PHARMO

FINAL

Post-Authorisation Safety Study Protocol

A retrospective cohort study to assess drug utilisation and long-term safety of galcanezumab in European patients in the course of routine clinical care

PHARMO Institute

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Country(-ies) of study	France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom
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Marketing authorisation holder

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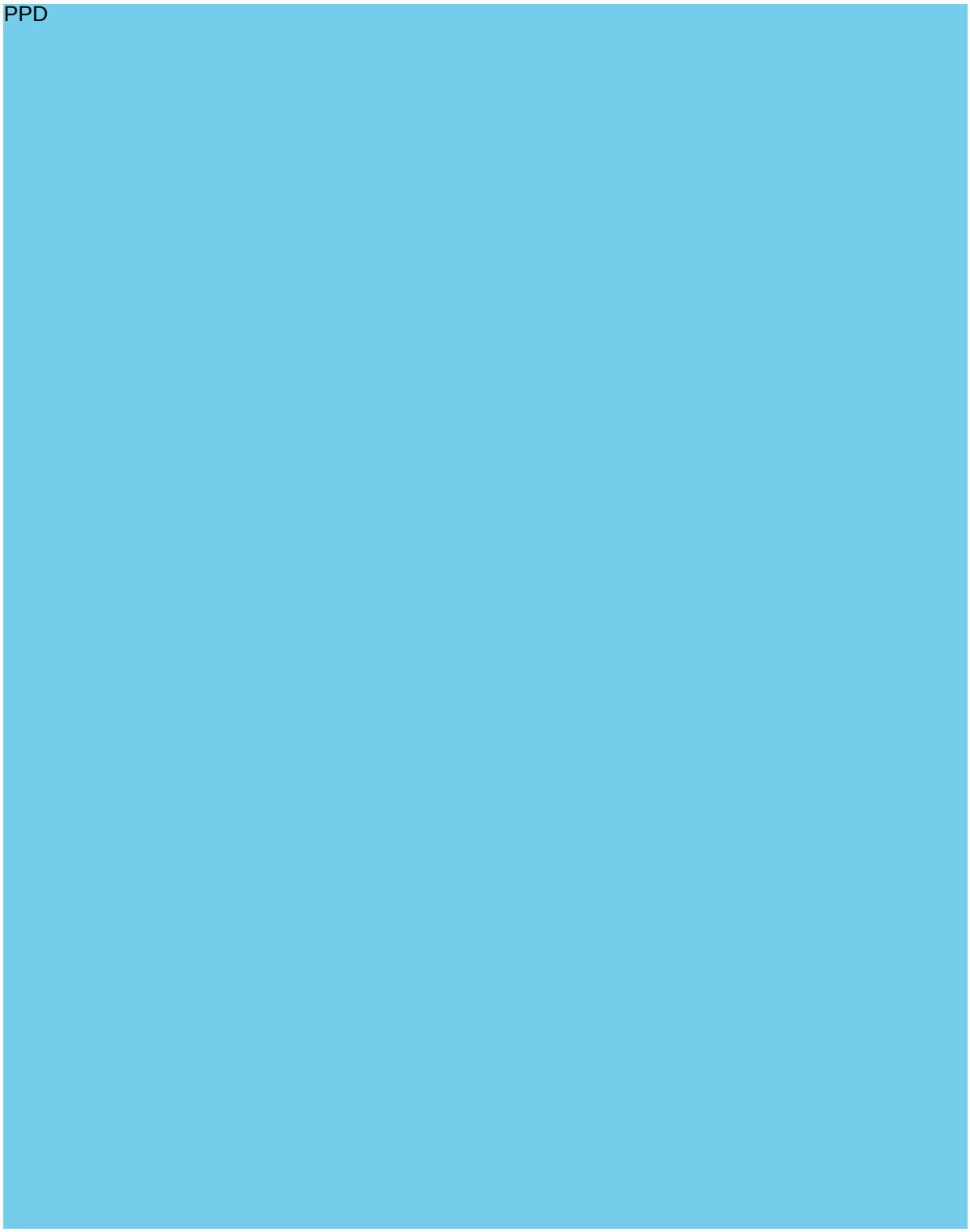
2. List of abbreviations

AP	Unstable angina pectoris
ARS	Agenzia regionale di sanità della Toscana database
ATC	Anatomical therapeutic chemical
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CH	Cluster headache
CPRD	Clinical Practice Research Data Link Gold
CM	Clinical modification
CV	Cardiovascular
DE	Germany
EMR	Electronic medical records
ES	Spain
EU	European Union
FR	France
GePaRD	German Pharmacoepidemiological Research Database
GM	German modification
HES	Hospital Episodes Statistics
HR	Hazard ratio
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
IQR	Interquartile range
IT	Italy
MI	Myocardial infarction
NL	Netherlands
NMSC	Non-melanoma skin cancer
NSAID	Nonsteroidal anti-inflammatory drug
PASS	Post-authorisation safety study
PCI	Percutaneous coronary intervention
PHARMO	PHARMO Database Network
SAP	Statistical analysis plan
SD	Standard deviation
SE	Sweden

SHR	Swedish Health Registers
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SNDS	Système National des Données de Santé
TIA	Transient ischaemic stroke
UK	United Kingdom

3. Responsible parties



4. Abstract

Title: A retrospective cohort study to assess drug utilisation and long-term safety of galcanezumab in European patients in the course of routine clinical care

Rationale and background: Galcanezumab is a humanised monoclonal antibody against human calcitonin gene-related peptide (CGRP) and is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month. As migraine is a chronic condition, continuous or intermittent long-term treatment is anticipated in routine clinical practice. Exposure to galcanezumab was limited in clinical trials. Therefore, infrequent adverse effects and effects which have a longer latency period, such as serious hypersensitivity and/or malignancy, could occur in real-world practice. Additionally, patients with recent cardiovascular (CV) events and/or serious CV risk as well as patients over the age of 65 years, who were excluded from the clinical trial population, might be part of the user population in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation.

Research question and objectives: The purpose of this study is to evaluate the utilisation and safety of galcanezumab with respect to serious hypersensitivity events and long-term safety (up to 5 years), including malignancy and cardiovascular events in routine clinical practice in Europe.

The primary objective is to characterise the utilisation of galcanezumab for the treatment of migraine and to assess the incidence of serious CV events, serious hypersensitivity reactions, and malignancies in real world clinical practice in Europe. This objective is primarily descriptive and aims to assess:

- the utilisation of galcanezumab overall and in special populations of interest, particularly:
    - patients ≥65 years of age
    - adult patients (≥18 years of age) with recent CV events and/or serious CV risk prior to initiating galcanezumab
    - patients ≥65 years of age with recent serious CV events and/or serious CV risk prior to initiating galcanezumab
- the incidence and distribution of time to serious CV events in adult patients who receive galcanezumab without recent serious CV events in the 12 months prior to initiating galcanezumab, overall, by age, gender, and duration of galcanezumab treatment and in the special populations of interest including:
    - patients ≥65 years of age

    - adult patients with recent serious CV events and/or serious CV risk prior to initiating galcanezumab
    - patients ≥65 years of age with recent serious CV events and/or serious CV risk prior to initiating galcanezumab
- the incidence of serious hypersensitivity reactions such as anaphylaxis in adult patients who receive galcanezumab, overall, by age, gender and in special populations of interest, particularly:
    - patients ≥65 years of age
- the incidence and distribution of time to malignancies (excluding non-melanoma skin cancers) in adult patients exposed to galcanezumab, overall, by age, gender, and category of duration of galcanezumab treatment, and in special populations of interest, particularly:
    - patients ≥65 years of age

The secondary objective is to provide context for incidence rates of serious CV events, serious hypersensitivity reactions, and malignancies seen in the galcanezumab-exposed migraine cohort by describing the incidence rates observed in a comparator cohort of migraine patients that initiated another prophylactic migraine medication and, as feasible, to conduct comparative safety analyses of serious CV events and malignancies. Non CGRP prophylactic migraine medications are small molecules that are typically less immunogenic than monoclonal antibodies. There is also uncertainty around the ability to accurately identify serious hypersensitivity events in secondary data. As such, formal comparative analyses for serious hypersensitivity events are not proposed; however, rates in the comparator cohort will be provided for context.

Study design: An observational, prevalent new-user cohort study using data from various population-based healthcare databases from seven different European countries.

Population: The source population will include all patients with a prescription or dispensing of galcanezumab in the population-based healthcare databases from seven different European countries including France (FR), Germany (DE), Italy (IT), the Netherlands (NL), Spain (ES), Sweden (SE) and the United Kingdom (UK). For the primary objective (utilization of galcanezumab and incidence of events), several exclusion criteria will be applied. In addition, subcohorts of patients with recent (within the last 6 months) serious CV events and/or serious CV risk prior to initiating galcanezumab and patients ≥65 years of age will be created.

To provide context for incidence rates of the safety events seen in the galcanezumab-exposed migraine cohort, migraine patients who initiate treatment with topiramate will be used as a

comparator cohort for analyses of serious cardiovascular events and malignancies. A formal comparative analysis for serious hypersensitivity reactions will not be undertaken due to the lack of an appropriate comparator and uncertainty around the ability to accurately identify these events in secondary data. Rates in the topiramate cohort will be provided for context.

The study period in each country of interest will start at the launch date of galcanezumab in the countries of interest. The end of the study period will depend on the available data at the end of data collection (Q3 2026) for each country. Assuming an average data lag time of approximately 1.5 years, the end of the study period will be Q4 2025 at maximum.

Variables:

Exposure

Primary objective: The exposure of interest will include any treatment with galcanezumab.

Secondary objective: The exposures of interest are prescription or dispensing of galcanezumab or comparator medication topiramate for migraine Galcanezumab initiators will include both incident and prevalent new users regarding prior topiramate use. An incident new galcanezumab user will not have used topiramate prior to the index date, while prevalent new galcanezumab users will have used topiramate prior to the index date prior to the index date (i.e first prescription/dispensing of galcanezumab within the study period).

