhamme	Version: 3.1
		Dissemination level: Public

When defining specific drugs, conditions, and co-morbidities, a systematic search of possible codes for inclusion was previously identified using CodelistGenerator R package (<https://github.com/darwin-eu/CodelistGenerator>). This software allows the user to define a search strategy and, using this will then query the vocabulary tables of the OMOP CDM to find potentially relevant codes. The codes returned will then be reviewed by two clinical epidemiologists to consider their relevance. In addition, the CohortDiagnostics R package (<https://github.com/OHDSI/CohortDiagnostics>) will be run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This will allow for a consideration of the validity of the study cohort of patients with the selected conditions, drugs, and co-morbidities in each of the databases and inform decisions around whether multiple definitions are required.

11. LIMITATIONS OF THE RESEARCH METHODS

In particular, the identification of CGRP antagonist users, the recording of the prescription of the drug, and the prescriptions themselves may vary across databases. A recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use will be unavoidable and might lead to overestimating treatment duration of treatment (considering a 90-day drug gap era). For databases where duration cannot be calculated due to e.g. missing information on quantity, dosing or end date, e.g., treatment duration will not be provided.

Stratification of incident migraine cohort by prophylactic treatment class will likely introduce some exposure misclassification since an intention-to-treat approach is taken and no washout will be applied. Also, the analytical pipeline does not allow to account for drug exposure time, discontinuation, or treatment switch.

In addition, the recording of events used for patient characterisation may vary across databases and might be captured in another care setting than the included database.

Previous exposure to smoking, drugs, and alcohol is of interest as these are risk factors for the outcomes of interest. However, these lifestyle factors are not systematically recorded and thus may be unavailable in databases. In turn, they will not be assessed.

Small cell counts may affect the analysis for some subgroup strata. If the numbers are too low, counts will not be disclosed for governance reasons.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the guideline on good pharmacovigilance practice (EMA/873138/2011), there will be no requirement for expedited reporting of adverse drug reactions as only secondary data will be used in this study.

13. GOVERNANCE BOARD ASPECTS

All data sources require approval from their respective IRB boards, except IQVIA DA Germany, which will not require any further specific approvals to undertake this study.

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14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study Report

A PDF report, including an executive summary and the specified tables and/or figures, will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the PDF report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15. OTHER ASPECTS

N/A

16. REFERENCES

17. ANNEXES

Appendix I: List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

Appendix II: ENCePP checklist for study protocols

Appendix III: Additional Information

APPENDIX I:

Appendix I. Table 1 Code list for drugs and conditions of interest

CONCEPT SET NAME	IDs
Erenumab	1510467
Eptinezumab	37499031
Fremanezumab	35200577
Galcanezumab	35200800
Migraine	318736
Erectile dysfunction	3655358 3655355 3655356 37016340 3655360 35626763 3655361 606412 606410 3655362 3655359 43531565 4177050 606407 45772922

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	1340324 4019657 37109304 44808863 760989 4343129 43021236 3655357 4022799 43021237 45769867
Insomnia	4086851 37110488 4115402 42689991 42689992 43530738 4204989 42690122 42690123 42690715 435657 434172 436522 374905 4102985 443544 3173994 4200883 4215402 4305303 435524 40482260 40480927 4132137 42690379 42690380
Hypertension	320128 316866

Appendix I. Table 2 Code list for conditions representing risk factors of interest

CONCEPT SET NAME	IDs
Diabetes	201820
Heart disease	321588
Chronic renal disease	46271022
Cancer diagnosis	443392
Asthma	317009
Gastroesophageal reflux disease (GERD)	318800
Hyperthyroidism	4142479
Hypopotassaemia	437833
Neurological disorders (Parkinson's disease and Alzheimer's or other dementias)	381270 4182210
Mental health disorders (anxiety, depression, PTSD)	436676 440383

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	442077 441542
Sleep disorders (sleep apnoea and restless leg syndrome)	35626941 313459
Prostate surgery and cancer radiation treatment	4250917
Pudendal nerve or artery lesions	4196277 36686418
Obesity and overweight	4215968 437525

Appendix I. Table 3 Code list for identifying prior exposure to drugs of interest