Outcomes

The outcomes of interest are serious CV events, serious hypersensitivity reactions and malignant neoplasms. Serious CV events under consideration include: hospitalisation for: myocardial infarction (MI), transient ischaemic stroke (TIA), ischaemic stroke, ischaemic heart disease, unstable angina pectoris (AP), percutaneous coronary intervention (PCI), coronary revascularisation and CV death. The final selection of CV outcomes will depend on the accuracy of the diagnosis within in each data source. Serious CV events will be reported as composite and individual outcomes. Serious hypersensitivity reactions will be identified by a hospitalisation or emergency care visit for anaphylaxis or allergy. As feasible, hospitalisations or emergency care visits for angioedema, acute asthma or acute bronchospasm, acute upper airway obstruction, epinephrine administration and death from serious hypersensitivity reactions (i.e. death after any of these events, to be detailed in the SAP) will additionally be assessed as part of this outcome. Malignant neoplasms will be identified as a diagnosis of any cancer, excluding non-melanoma skin cancer (NMSC). Malignancies will be reported as a composite outcome (all malignancies, excluding NMSC), and by type of the first malignancy (i.e. per primary cancer site).

All outcomes of interest will be identified by using the database specific coding systems (e.g. READ codes in the UK, International Classification of Diseases (ICD) 9th or 10th revision, or International Classification of Primary Care (ICPC) in the Netherlands), as well as the specific

provenance of the data (e.g. hospital admission, primary care or emergency care visits). The specific diagnostic codes to identify the outcomes of interest will be included in the statistical analysis plan (SAP). Furthermore, table shells will be provided in this document to show which results will be delivered.

Covariates

Demographic and clinical covariates will be considered for descriptive purposes and as confounders in the comparative study. All available data prior to start of the treatment will be used to assess baseline demographics and clinical covariates.

Data sources: All data will be obtained from seven European databases. The following databases will be used:

- SNDS (Système National des Données de Santé) from France
- GePaRD (German Pharmacoepidemiological Research Database) from Germany
- ARS (Agenzia regionale di sanità della Toscana database) from Italy
- PHARMO (The PHARMO Database Network) from the Netherlands
- SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) from Catalonia, Spain
- SHR (Swedish Health Registers) from Sweden
- CPRD (The Clinical Practice Research Data Link Gold plus Hospital Episodes Statistics (HES) Data) from the UK

Study size: The number of galcanezumab-exposed patients will depend on the uptake of galcanezumab in each country. The descriptive outcomes in the primary objective as well as the incidence rates as part of the secondary objective will be presented in the final report regardless of the size of the study population. The comparative analyses will only be performed if target sample sizes are attained that will allow us to detect a 2-fold difference in the primary outcome of serious CV events with 80% power for the composite endpoint of serious CV events (N = 7,245 person-years in galcanezumab-exposed patients per database).

Data analysis: Descriptive statistics for demographic and clinical characteristics at baseline will be provided. Incidence rates for serious CV events, serious hypersensitivity reactions and malignant neoplasms will be presented for the galcanezumab-exposed and topiramate cohort and will be estimated by dividing the number of events of interest by the person-time at risk. If feasible, based on accrual of target sample size, comparative analyses will be conducted to compare the incidence of serious CV and malignancy events among migraine patients that are new users of galcanezumab with propensity score-matched users of topiramate. This will be further detailed in the SAP. Relative risks for the outcomes of interest will be estimated as

hazard ratios (HRs). All analyses will be done for each country separately and a meta-analysis will be considered depending on the appropriateness of combining data sources.

Milestones:

Registration in the EU PAS Register: 17 January 2019

Study progress reports will be provided annually with the PSUR starting 30 November 2019

Start of data collection: 30 June 2020

End of data collection: 30 September 2025

Interim report: 31 December 2023

Final report of study results: 31 December 2026

5. Amendments and updates

Amendment 1

Removal of CH cohort

Lilly has not received approval in the EU for the use of galcanuzumab in patients with CH. Therefore the analyses in the cohort of galcanezumab users with a CH diagnosis is no longer needed and the focus will be on patients with migraine only. The cohort of galcanezumab users with a CH diagnosis is therefore deleted from this protocol.

Additional exclusion criteria

The following additional exclusion criteria will be applied to form the main cohort:

- Have a recorded diagnosis of epilepsy in the entire available history or evidence of use of antiepileptics (excluding topiramate and valproic acid) in the 12 months prior to the index date (as topiramate is indicated for both epilepsy and migraine)
- Have a recorded diagnosis of any malignancy or evidence of drugs used solely for the treatment of cancer during all available database history prior to or on the index date

In addition, for the overall incidence analysis of serious CV events, patients with a recorded diagnosis for a serious CV event in the 12 months prior to or on the index date will be excluded in order to estimate true incidence rates rather than prevalence rates.

Cohort allocation

Patients are not allowed to enter both the galcanezumab and the topiramate cohort. Patients switching from topiramate to galcanezumab or from galcanezumab to topiramate during the study period will be included in the galcanezumab cohort only.

Revision of study cohort selection flowchart

The flow chart showing the study cohort selection is revised for clarity.

6. Milestones

Table 6.1: Milestones

Milestone	**Planned date**
Registration in the EU PAS Register	17 January 2019
Start of data collection	30 June 2020
End of data collection	30 September 2025
Study progress reports	To be provided annually with the PSUR starting 30 November 2019
Interim report	31 December 2023*
Final report of study results**	31 December 2026

*Interim report will be provided no later than 31 December 2023 but may occur earlier based on accrual of galcanezumab-exposed person-years.

**At the time of the final report of study results (31 December 2026), it will be determined whether an additional report with an extended data collection period would be useful for assessing events with long latency (see Section 9.2.3 for further information).

7. Rationale and background

Galcanezumab (ATC code N02CD02; trade name Emgality®) is a humanised monoclonal antibody that binds calcitonin gene-related peptide (CGRP) and inhibits its biologic activity without blocking the CGRP receptor. In clinical trials, galcanezumab provided effective prophylactic treatment for episodic and chronic migraine compared to placebo.[1-3] In the European Union (EU), galcanezumab is indicated for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

As migraine is a chronic condition, continuous or intermittent long-term use is anticipated in routine clinical practice. Therefore, adverse effects which have a longer latency period such as malignancy and/or are infrequent such as serious hypersensitivity could occur. Additionally, patients with recent acute CV events and/or serious CV risk, as well as patients over the age of 65, were excluded from the clinical trial population and use in this group of patients may also occur in everyday clinical practice. The implications of long-term inhibition of CGRP are unknown, including the impact on long-term safety. As a result, the long-term safety of galcanezumab in larger patient populations requires further characterisation.

8. Research questions and objectives

8.1 Primary objective

The purpose of this study is to evaluate the utilisation and safety of galcanezumab with respect to serious hypsersensitivity events and long-term safety (up to 5 years) including malignancy and cardiovascular events in routine clinical practice. The primary objective is to characterise the utilisation of galcanezumab for the prophylaxis of migraine and to assess the incidence of serious CV events, serious hypersensitivity reactions, and malignancies in real-world clinical practice in Europe. This objective is primarily descriptive and aims to assess:

1. the utilisation of galcanezumab overall and in special populations of interest, particularly:
    - patients ≥65 years of age
    - patients ≥18 years of age with recent (within the last 6 months) serious CV events and/or serious CV risk prior to initiating galcanezumab
    - patients ≥65 years of age with recent (within the last 6 months) serious CV events and/or serious CV risk prior to initiating galcanezumab
2. the incidence and distribution of time to serious CV events in adult patients (≥18 years of age) who receive galcanezumab without a serious CV event in the 12 months prior to initiating galcanezumab, overall, by age, gender, and duration of galcanezumab treatment and in special populations of interest including:
    - patients ≥65 years of age
    - patients ≥18 years of age with recent (within the last 6 months) serious CV events and/or serious CV risk prior to initiating galcanezumab
    - patients ≥65 years of age with recent (within the last 6 months) serious CV events and/or serious CV risk prior to initiating galcanezumab
3. the incidence of serious hypersensitivity reactions such as anaphylaxis in patients ≥18 years of age who receive galcanezumab, overall, by age, gender and in special populations of interest, particularly:
    - patients ≥65 years of age
4. the incidence and distribution of time to malignancies (excluding non-melanoma skin cancers) in adult patients ≥18 years of age who receive galcanezumab, overall, by age, gender, category of duration of galcanezumab treatment and in special populations of interest, particularly:
    - patients ≥65 years of age

8.2 Secondary objective

The secondary objective is to provide context for incidence rates of serious CV events, serious hypersensitivity reactions, and malignancies seen in in patients using galcanezumab for the treatment of migraine by describing the incidence rates observed in a comparator cohort of patients with migraine initiated on topiramate, a non CGRP migraine prophylaxis medication and, as feasible, to conduct comparative safety analyses of serious CV events and malignancies. Non CGRP prophylactic migraine medications are small molecules that are typically less immunogenic than monoclonal antibodies. There is also uncertainty around the ability to accurately identify serious hypersensitivity events in secondary databases. As such, formal comparative analyses for serious hypersensitivity events are not proposed; however, rates in the comparator cohort will be provided for context.

9. Research methods

9.1 Study design

This will be an observational, prevalent new-user cohort study utilising European secondary data sources.

9.1.1 Rationale for study design

To understand the utilisation of galcanezumab in Europe and to obtain a robust estimate of the incidence of serious CV outcomes, serious hypersensitivity reactions and malignancies – for the primary objective, we will identify an initial cohort of all galcanezumab users with patient accrual beginning at the launch of galcanezumab in those European countries from which healthcare database information will be used for this study (see Section 9.4 'Data sources').

In databases such as ARS and SNDS that do not include out-patient diagnoses for assessment of the indication of use, it will be challenging to define migraine cohorts as proposed in Section 9.2.2. Therefore, algorithms will be developed in close collaboration with clinical experts based on specific (medication-based) parameters of care patterns to distinguish between use of topiramate for epilepsy and use of topiramate for migraine.

An incident new user design was considered to prevent depletion of susceptibles and to minimise the risk of missing early events. Typically, with this design, patients must be new users of the drug of interest and comparator medications and must not have previous use of either. These requirements are made to account for a healthy user effect, whereby patients experiencing adverse effects discontinue and switch therapy, while patients doing well continue therapy. This design was not considered feasible, as a substantial portion of galcanezumab users are likely to have prior use of prophylactic migraine treatment due to the

timing of marketing approval and formulary status. Therefore, this study will utilize a prevalent new-user design that allows for previous use of comparator medications.
Some of the outcomes of interest require a look-back period for accurate assessment. Considering that the choice of the required look-back period will affect the sample size, these periods were chosen based on a trade-off between sample size and accurate assessment of characteristics. For baseline characteristics, 12 months has been selected as the most appropriate balance between these two. A six-month baseline period was considered; however, it is assumed that baseline characteristics will be less accurately captured. We do not expect that the extension to 12 months will have a large impact on the sample size. To interrogate the indication of use for galcanezumab and comparator with the highest possible sensitivity we will use all available historic diagnostic information. Also, all available historic information will be used for other non-acute variables as deemed appropriate. The selected time windows used will be detailed in the SAP per characteristic.

9.1.2 Uptake of galcanezumab

The timelines associated with a database analysis depend on the time of launch and the volume of dispensings, but also on the time lag needed to have access to recorded data. Due to all these factors, there is always uncertainty about the time needed to reach the targeted number of patients required to perform the study analyses. To minimise this uncertainty, the first patient monitoring report will be prepared in 2020 (approximately 1 year after expected product launch) and then annually until 2025, to evaluate the number of patients treated with galcanezumab available in the different databases. These monitoring updates will include the number of patients with a prescription/dispensing of galcanezumab (overall, per calendar year and among patients aged ≥65 years and <18 years) as well as the length of available database follow-up and will be provided as part of the annual study progress reports with the PSUR.

9.2 Setting

9.2.1 Source population

The source population for this study will be based on patient-data from seven different European databases (see Section 9.4 for description of data sources):

- SNDS (Système National des Données de Santé) from France
- GePaRD (German Pharmacoepidemiological Research Database) from Germany
- ARS (Agenzia regionale di sanità della Toscana database) from Italy
- PHARMO (The PHARMO Database Network) from the Netherlands
- SIDIAP (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària) from Catalonia, Spain

- SHR (Swedish Health Registers) from Sweden
- CPRD (The Clinical Practice Research Data Link Gold plus Hospital Episodes Statistics data (HES)) from the UK

The table below presents an overview of the general and outcome-specific characteristics of these databases.

Table 9.1: Overview of databases to be used for the study

	Database						
	SNDS	**GePaRD**	**ARS**	**PHARMO**	**SIDIAP**	**SHR**	**CPRD**
General							
Country	France	Germany	Italy	Netherlands	Spain	Sweden	UK
Number of country inhabitants, millions	66.6	82.4	59.2	17.1	46.4	10.0	66.8
Type of database	Claims	Claims	Claims	EMR	EMR	Administrative	EMR
Current number of patients in database, millions	66	±25	±3.5 per year	1.3	5.1 (1.7 linked to hospital data)	>10.0	5.7 (approx. 55% linked to HES data)
Database updates	Yearly (Q3)	Yearly (Q2)	Every 2 months	Yearly (Q4)	Yearly (April)	Yearly for hospital care, monthly for dispensed prescriptions	Yearly (Q2)
Exposure							
Prescription/dispensing	Disp.	Disp.	Disp.	Disp.	Both	Disp.	Pres.
Out-patient Rx	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Coding of drugs	ATC	ATC	ATC	ATC	ATC	ATC	Gemscript
Dosing regimen	Yes	No	No	Yes	Yes	Yes	Mostly available
Outcomes							
Hospitalisations	Yes	Yes	Yes	Yes	For hospital linked patients only	Yes	For HES-linked patients only
Out-patient diagnoses	No	Yes (GP and specialist)	No	Yes (based on GP recorded diagnoses only)	Yes (based on GP records)	Yes (for out-patient specialist care)	Yes
Coding of disease	ICD-10	ICD-10-GM	ICD-9-CM	ICPC (GP), ICD-10 (hospitalisations)	ICD-10 (ICD-9 for hospital data)	ICD-10	READ (ICD-10 for HES data)

EMR = Electronic medical records; HES = Hospital Episodes Statistics; ATC = Anatomical therapeutic chemical; ICD = International Classification of Diseases; GM = German modification; CM = Clinical modification; ICPC = International Classification of Primary Care.

9.2.2 Study population

For the progress reports (monitoring uptake of galcanezumab) the following inclusion and exclusion criteria will be applied:

Inclusion criteria

- Receive a prescription/dispensing for galcanezumab during the study period.

Exclusion criteria

- No exclusion criteria will be applied.

To determine utilization of galcanezumab, the incidence rates of the safety outcomes of interest and the secondary objectives all patients meeting the following criteria during the study period will be eligible for inclusion in the galcanezumab or comparator topiramate main cohorts:

Inclusion criteria

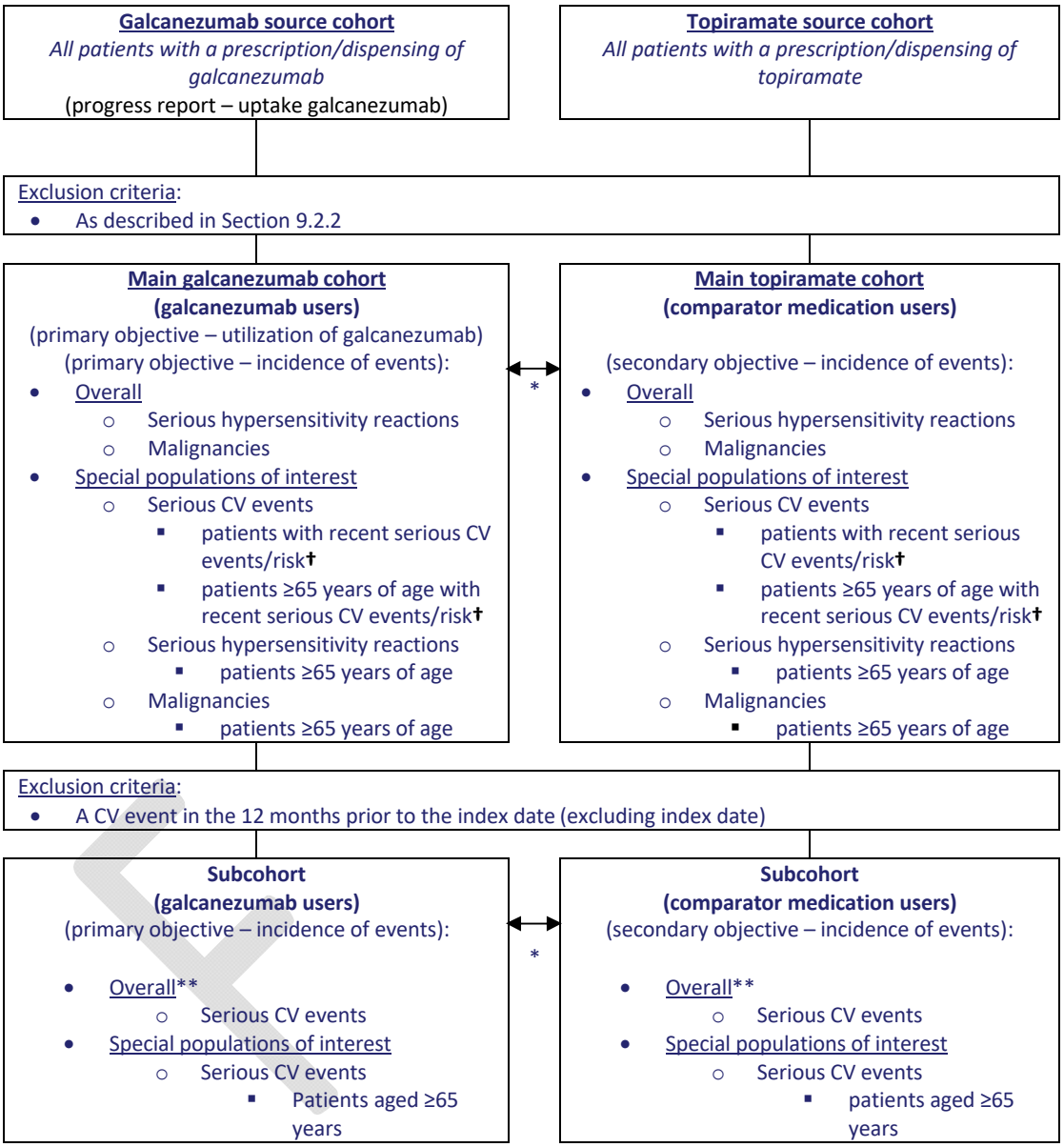
- Receive a prescription/dispensing for galcanezumab or topiramate during the study period

Exclusion criteria

- Have missing data on age and sex
- Are aged <18 years at the index date
- Have missing dates for start and end of enrolment in the database
    - Note that "end of enrolment" could also be end of available data.
- Start and end date of available data in the database not lying within the overall period of data availability in the database
- Have <12 months of valid database prior to the index date
- A prescription/dispensing for galcanezumab in all available database history prior to the index date
- A prescription/dispensing for non-galcanezumab CGRP antagonists in the 12 months prior to the index date
- Have a recorded diagnosis of CH (as cluster headache not an approved galcanezumab indication in the EU) in the entire available history prior to the index date
- Not having a recorded diagnosis for migraine during all available history or not using triptans and/or ergotamine in the 12 months prior to or on the index date
- Have a recorded diagnosis of epilepsy in the entire available history or evidence of use of antiepileptics (excluding topiramate and valproic acid) in the 12 months prior to the index date (as topiramate is indicated for both epilepsy and migraine)
- Have a recorded diagnosis for any malignancy or evidence of drugs used solely for the treatment of cancer during all available database history prior to or on the index date

- For the outcome of serious CV event only: a recorded diagnosis for a serious CV event in the 12 months prior to the index date (excluding index date)

Several study cohorts will be created as described below and as presented in Figure 9.1.



*Galcanezumab users eligible for the primary objectives will be matched (see Section 9.7.4) to comparator medication users for the secondary objective; **users without serious CV event in the 12 months prior to the index date (excluding index date); †This group will include patients with prevalent CV disease as well and the occurrence of serious CV events during follow-up will likely not be incident although presented as incidence rates

Figure 9.1 Flow chart of study cohort selection

Code lists and identification algorithms will be created in close collaboration with the participating databases and medical experts and will be described in the SAP. Detailed knowledge of the healthcare system for each country is necessary to provide the correct

definitions. We will identify patients with migraine using both recorded inpatient and out-patient diagnoses based on the specific coding system used by the individual databases (e.g. READ in CPRD, ICD-9 in PHARMO, ICD-10 in SIDIAP, GePaRD and PHARMO, and ICPC in PHARMO), as well as the specific provenance of the data (e.g. hospital admission, primary care or emergency care visits). For databases such as ARS and SNDS that do not include out-patient diagnoses for assessment of the indication of use, algorithms will be developed based on specific (medication-based) parameters of care patterns to distinguish between the migraine and epilepsy (relavent to distinguish between topiramate use for migraine versus epilepsy).

Galcanezumab source cohort

This cohort will include all patients with a prescription/dispensing of galcanezumab without applying any exclusion criteria in order to monitor the uptake of galcanezumab.