CONCEPT SET NAME	IDs
Triptans and ditans	21604375
Antiepileptics (topiramate, valproate)	742267 745466
Tricyclic antidepressants (amitriptyline)	710062 721724 743670
Beta-blockers (e.g., propranolol, metoprolol, timolol)	21601682 21601666
PDE5 inhibitors (e.g., sildenafil, vardenafil, tadalafil and avanafil) and Alprostadil	21602645 1381504
Zolpidem and zopiclone	744740 19044883 757352
benzodiazepines	21604565
SSRIs	21604709
SNRIs	21604687
Other antidepressant drugs (SARIs, TeCA, etc)	21604719 21604729 21604726
Diuretics	21601461
Beta-blockers	21601664
ACE inhibitors	21601784
Angiotensin II receptor blockers	21601823
Calcium channel blockers	21601744
Alpha-blockers	21600410
Alpha-2 receptor agonists	21600416
Combined alpha and beta-blockers	21601698
Vasodilators	21600316

Some concept sets included within this table represent the fourth level of ATC codes, indicating the chemical/therapeutic/pharmacological subgroup. However, this code will be used to identify all descendants to be included within each concept set.

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	Authors: J.Politi, K.Verhamme		Version: 3.1
	Dissemination level: Public		

APPENDIX II: ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Study title: DARWIN EU® - CGRP antagonists - treatment patterns and users characteristics

EU PAS Register® number: N/A

Study reference number (if applicable): N/A

EU PAS Register® number:

Study reference number (if applicable):

Section 1: Milestones	Yes	No	N/A	Section Number
1. Does the protocol specify timelines for				
1.1.1 Start of data collection				
1.1.2 End of data collection	X			
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.	X			

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)	X			
2.1.2 The objective(s) of the study?	X			
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X			
2.1.4 Which hypothesis(-es) is (are) to be tested?				
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?				

Comments:

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	X			
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X			
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X			

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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))			X	8.8 Analysis
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)			X	

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	X			8.5 Study Population
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	X			8.3 Study Period
	4.2.2 Age and sex	X			8.6.3. Other covariates
	4.2.3 Country of origin				8.2 Study Setting and Data Sources
	4.2.4 Disease/indication	X			8.6.1. Exposures
	4.2.5 Duration of follow-up	X			8.4 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)	X			8.5 Study Population with inclusion and exclusion criteria

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)	X			8.6.1. Exposures And 8.8 Analysis
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)			X	
5.3	Is exposure categorised according to time windows?			X	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)			X	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?			X	
5.6	Is (are) (an) appropriate comparator(s) identified?			X	

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?	X			8.6.2. Outcomes

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6.2 Does the protocol describe how the outcomes are defined and measured?	X			8.6.2. Outcomes
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)		X		
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)		X		

Comments:

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

Comments:

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)			X	

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)	X			8.2 Study Setting and Data Sources
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X			8.2 Study Setting and Data Sources
9.1.3 Covariates and other characteristics?	X			8.6.3. Other covariates
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)	X			8.2 Study Setting and Data Sources
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X			8.2 Study Setting and Data Sources
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X			8.2 Study Setting and Data Sources

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9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	X			
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X			8.6.2. Outcomes
9.3.3 Covariates and other characteristics?	X			8.6.3. Other covariates
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)			X	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	X			8.8 Analysis
10.2 Is study size and/or statistical precision estimated?			X	
10.3 Are descriptive analyses included?	X			8.8.2 Descriptive statistics
10.4 Are stratified analyses included?	X			8.8 Analysis
10.5 Does the plan describe methods for analytic control of confounding?			X	
10.6 Does the plan describe methods for analytic control of outcome misclassification?			X	
10.7 Does the plan describe methods for handling missing data?			X	
10.8 Are relevant sensitivity analyses described?			X	

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)	X			9. Data management
11.2 Are methods of quality assurance described?	X			10. Quality Control
11.3 Is there a system in place for independent review of study results?			X	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				11. Limitations of the research methods
12.1.1 Selection bias?				
12.1.2 Information bias?	X			
12.1.3 Residual/unmeasured confounding?				

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(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)	X			Table 8.2. Description of the selected Data Sources.

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?	X			13. Governance board aspects
13.2 Has any outcome of an ethical review procedure been addressed?			X	
13.3 Have data protection requirements been described?	X			9.2 Data storage and protection

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?	X			4. Amendments and updates

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)?	X			14. Plans for disseminating and communicating study results
15.2 Are plans described for disseminating study results externally, including publication?	X			14. Plans for disseminating and communicating study results

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 07/06/2024

Signature: _____