Main galcanezumab cohort

Utilization of galcaenzuamb and the incidence of serious hypersensitivity reactions and malignancies will be evaluated in the main galcanezumab cohort presented in Figure 9.1. Within this cohort, the following special populations of interest will be created:

1) patients aged ≥65 yearson the index date
2) patients with recent (within the last 6 months) serious CV events/risk before the index date
3) patients aged ≥65 years ánd with recent (within the last 6 months) serious CV events/risk.

The incidence of serious hypersensitivity reactions and malignancies will be estimated in the main cohort and in special population of interest 1). The incidence of serious CV events will be estimated in special populations of interest 2) and 3).

Subcohort (galcanezumab users)

The incidence of serious CV events will be evaluated in the subcohort of eligible galcanezumab as presented in Figure 9.1, without a recorded diagnosis of a CV event in the 12 months prior to the index date (excluding index date). Within this subcohort, a special population of interest group of patients aged ≥65 years will be created in which the incidence of serious CV events will be estimated as well.

Main cohort (galcanezumab and comparator medication users) and subcohort (galcanezumab and comparator medication users)

Eligible galcanezumab users will be retained for the secondary (comparative) objective. To provide context for rates of serious cardiovascular events and malignancies, patients who initiate treatment with topiramate will be used as a comparator cohort. If the number of available comparator medication users is prohibitively small, the comparator cohort may be expanded to include patients exposed to sodium valproate/valproic acid or other appropriate comparator medications, with appropriate discussion of underlying considerations and

limitations provided in study reports. Justification for the selection of topiramate as the reference cohort is provided below.

Serious CV events and malignant neoplasms

Comparator medications used for the prophylaxis of migraine include antiepileptics (divalproex sodium, sodium valproate, topiramate, and gabapentin), beta-blockers (metoprolol, propranolol, oral timolol, nadolol, atenolol, and nebivolol), calcium channel blockers (verapamil), and antidepressants (amitriptyline and venlafaxine). Physician's choice of prophylactic migraine therapy often accounts for a patient's co-morbid conditions. Beta-blockers, calcium channel blockers, and anti-depressants were therefore not included as comparator medications for evaluation of CV events due to their association with existing cardiovascular comorbidities and risk for a future serious cardiovascular event.

Topiramate was selected as the comparator medication due to the high prevalence of use among migraine patients and the absence of evidence of channeling bias based on approved indications. Other antiepileptics were not considered due to their low prevalence of use among migraine patients and approval for indications that are associated with cardiovascular risk.

There is no known association between topiramate and malignancy outcomes, and no channeling bias associated with malignancy risk is expected. As a result, topiramate was also selected as the comparator for the malignancy outcome.

Serious hypersensitivity reactions

Non CGRP monoclonal antibody prophylactic migraine medications are small molecules that are typically less immunogenic than monoclonal antibodies. There is also uncertainty around the ability to accurately identify serious hypersensitivity events. As such, formal comparative analyses are not proposed; however, rates in the comparator cohort will be provided for context.

Eligible topiramate users as selected from Figure 9.1 will be eligible for inclusion in the comparator cohort.

All eligible galcanezumab users and all eligible comparator medication users as defined in Figure 9.1 above will be included in the assessment of incidence of serious CV events, serious hypersensitivity reactions, and malignancies. As feasible, comparative safety analyses of CV events and malignancy will be conducted between all eligible galcanezumab users and all eligible comparator medication users.

9.2.3 Study period

For each of the databases, the study will start at the launch date of galcanezumab in each country of interest. The end of the study period will depend on the available data at the end of data collection (Q3 2026) for each country. Assuming an average data lag time of approximately 1.5 years, the end of the study period will be around Q4 2025 at the latest. Table 9.2 provides an overview of the expected availability of data per milestone, considering that data lag times differ per country.

In a long-term safety study, insufficient follow-up post drug exposure can influence the ability to accurately assess a delayed safety risk such as malignancy. Length of follow-up is influenced by (1) years of data available post launch, (2) the rate of drug uptake in the market and (3) the stability of patients in the dataset. Although the European Commission granted marketing authorisation for galcanezumab on 14 November 2018, galcanezumab launch/reimbursement dates differ across the countries included in this analysis. As of 4 November 2019, galcanezumab has been launched and is being reimbursed in Germany and Sweden; launched, but not yet reimbursed in Italy, UK and the Netherlands; and not yet launched in Spain and France. Therefore, based on the data collection schedule in table 9.2 and a final study report commitment date of 31 December 2026, 5-6 years of post-launch data would be expected in Germany, Sweden, Italy, UK and the Netherlands. However, the uptake of galcanezumab is unknown and could differ pre and post reimbursement. Later launch/reimbursement dates and slow market uptake could reduce the number of patients with multiple years of data post receipt of galcanezumab.

Therefore, a patient count per calendar year in each country/dataset including mean (SD) and median (IQR) length of follow-up will be included in the interim and final study reports. Based on these results, at the time of the final study report, it will be determined whether an additional report where the data collection time period is extended in certain countries would be useful for assessing events with long latency.

Table 9.2: Expected availability of data per milestone for all study databases

Milestone*	**Planned date**	**Expected end of data availability up to and including**						
		ARS (IT)	**CPRD (UK)**	**GePaRD (DE)**	**PHARMO (NL)**	**SHR (SE)**	**SIDIAP (SP)**	**SNDS (FR)**
Monitor 1	30 Nov 2020	Q2 2020	2019	2018	2019	2019	2019	2019
Monitor 2	30 Nov 2021	Q2 2021	2020	2019	2020	2020	2020	2020
Monitor 3	30 Nov 2022	Q2 2022	2021	2020	2021	2021	2021	2021

Milestone*	Planned date	Expected end of data availability up to and including						
		ARS (IT)	CPRD (UK)	GePaRD (DE)	PHARMO (NL)	SHR (SE)	SIDIAP (SP)	SNDS (FR)
Monitor 4	30 Nov 2023	Q2 2023	2022	2021	2022	2022	2022	2022
Monitor 5	30 Nov 2024	Q2 2024	2023	2022	2023	2023	2023	2023
Monitor 6	30 Nov 2025	Q2 2025	2024	2023	2024	2024	2024	2024
Interim report	31 Dec 2023	Q2 2023	2022	2021	2022	2022	2022	2022
Final report of study results	31 Dec 2026	31 Aug 2026	2025	2024	2025	2025	2025	2025

*Monitors to be provided as part of the annual study progress reports with the PSUR.

9.2.4 Inclusion and exclusion criteria

Cohort inclusion and exclusion criteria are described in Section 9.2.2.

9.2.5 Cohort start

For the progress reports and the primary objective, the date of the first recorded prescription/dispensing of galcanezumab or topiramate in the study period will be defined as the cohort entry ('index date').

Because galcanezumab is new to the market and expected to be prescribed in a later treatment line than topiramate, it is likely that some galcanezumab users will have used topiramate prior to their index date. Therefore, for the secondary objective only, the inclusion and exclusion criteria will be assessed at each dispensings date of topiramate rather than only at the index date as defined for the progress report and the primary objective. As a consequence, the index date of topiramate users might shift.

9.2.6 Follow-up and time at risk

Eligible patients will be followed up from the index date until either occurrence of the outcome being assessed, the last date of follow-up available in the database, the study period, or death, whichever occurs first.

Additional definitions for the time at risk specific to each outcome are provide below:

- Serious CV events; time between index date and the minimum date of one of the following:

- discontinuation of index treatment (See Section 9.3.1)
- first dispensing of a non-galcanezumab CGRP antagonist after the index date

A sensitivity analysis will be performed where the following additional censoring criterion for galcanezumab users only will be applied when determining time at risk: first dispensing of the comparator drug.

- Serious hypersensitivity reactions; the risk window will be the day of and the day after the index date. A sensitivity analysis will be performed expanding the risk window to include time to discontinuation of index treatment (See Section 9.3.1)
- Malignancies; no additional definition for the time at risk than specified above.
  Due to the long latency period of this outcome, patients will not be censored upon discontinuation of index treatment or a dispensing of a non-galcanezumab CGRP antagonist after the index date. Additionally, galcanezumab users will not be censored upon dispensing of topiramate after index date.

Note that patients are not allowed to enter both the galcanezumab and the topiramate cohort. Patients switching from topiramate to galcanezumab or from galcanezumab to topiramate during the study period will, by definition, be included in the galcanezumab cohort only.

9.3 Variables

9.3.1 Exposures of interest

The primary exposure of interest is galcanezumab. Topiramate is selected as the comparator medication. Galcanezumab and topiramate use will be identified by prescription or pharmacy fill data using the database specific coding system (e.g. Anatomical Therapeutic Chemical [ATC] Classification, British National Formulary [BNF]/Multilex coding; see Table 9.1). The first prescription/dispensing of galcanezumab or comparator medication will be defined as the index date. We will consider patients as new users if they do not have a prescription/dispensing recorded in the 12 months prior to index date.
For the assessment of serious CV events and serious hypersensitivity reactions, an as treated approach will be taken. Patients will be considered exposed to galcanezumab up to 4 months after the last dispensing/prescription to account for the long elimination half-life. For other medication the duration of each prescription/dispensing will be calculated by dividing the amount prescribed/dispensed by the prescribed dose recorded in the database (if available) and otherwise the duration of use will be estimated based on the assumed or defined daily dose. Episodes of treatment will be created for galcanezumab and comparator medication for all prescriptions/dispensings as long as the number of days between end of previous prescription/dispensing and the start of the new prescription/dispensing is less than the defined allowed gap (90 days for both galcanezumab and topiramate). We will consider

patients as having discontinued treatment if there is a gap in a series of successive prescriptions/dispensings of the index drug that is larger than the defined allowed gap. The estimated end of the prescription/dispensing will be defined as the date of discontinuation, at which point patients' follow-up time will be censored. If follow-up ends without a patient exceeding the allowable gap, the patient will not be considered as discontinued.

Malignancy outcomes require a long latency period, and as a result, are not easily attributed to a particular drug exposure. To account for this ambiguity, the assessment of malignancies will consider a modification of an intent to treat approach where patients exposed to topiramate will be considered exposed until treatment with galcanezumab. Once a patient is exposed to galcanezumab, the patient will continue to accrue follow-up time regardless of treatment received or discontinuation of treatment. Although this approach is considered conservative from the standpoint that attribution of a malignancy to galcanezumab will not be missed, it ignores the duration of galcanezumab exposure and exposure to other treatments. The implications of this approach will be discussed in Section 9.9.

9.3.2 Outcomes of interest

The outcome events of interest include a recorded diagnosis of:

- serious CV events
- serious hypersensitivity reactions
- malignancies

as identified from in- or out-patient electronic medical records. Serious events will be defined according to recorded hospitalisations. Events of interest will be identified using the event-specific codes based on the coding system(s) used in the databases of interest (e.g. READ, ICD-9, ICD-10, or ICPC according to the coding systems presented in Table 9.1) as well as the specific provenance of the data (e.g. hospital admission, primary care or emergency care visits). Diagnostic codes and algorithms to identify the outcomes of interest will be created upon completion of the protocol and be described in the SAP.

Serious CV events

Serious CV events will be comprised of multiple serious ischaemic events and will be reported as composite outcome and as separate outcomes. Outcomes under consideration include: hospitalisation for MI, TIA, ischaemic stroke, ischaemic heart disease, AP, PCI, coronary revascularisation and CV death (i.e. death after any of these events, to be detailed in the SAP). The final selection of CV outcomes will depend on the accuracy of the diagnosis within in each data source.

Serious hypersensitivity reactions

Serious hypersensitivity reactions will be identified by a hospitalisation or emergency care visit for anaphylaxis or allergy based on the clinical criteria proposed by the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) (see Figure 9.2).[7] As feasible based on the information available in the different databases, hospitalisations or emergency care visits for angioedema, acute asthma or acute bronchospasm, acute upper airway obstruction, epinephrine administration and death from serious hypersensitivity reactions (i.e. death after any of these events, to be detailed in the SAP) will additionally be assessed as part of this outcome.

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Figure 9.2 Clinical criteria for diagnosing anaphylaxis[7]

Malignancies

Malignant neoplasms will be identified as a new diagnosis for any cancer, excluding non-melanoma skin cancer (NMSC). Malignancies will be reported as a composite outcome (all malignancies, excluding NMSC) and by type of the first malignancy (i.e. per primary cancer site). Patients with prior malignancies will be excluded.

An overview of the different study populations for each of the objectives and the corresponding analyses is provided in Table 9.3.

Table 9.3: Overview of objectives, corresponding analyses and study populations

Objective	Analysis	Galcanezumab population	Comparator population
Progress reports	Characterise the utilisation of galcanezumab	All galcaenzumab users	None

Primary	Characterise the utilisation of galcanezumab	Utilization of galcanezumab: main cohort and in the following special populations of interest: • ≥65 years of age • recent serious CV events and/or serious CV risk • ≥65 years of age with recent serious CV events and/or serious CV risk	None
	Incidence of outcomes	Incidence of serious hypersensitivity reactions and malignancies: main cohort and in the following special populations of interest: • ≥65 years of age Incidence of serious CV events: subcohort (excluding those with a CV event in the 12 months prior to galcanezumab initiation from the main cohort) and in the following special populations of interest: • ≥65 years of age (from subcohort) • recent serious CV events and/or serious CV risk (from main cohort) ≥65 years of age with recent serious CV events and/or serious CV risk (from main cohort)	None
Secondary	Comparison of serious CV events	Subcohort (excluding those with a CV event in the 12 months prior to galcanezumab initiation from the main cohort) and in the following special populations of interest: • ≥65 years of age (from subcohort) • recent serious CV events and/or serious CV risk (from main cohort) • ≥65 years of age with recent serious CV events and/or serious CV risk (from main cohort)	Subcohort (excluding those with a CV event in the 12 months prior to galcanezumab initiation fro the main cohort) and in the following special populations of interest: • ≥65 years of age (from subcohort) • recent serious CV events and/or serious CV risk (from main cohort) • ≥65 years of age with recent serious CV events and/or serious CV risk (from main cohort)
	Comparison of serious hypersensitivity reactions	Main cohort and in the following special populations of interest: • ≥65 years of age	No formal comparison; rates in the topiramate cohort will be provided for context
	Comparison of malignancies	Main cohort and in the following special populations of interest: • ≥65 years of age	Main cohort and in the following special populations of interest: • ≥65 years of age

9.3.3 Demographic and baseline characteristics

The following covariates will be considered for descriptive purposes and as confounders in the comparative study. Except for length of follow-up, a look-back period of at least 12 months will be used to assess baseline demographics and clinical covariates. Look-back periods, codes and algorithms to identify these characteristics will be developed and described in detail in the SAP.

- Age
- Gender
- Calendar year of index date
- Available database history
- Available database follow-up (stratified by calendar year of index) (i.e. time from index date until the last date of follow-up available in the database, the study end date, or death, whichever occurs first).
- Reason for end of database follow-up (end of data collection, end of study period, deceased)
- Reason for end of time at risk for the outcome serious CV event
- Duration of available database follow-up by reason for end of time at risk for the outcome serious CV event
- Medication history
    - Antimigraine preparations (e.g. ergotamine, triptans, CGRP antagonists)
    - Biologics
    - Opioids
    - Non-steroidal anti-inflammatory drugs (NSAIDs) (limited to prescribed medication only)
    - Antidepressants
    - Botulinum toxin
    - CV medication (categorised, e.g. beta-blockers, ACE inhibitors)
- History of serious CV events
    - MI
    - TIA
    - Ischaemic stroke
    - Ischaemic heart disease
    - AP
    - PCI
    - Coronary revascularisation
- History of serious hypersensitivity reactions

- CV risk factors
    - Smoking status (available in CPRD, PHARMO and SIDIAP; in other databases by using proxies from smoking-related diagnosis and smoking cessation drugs)
    - BMI (available in CPRD, PHARMO and SIDIAP; in other databases based on obesity-related diagnostic codes as available)
    - Hypertension
    - Hyperlipidaemia (lipid levels available in CPRD, PHARMO and SIDIAP; in other databases by using coded hyperlipidaemia diagnoses or proxies based on drug utilisation)
    - Type 2 diabetes mellitus
    - Impaired renal function
    - History of haemorrhagic stroke
- Comorbidities
    - Psychiatric disorders
    - Heart failure
    - Peripheral vascular disease
- Days of supply for acute migraine medication
- Traceable start of migraine
- Length of migraine disease
- Healthcare utilisation measures (e.g. number of drugs, hospitalisations, exact measures to be defined in the SAP)

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9.4 Data sources

This study will be conducted by using European databases that comprise routine healthcare data. This will provide a reflection of real-world circumstances and prescribing behaviours. The databases have been selected based on their geographic location, the availability of population-based data on drugs, plus their recognised reputation in the area of drug utilisation and safety research. Multiple countries are included in order to provide international data and to guarantee sufficient exposure to galcanezumab.

The data for this study will be retrieved from seven databases: Système National des Données de Santé (SNDS) from France, German Pharmacoepidemiological Research Database (GePaRD) from Germany, Agenzia regionale di sanità della Toscana database (ARS) from Italy, the PHARMO Database Network (PHARMO) from the Netherlands, Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Catalonia, Spain, Swedish Health Registers (SHD) from Sweden and The Clinical Practice Research Data Link Gold

(CPRD) from the UK. Annex 3 presents the ability of data sources to identify relevant variables which is underlying the selection of these databases.

All of the databases comply with European guidelines on the use of medical data for medical research and have been (partly) validated for pharmacoepidemiological research.[8-20] More details on the individual databases are provided in the following sections.

9.4.1 The Système National des Données de Santé (SNDS) - France

The SNDS (Système National des Données de Santé) database is the nationwide healthcare insurance system database with individual anonymous information on all reimbursed out-patient claims linked to the national hospital-discharge summaries database system (Programme de médicalisation des systèmes d'information - PMSI) and the national death registry, using a unique national pseudonymised identifier. It currently includes 98.8% of the French population, more than 66.6 million persons from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires. The SNDS contains individual pseudonymised information on[14]:

- General characteristics: gender, year of birth, affiliation scheme, area of residence;
- Date of death for those concerned and cause of death with a lag of 2-3 years;
- Long-term disease (LTD) and associated ICD-10 codes with starting and ending date. LTD mainly includes costly chronic diseases. LTD registration is obtained at the request of a patient's practitioner and validated by the health insurance system physician. Once registered, patients receive full (i.e. 100%) reimbursement for expenditure related to the LTD. The LTD information is specific for the diagnosis (very low risk of false positives), but not sensitive because not all patients with the disease ask to benefit from a LTD;
- Out-patient reimbursed healthcare expenditures: visits, medical procedures, nursing acts, physiotherapy, medical imageries, lab tests, drugs, medical devices, transports, sick leaves… with prescriber and professional caregiver information (medical or paramedical specialty, private/public practice), dates (prescription and dispensing), and codes (but not the medical indication nor result);
- Hospital-discharge summaries from the PMSI: ICD-10 diagnosis codes (primary and associated diagnosis) for all private and public medical, obstetric and surgery hospitalisations, with the date and duration of hospitalisation, medical procedures, and cost coding system, as well as most of very costly drugs. The hospital discharge summary includes the medical unit summaries when the patient is hospitalised successively in several medical units.

Non-hospital data are updated every month and hospital-discharge summaries yearly at the end of Q3 for the previous year. Access to SNDS is regulated and needs approval from the National Institute of Health Data (Institut National des Données de Santé - INDS) and French

data protection commission (Commission Nationale de l'Informatique et des Libertés - CNIL). Further details on coding systems and database lag time are presented in Table 9.1.

9.4.2 German Pharmacoepidemiological Research Database (GePaRD) - Germany

GePaRD is based on claims data from four statutory health insurance providers in Germany and currently includes information on more than 25 million persons who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on all reimbursable drug dispensations and all reimbursable out-patient (i.e., from general practitioners and specialists) and in-patient diagnoses and services. Per data year, there is information on approximately 17% of the general population and all geographical regions of Germany are represented. Further details on coding systems and database lag time are presented in Table 9.1.

9.4.3 Agenzia regionale di sanità della Toscana database (ARS) - Italy

The ARS database includes pseudonymised patient-level information on the utilisation of healthcare services reimbursed by the National Healthcare Service (NHS) and delivered to all subjects who are residents and registered with a general practitioner in Tuscany, Italy. ARS covers 3.7 million residents in Tuscany. Data is available since 2003. The database contains demographic data, hospitalisation data (including discharge diagnoses and procedures), emergency visits (including diagnosis and procedures), causes of death, utilisation of secondary care visits and diagnostic procedures, mental health registry, exemptions from co-payment for chronic diseases, pathology registry and out-patient dispensing data both upon specialist and primary care prescription. Drugs that are purchased over the counter (OTC) are not recorded into the database. As for medications administered during hospitalisation, total amount per day and hospital ward is tracked. Deterministic record linkage of drugs used during hospital stay with patient IDs is not possible. However, probabilistic linkage can be performed and high accuracy is expected for those drugs with low prevalence of use. Further details on coding systems and database lag time are presented in Table 9.1.

9.4.4 PHARMO Database Network (PHARMO) - Netherlands

The PHARMO Database Network is a population-based network of electronic healthcare databases combining data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms [10,21].

The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 4 million (25%) residents of a well-defined population for an average of ten years. Data collection period, catchment area and overlap between data sources differ. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other available information is dependent on the data source. Further details on coding systems and database lag time are presented in Table 9.1. To address the objectives of the present study the PHARMO databases described below will be used.

General Practitioner Database

The General Practitioner (GP) Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO ATC Classification System [22]. Diagnoses and symptoms are coded according to the ICPC [23], which can be mapped to ICD codes, but can also be entered as free text. GP data cover a catchment area representing 3.2 million residents.

Out-patient Pharmacy Database

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO ATC Classification System [22]. Out-patient pharmacy data cover a catchment area representing 4.2 million residents.

Hospitalisation Database

The Hospitalisation Database comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required (i.e. in-patient records) from the Dutch Hospital Data Foundation [24]. The records include information on hospital admission and discharge dates, discharge diagnoses and procedures. Ambulatory consultations and in-patient medication are not included in this database. Diagnoses are coded according to the WHO ICD-10 (and ICD-9-CM before 2013) [25] and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures [20] which links to the Dutch Healthcare Authority declaration codes [26] and the Dutch Classification of Procedures [27]. The Dutch Hospital Data Foundation collects hospitalisation records from nearly all hospitals in the Netherlands. With permission from each hospital the data are linked for research purposes

with the PHARMO Database Network via a trusted third party. Currently, PHARMO has access to data of over 80% of the hospitals in the Netherlands.

9.4.5 Sistema d'Informació per al Desenvolupament de la Investigació en Atenció (SIDIAP) - Spain

The SIDIAP database includes the information coded by GPs using ICD-10 codes and some structured forms for registering common clinical variables (smoking, alcohol drinking, body mass index, blood pressure, etc.), linked pharmacy invoice data from the official reimbursement database, and linked hospitalisation data for a subset (around 30%) of the population in the database.

SIDIAP has been collecting data from 2000 (research usable data from 2006 onwards), and the database is updated on an annual basis. The SIDIAP database is comprised of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 6 million patients (approximately 80% of the total of 7.5 million population of Catalonia). Further details on coding systems and database lag time are presented in Table 9.1.

9.4.6 Swedish Health Registers (SHR) - Sweden

The SHRs cover all Swedish residents, are held by the National Board of Health and Welfare in Sweden and include, among others, the Prescribed Drug Register, the Cause of Death Register and the Patient Register. All registers contain personal identification numbers, which allows linkage of all Swedish Health Registers on a patient level.

The Prescribed Drug Register contains information on all prescriptions filled at pharmacies in Sweden and is updated on a monthly basis. Data can be captured on dispensed drugs using anatomic therapeutic chemical (ATC) codes, prescription date, dispensing date, dose, pack size, healthcare professional issuing the prescription, as well as sex, age and residency of the patient. Complete data from the register is available from 1 July 2005.

Date and cause of death can be obtained from the Cause of Death Register. The statistics on causes of death comprise all deaths, covering Swedish residents, whether the person in question was a Swedish citizen or not and irrespective of whether the deaths occurred in Sweden or while they were abroad. The quality of the statistics varies, depending on the examinations made to define the underlying cause of death and due to changes in the classification system or the processing methods. Complete data from the register is available from 1 January 2000.

The national Patient Register contains patient data, geographical data, administrative data and medical data for both inpatient and out-patient hospital care in Sweden. The register contains main and secondary diagnosis codes (according to current version of ICD) for each

admission and out-patient hospital visit as well as procedure codes. The register contains complete inpatient data from 1 January 1987, with a coverage of approximately 99%, as well as complete out-patient data from 1 January 2001. Further details on coding systems and database lag time are presented in Table 9.1.

9.4.7 The Clinical Practice Research Data Link Gold plus Hospital Episodes Statistics (HES) Data (CPRD) - UK

The CPRD contains anonymised diagnostic and prescribing information recorded by GPs as part of their routine clinical practice in the UK. The database coverage is approximately 5 million active patients (between 4% to 7% of the UK population, depending on calendar year) and over 13 million active and inactive patients. These data are linkable, at least partially, with other healthcare data sets (e.g., hospitalisation records, national mortality data, cancer registry data) via the patient's National Health Service (NHS) number, gender, date of birth, and postal code.

The CPRD comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, medical procedures, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to a UK-specific coding system (Gemscript codes). Detailed information on prescriptions written by GPs, including prescribed dose and duration, is automatically recorded in the database in most instances. READ codes are used to record diagnoses. Additional diagnostic information based on ICD-10 and procedural coding can be found in other sources such Hospital Episode Statistics (HES), which is, however, available only for approximately 50% of the patients registered in England. Data on drugs prescribed/administered in the hospital setting are not available. Further details on coding systems and database lag time are presented in Table 9.1.

9.5 Study size

The descriptive outcomes in the primary objective as well as the incidence rates as part of the secondary objective will be presented in the final report regardless of the size of the study population (note: results for N<5 will not be presented due to privacy restrictions). The comparative analyses will only be performed if sample sizes allow. Galcanezumab was approved on 14 November 2018 and is currently pending launch in many European countries, so the number of galcanezumab-exposed patients will depend on the uptake of galcanezumab in Europe. Country-specific launches and reimbursement may elongate the time before uptake is sufficient for this study. Therefore, cohort sizes will be monitored regularly (see

Section 9.1.2). Patient accumulation will also influence the decision with regard to the timing of the interim report.

For the comparative analyses, we aim to have a sample size that will allow us to detect a 2-fold difference in the primary outcome of composite serious CV events. Assuming a power of 80%, a 2-sided significance level of 0.05 and a 1:2 matching ratio of galcanezumab vs. comparator users, at least 7,245 person-years of follow-up in galcanezumab-exposed patients will be required in each database. This is based on an age-adjusted background incidence rate for major CV events of 22.6 per 10,000 person-years in a female population with active migraine (without aura), regardless of treatment.[28] In this study major CV event was defined as the first occurrence of any of the following events: nonfatal ischaemic stroke, nonfatal MI, or ischaemic CV disease death. Calculations were based on the population with active migraine (without aura) as the lowest background incidence rate was observed in this group (i.e. requiring the highest sample size). However, the study populations in the current study will include migraine patients with aura who have a higher background rate (i.e. requiring a lower sample size). Study size projections will be monitored during the study period, taking into account observed incidence rates and person-years accumulation.

9.6 Data management

Routine procedures or practice will include checking electronic files, maintaining security and data confidentiality and following analysis plans. Each research partner will maintain any patient-identifying information securely on site according to internal standard operating procedures or guidance documents or routine practice.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed, with periodic backup of files to tape. Each centre will follow its standard institutional procedures or routine practice to restore files in the event of a hardware or software failure. Further details per database are provided below.

9.6.1 Database-specific data management

The Système National des Données de Santé (SNDS) – France

Database extraction criteria will be described in a data extraction plan (DEP) approved prior to initiating extraction, done by Caisse Nationale d'Assurance Maladie, the database provider. Several controls will be done by the Bordeaux data manager in charge of the project to validate the integrity of data extracted.

German Pharmacoepidemiological Research Database (GePaRD) – Germany

GePaRD is based on deterministically linked claims data. The linkage of out-patient, hospital and dispensation data is performed at each statutory health insurance provider (SHI) based on insurance member identifiers. The SHIs deliver the data to a third party trust center where the data is pseudonymised and delivered to BIPS according to the data protection concept. Comprehensive plausibility checks are performed before pseudonymisation, as well as before inclusion of new data into GePaRD.

Agenzia regionale di sanità della Toscana database (ARS) – Italy

The ARS database combines data from different healthcare databases that records healthcare episodes delivered to Tuscan inhabitants and reimbursed by the NHS. Patient-level information collected in such databases is deterministically linked through a pseudo-anonymised universal regional identification code.

Patients registered in the population registry can be potentially followed in all the available administrative databases (population registry, reimbursed drug dispensing for out-patients, hospital discharge records, etc.). In addition, ARS has stable relations with regional healthcare providers which have in custody electronic medical records and results from diagnostic tests which, in case of need, can be linked for the purposes of a specific study. This would provide additional variables for a subpopulation of the Tuscan inhabitants, or clinical information to be used for validation purposes in a subsample.

ARS' core data is currently mapped to the OMOP CDM, version 5.

ARS' database is updated approximately every month, with a lag time of 3-4 months. Transactional data may still be incomplete, and data of each year is consolidated by the end of March of each year.

PHARMO Database Network (PHARMO) – Netherlands

The PHARMO Database Network combines data from different healthcare databases (pharmacy, hospital, GP etc.). These different databases are probabilistically linked through validated algorithms that do not invade the privacy of the patients [10,21]. Before linkage of the different databases, patients for whom crucial information needed for linkage is missing (date of birth, gender, GP) are removed.

Healthcare databases are used as administration tools in patient care and have their limitations with regard to their use in scientific research. For example, the completeness of data may differ per healthcare center. Therefore, with each update of the database the completeness of registration per healthcare center is evaluated (overall and within specific care areas, number of records, internal consistency and comparison of calendar years).

For each study, specific study checks on the linked data are performed. These partially depend on which specific databases are required for the study and their importance to the selection of patients or outcomes. For each database it is determined per patient from which time point onwards the patient is registered in the specific database and from which time point the patient is lost to follow-up (due to for example death or moving out of the PHARMO catchment area). Patients are regarded eligible to be included in a study if they are registered and can be followed in all required databases.

Sistema d'Informació per al Desenvolupament de la Investigació en Atenció (SIDIAP) – Spain

The SIDIAP database is the result of the deterministic linkage of primary care electronic medical records and pharmacy dispensation data. The linkage and anonymisation, as well as the storage of all raw data, is done by the main health provider in the region, the Catalan Institute of Health (Institut Catala de la Salut or ICS in Catalan language). Pseudonymised data is extracted on a study-per-study basis and delivered to researchers following a bespoke data sharing agreement.

Swedish Health Registers (SHR) – Sweden

The Swedish national health care registries offer high quality data for research with nation-wide coverage and close to complete data for most available variables. Patient-level data from each register is available for research upon prior ethics approval and individual patients can be linked between all SHRs via the personal identifier given to all Swedish citizens. The national health care registries to be used in this study are the Patient Register, the Prescribed Drug Register, and the Cause of Death Register, which are all held by the National Board of Health and Welfare (NBHW).

The linkage via the personal identifier will be performed by the NBHW following an ethical approval by the Swedish Ethical Review Board and data application to the NBHW, and will be anonymised prior to delivery. The register-based data are known to have a high degree of completeness. Reporting of certain variables used in this study is not voluntary so for health care visits and dispensed prescriptions all the necessary information can be expected to be present. Missing data resulting from the very unlikely event that a patient's health care visit or dispensed prescription would not have been captured at all by the registerscould not be identified.

The Clinical Practice Research Data Link Gold plus Hospital Episodes Statistics (HES) Data (CPRD) – UK

The patient-specific data on diagnoses, drug prescriptions and related information in the CPRD are recorded by trained general practitioners (GP) on their local workstation in the office as part of their daily routine, i.e. when they see patients and update the patients' health records.

Prescriptions issued by the GP are recorded directly on computer, and a print-out is given to the patient. The data are downloaded on a regular basis onto a central server, administered by the CPRD. The entire dataset of anonymous data can be downloaded by approved CPRD licensees. Local programmers in the various research groups that have access to CPRD data further organise the data based on the specific needs of the researchers. Upon request by researchers, the programmer hands out datasets (ASCII-files) which can then be analysed by the researchers. The data are stored in a protected and safe way at the local research institutions. Datasets and additional information must not be stored after the finalisation of a given project; the CPRD asks researchers to destroy datasets after termination of research projects to protect confidentiality and to reduce the risk of misuse of the data for purposes other than the predefined research projects.

9.6.2 Common programs

The aim of this multi-country study is to apply common techniques in different databases. Differences between the results from the different databases should be due to database differences and differences in healthcare systems, and not due to programming differences. Complete centralisation of analysis is not possible due to local governance. More importantly, PHARMO also does not advocate central analysis as local expertise of the database and healthcare system is essential to prepare the data for analyses and interpretation.

Code lists and identification algorithms will be created in close collaboration with the participating databases and medical experts and will be described in the SAP. Detailed knowledge of the healthcare system is necessary to provide the correct definitions.

A schematic overview of the proposed working model is visualised in Figure 9.3 and includes:

- generation of local data according to the common data model
    - local experts prepare their research files based on the common data model, following their local database processing scripts and quality control
    - variations in the local definition of study variables will be envisioned to allow for sensitivity analyses to address heterogeneity of data
- centralising program development at PHARMO in SAS
    - double programming in R by the other database holder, which allows for validation and quality control of the common programs
    - the two programs (SAS and R) will be run on the same simulated dataset to verify consistency between the outputs
- shared analysis scripts that can run on the databases locally
- shared table shells for preparation of reports

- possible heterogeneity in results will be discussed with the local teams and interpreted in the light of the sensitivity analysis addressing heterogeneity of local data

All data, except for Sweden and Italy, will be analysed using SAS programs (SAS Institute Inc., Cary, NC, USA) and conducted under Windows using SAS version 9.3 or updates. Italy and Sweden will analyse their data using R 3.5.0 (The R Project for Statistical Computing, www.r-project.org) or updates.

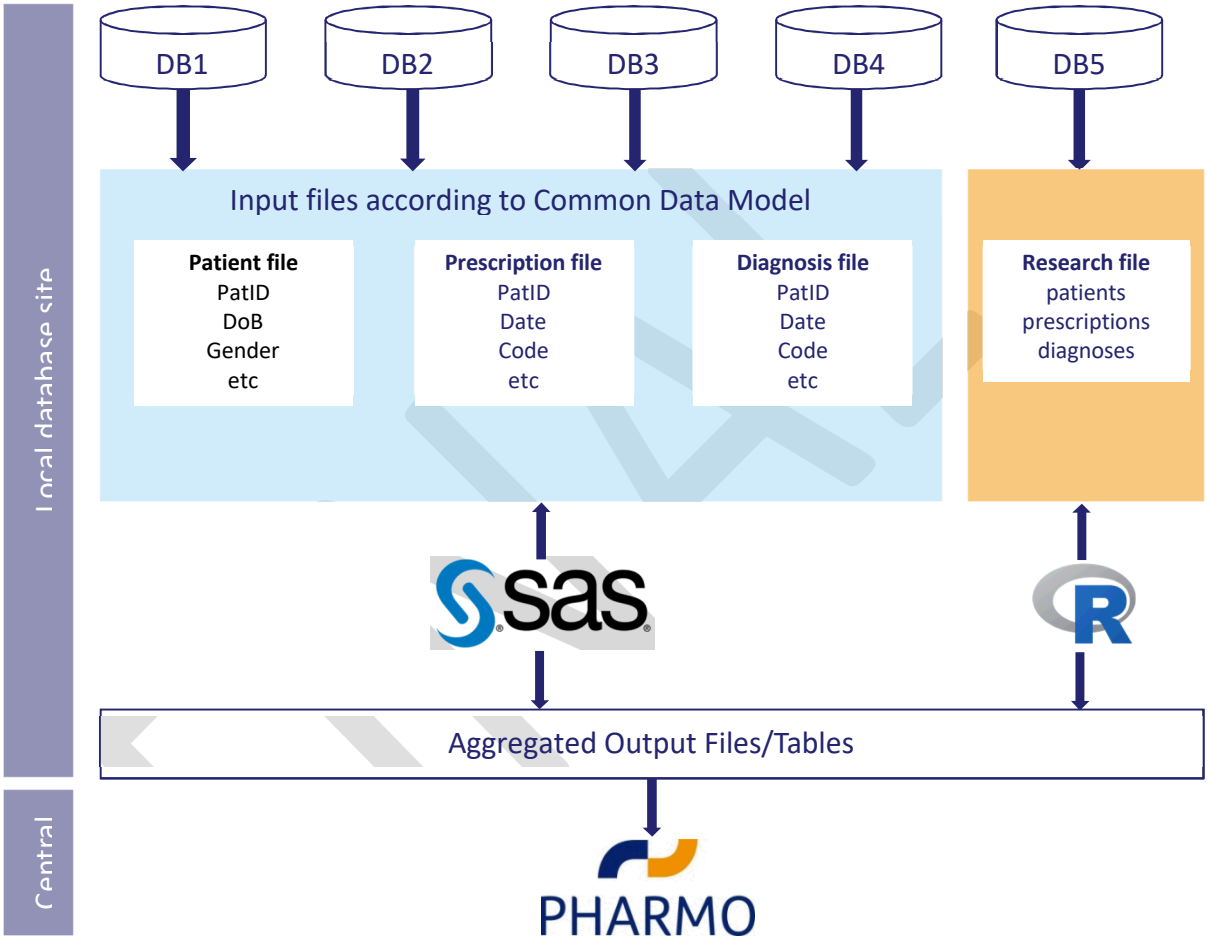

Figure 9.3 Schematic overview of the common programs for multi-country studies

9.7 Data analysis

9.7.1 Demographic, baseline and treatment characteristics

A flow chart of cohort attrition will be provided. For all study cohorts, demographic and baseline clinical characteristics of study patients initiating galcanezumab or comparator medication in the (prophylactic) treatment of migraine will be described using numbers and

percentages for categorical variables and mean, standard deviation (SD), median and interquartile range (IQR) for continuous variables in each individual database.

Galcanezumab treatment characteristics (i.e. treatment duration, reason for end of observation [switch, add-on, cessation, end of follow-up], and dose) will be summarised.

Demographic, baseline and treatment characteristics will also be summarised for the galcanezumab and comparator medication treatment cohorts and for the special populations of interest:

- patients ≥65 years of age
- patients with recent (within the last 6 months) serious CV events and/or serious CV risk prior to index date
- patients ≥65 years of age with recent serious CV events and/or serious CV risk prior to index date

9.7.2 Incidence of outcomes of interest

The risk of the outcomes of interest (i.e. serious CV events, serious hypersensitivity reactions, and malignancies) will be estimated separately and presented as incidence rates, i.e. the number of events of interest divided by person-time at risk, along with 95% confidence intervals (CIs) for the all and the matched galcanezumab and topiramate users, overall and per special population of interest. Rates will be presented by database (details and table/figure shells will be provided in the SAP).
Rates of malignancy will be provided overall and by system organ class and rates for serious CV events will be provided as composite outcome and as separate outcome. The risk of serious CV events and malignancies will be assessed per gender and per category of duration of uninterrupted treatment (for galcanezumab users only).

9.7.3 Distribution of time to malignancies and serious CV events

The distribution of time to malignancies (overall and per primary cancer site) and serious CV events (overall and per serious CV event) will be estimated by presenting the time to malignancy in a Kaplan-Meier survival curve.

9.7.4 Matching

It is likely that topiramate and galcanezumab are not per definition prescribed in the same stage of treatment or medical health status when taking into account risk factors for the outcomes of interest. Therefore, propensity score matching will be performed to assure more

comparable treatment groups and to decrease channelling bias. To ensure comparable treatment groups, the following characteristics will be considered for propensity score matching galcanezumab users with a diagnosis of migraine 1:2 to users of comparator medication as (prophylactic) treatment of migraine:

- Age
- Gender
- Calendar year of index date
- Non-index migraine preventive medication class during baseline
    - Ergotamine, triptans, CGRP antagonists, antiepileptics, antidepressants
    - Number of different classes
- Length of migraine disease
- Line of migraine therapy
- Other baseline parameters that would influence the outcome directly (i.e. CV medication)
- History of events

Exact details for the matching will be outlined in the SAP (e.g. high dimensional propensity score matching will be considered); the aim is to include as many patients as possible. The matching ratio of 1:2 may be reconsidered as appropriate based on the available sample sizes. If feasible, exact matching will be performed for at least age, gender and calendar year of index date.

9.7.5 Comparative safety analyses

Prior to beginning any comparative analyses, baseline characteristics for the galcanezumab and comparator cohorts will be examined. Adjustments to the cohort definitions will be made, as necessary, to ensure baseline comparability between the groups.

Comparisons of the safety outcomes of interest between galcanezumab users with migraine and propensity score matched comparator medication users with migraine will be conducted using Cox proportional-hazards regression. Variables that remain unbalanced after propensity score matching will be included in the regression model. For example, prior use of the comparator drug is considered an important variable for which adjustment is needed especially for the analyses of adverse effects which have a longer latency period such as malignancy.

The time-to-event will be calculated from the index date to the first occurrence of the outcome of interest. Relative risks will be estimated as HRs with 95% CIs. If sample size allows, comparative analyses will also be performed for the special populations of interest (i.e. patients with recent serious CV events and/or serious CV risk prior to initiating galcanezumab or patients ≥65 years of age). Comparative analyses will be conducted separately in each

database. For serious CV events and hypersensitivity reactions, sensitivity analyses will be performed in which a wash-out period will be applied to patients switching from comparator medication by not analysing events in a specified period after switch (periods per outcome to be defined in SAP). For malignancies, sensitivity analyses will be performed using different latency periods in which events will not be counted (e.g. 3 months, 6 months, 1 year) and by duration of treatment (e.g. <6 months, 6-12 months, 12-18 months, etc.). If the primary analysis reveals significant results in favour of either galcanezumab or the comparator, a sensitivity analysis will be conducted assessing time since initiation of index medication, allowing for various latency periods (e.g. 1 year, 2 years, etc. from the start of index treatment). The pattern of results from these analyses will aid in the identification of detection bias and potential clustering of events after initiating therapy.

9.8 Quality control

Standard operating procedures at each research center will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All programming written by the executing researcher will be reviewed independently by a senior researcher. All key study documents, such as the SAP and study reports, will undergo quality control and senior scientific review.

9.9 Limitations of the research methods

The most important uncertainty for the current study lies with the uptake of galcanezumab, which may decrease the precision of the estimates from the study. Galcanezumab was approved in November 2018 and is currently pending launch in several European countries. Country-specific launch and reimbursement may elongate the time before uptake is sufficient for this study. Each progress report will include the number of galcanezumab users available in the databases at that moment in time. The population of patients ≥65 years old with migraine will be relatively small due to the decreasing prevalence of migraine with age. This may have an impact on the feasibility of the proposed subgroup analysis of this population.

Furthermore, it is important to keep in mind that secondary healthcare databases are used for this study. Healthcare databases are primarily administration tools in patient care and have their limitations with regard to their use in scientific research, mainly related to the type and completeness of the recorded information. Information on indication of use and severity of migraine may not be recorded for all patients/databases and proxies/algorithms may need to be used as the medical records do not include this information either. This mainly applies to

databases such as ARS and SNDS in which out-patient diagnoses are not recorded. Also, not all potential confounders (e.g. life style factors) are recorded in the databases, and not all variables contain the information in desired detail. This is especially important as prescribing of galcanezumab may be channelled to patients with more severe migraine. This channelling bias specifically affects the comparative analyses for the relative risk assessment of the events of interest, and has the potential to bias the results away from the null.

Topiramate, the comparator for serious CV events and malignancies, is indicated for both epilepsy and migraine. To avoid confounding by indication topiramate users with epilepsy will be excluded from the comparator cohort. However, this may exclude patients with both migraine and epilepsy as well and we do not want to exclude a large portion of the patient population. Literature indicates that about 6% of migraine patients also have epilepsy[29] and galcanezumab development program had less than 1% of patients with a history of epilepsy or seizures. Prevalence rates of these combined indications are expected to be low based on explorations in the data from the PHARMO Database Network in the Netherlands (approximately 2% among users of topiramate with migraine) as well as a previous study using CPRD data from the UK (1.7% among GP-diagnosed migraine population[30]). To assess the impact of excluding these patients, sensitivity analyses including these patients will be performed.

Furthermore, databases often do not record the intended duration of use of each prescription (days of supply). This needs to be estimated from dispensed amount or the interval between consecutive prescriptions and can result in misclassification of drug exposure.

Misclassification of endpoints as well as confounders is possible. For the different databases that will be used, validation studies have shown that coding is reliable in the databases and that these databases are suitable for pharmacoepidemiological research. All databases have the ability to follow-up patients for a period of 5 years. However, this will only be possible for a subgroup of the study population and may therefore be hindering the conduct of comparative safety analyses for long-term outcomes (i.e. malignancies).

Also, malignancy outcomes require a long latency period, and as a result, are not easily attributed to a particular drug exposure. To account for this ambiguity, the primary analysis considers the risk of malignancy associated with the use of galcanezumab, regardless of subsequent medication changes. Although this approach is considered conservative from the standpoint that attribution of a malignancy to galcanezumab will not be missed, it ignores the duration of exposure to other medication. Typically, the risk of malignancy increases with increasing exposure to an identified risk factor. If galcanezumab were a risk factor for malignancy, combining patients with varying durations of exposure has the potential to bias the measure of association towards the null. To address this issue, an analysis that examines the duration of galcanezumab exposure use will be performed.

Finally, there are differences in timing of data updates in the various databases (medical records are continuously updated, administrative databases are updated only once per year in most instances). However, as data extraction will be repeated during the course of the study, this should allow for the most recent and "up-to-date" data to be used.

9.10 Other aspects

None

10. Protection of human subjects

The study will be conducted in accordance with Good Epidemiology Practices[31]. This is a retrospective, non-interventional study and does not pose any risks for patients. Confidentiality of patient records will be maintained at all times. All data used for the study will be de-identified with no breach of confidentiality with regards to personal identifiers or health information. Each database research partner will apply for an independent ethics committee review and/or other approvals according to local regulations. All study reports will contain aggregate data only and will not identify individual patients or physicians. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study subjects. Medical record abstraction, if available, will only be performed after receiving a waiver of authorisation from the relevant data holder's privacy board and approval from an Institute Review Board (IRB). At no time during the study will the sponsor receive patient identifying information except when it is required by regulations in case of reporting of adverse events.

11. Management and reporting of adverse events

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. No expedited reporting of adverse events or reactions is required. The protocol-defined AEs are specified in Section 9.3. All protocol-defined AEs collected will be summarised in the interim and final study reports.

12. Plans for disseminating and communicating study results

Upon study completion and finalisation of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal standards of the

marketing authorisation holder and the International Committee of Medical Journal Editors (ICMJE) guidelines.

For applicable non-interventional PASS (in the EU or mandated by an EU Health Authority outside the EU), the final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorised within two weeks after first acceptance for publication.

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Annex 1. List of stand-alone documents

Not applicable.

Annex 2. ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: A retrospective cohort study to assess drug utilisation and long-term safety of galcanezumab in European patients in the course of routine clinical care

EU PAS Register® number: EUPAS27594
Study reference number (if applicable): I5Q-MC-B002

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]	☒	☐	☐	9.2.3
1.1.2 End of data collection[2]	☒	☐	☐	9.2.3
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6

[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 1: Milestones	Yes	No	N/A	Section Number
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

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
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* 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)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
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))	☒	☐	☐	9.7.5
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?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.3.3
4.2.2 Age and sex	☒	☐	☐	9.3.3
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.6
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.7.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.2.2
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.2

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
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.7

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
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:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1.1 & 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

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)	☒	☐	☐	9.7

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)	☒	☐	☐	9.2.1 & 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.2.1 & 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.2.1 & 9.4

Section 9: Data sources	Yes	No	N/A	Section Number
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)	☒	☐	☐	9.2.1 & 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2.1 & 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2.1 & 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.2.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.2.1
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.2.1
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4 & 9.6.1

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.5
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
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.5
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	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:

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?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	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).	☒	☐	☐	9.9
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)	☒	☐	☐	9.1.2

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?	☒	☐	☐	9.6.1

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: PPD

Date: dd/Month/year

Signature: _____

Annex 3. Ability of data sources to identify relevant variables

Table 4. Ability of data sources to identify relevant variables	**PHARMO (NL)**	**CPRD (UK)**	**SNDS (FR)**	**GePaRD (DE)**	**SIDIAP (SP)**	**ARS (IT)**	**SHR (SE)**
Ability to identify adults with migraine receiving galcanezumab	✓[1]	✓[1]	✓[1]	✓[1]	✓[1]	✓[1]	✓[1]
Ability to identify adults with cluster headache receiving galcanezumab	✓[1]	✓[1]	✓[1]	✓[1]	✓[1]	✓[1]	✓[1]
Ability to determine representativeness of study population to the target population	✓[2]	✓	✓	✓	✓	✓[2]	✓
Ability to determine migraine type and severity	✓[3]	✓[3]	✓[3]	✓[3]	✓[3]	✓[3]	✓[3]
Ability to identify outcomes of interest	✓	✓	✓	✓	✓	✓	✓
Serious cardiovascular events	✓	✓	✓	✓	✓	✓	✓
Serious hypersensitivity events	✓	✓	✓	✓	✓	✓	✓
Malignancies	✓	✓	✓	✓	✓	✓	✓
Ability to follow patients for a period of 5 years	✓	✓	✓	✓	✓	✓	✓
Ability to identify cardiovascular risk factors	✓[4]	✓	✓	✓	✓	✓	✓
Smoking status	✓[4]	✓[4]	-[6]	-[6]	✓[4]	-[7]	-[6]
BMI	✓[4]	✓[4]	-[8]	-[8]	✓[4]	-[7]	-[8]
Hypertension	✓	✓	✓	✓	✓	✓	✓
Lipid levels	✓[4]	✓[4]	-	-[9]	✓[4]	-	-
Type 2 diabetes mellitus	✓	✓	✓	✓	✓	✓	✓
Ability to identify populations of special interest	✓	✓	✓	✓	✓	✓	✓
Age ≥65 years	✓	✓	✓	✓	✓	✓	✓
Recent history of cardiovascular events	✓	✓	✓	✓	✓	✓	✓
Patients at high risk for cardiovascular events	✓	✓	✓	✓	✓	✓	✓
Ability to confirm/adjudicate outcomes[5] I = Validation by medical chart review II = HES data and/or questionnaires III = Plausibilisation by patient profile review or validation of outcome algorithm in external data	I	II	III	III	I	I	I

[1]Based on recorded diagnosis and/or algorithm based on specific associated care parameters and/or patient profile review; [2]Based on recorded diagnosis of migraine and/or dispensing of migraine-specific drugs; [3]Severity will be based on a proxy, type is only available when recorded by GP; [4]Certain risk factors are available only for a subset of patients; [5]Validation of outcomes is out of the scope of the current proposal; [6]Only smoking-related diagnosis and smoking cessation drugs; [7]Only in women before pregnancy;[8]Coded obesity diagnosis can be used as proxy; [9]Coded hyperlipidaemia diagnosis can be used as proxy